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# BMJ Open

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

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## 23 **ABSTRACT**

### 24 **Introduction**

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

### 32 **Methods and analysis**

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

### 41 **Ethics and dissemination**

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

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4 **45 Trial Registration**

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6 46 Our study has been registered in PROSPERO (CRD42020192131)  
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9 **47 Keywords: Aliskiren; combination therapy; clinical outcome**  
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For peer review only

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4 **48 Strengths and limitations of this study**

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6  
7 49 • This will be the first study that systematically summarizes the effectiveness, safety and  
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9 50 tolerability of aliskiren combination therapy.  
10  
11 51 • When sufficient data are available, we will compare clinical outcomes of different  
12  
13 52 aliskiren combination therapies.  
14  
15 53 • If the included reviews in our study are not of high quality, we will re-analyze each  
16  
17 54 outcome using the random effects model.  
18  
19 55 • The methodological quality of the eligible reviews will be evaluated using AMSTAR2 for  
20  
21 56 assessing risk of bias.  
22  
23 57 • The results of this umbrella review are an asset to patients, clinicians and researchers,  
24  
25 58 help them to better acknowledge the scientific value of aliskiren combined use.  
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## 60 INTRODUCTION

61 Aliskiren is the first in a new class of oral, non-peptide, low molecular weight direct renin  
62 inhibitor (DRI). It has been approved by the US Food and Drug Administration (FDA) for the  
63 management of hypertension in 2007<sup>[1]</sup>. As studies revealed, aliskiren is effective in  
64 controlling blood pressure as monotherapy<sup>[2,3]</sup>. Furthermore, researchers found that aliskiren  
65 could provide more anti-hypertension efficacy when combined with other kinds of blood  
66 pressure medicines<sup>[4-8]</sup>. An increasing number of clinical trials and systematic reviews have  
67 assessed the anti-hypertension efficacy and tolerability of aliskiren combination therapies  
68<sup>[4,9,10]</sup>. However, there has yet to be a comprehensive evidence map that summarizes the wide  
69 array of health benefits and safety of aliskiren combination treatments. As noted above,  
70 existing systematic reviews on aliskiren combination treatments focused on single health  
71 outcomes, and most reviews evaluated only one type of combination treatment rather than  
72 exploring the multiple combination treatments. In addition, due to the diversity in settings,  
73 types and outcomes of aliskiren combination treatments, the quality of these reviews were  
74 varied. Umbrella reviews can systematically appraise evidence in the published literature by  
75 evaluating meta-analyses of multiple combination treatment on multiple outcomes<sup>[11]</sup>. We  
76 would perform an umbrella review of systematic reviews to holistically evaluate and  
77 summarize existing systematic reviews that assess the efficacy, safety and tolerability of  
78 aliskiren combination therapy.

## 79 METHODS

80 Protocol development



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4 81 This umbrella review protocol follows the Joanna Briggs Institute Methodology for Umbrella  
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6 82 Reviews [12]. This protocol was also developed to align with the Preferred Reporting Items for  
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9 83 Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement [13] and has  
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11  
12 84 been registered with the PROSPERO database for systematic reviews (CRD42020192131).

### 14 85 **Eligibility criteria**

16  
17 86 We used the population, intervention, comparator, outcomes and study design structure in  
18  
19  
20 87 formulating the scope of this umbrella review.

22 88 **Population:** This umbrella review will include systematic reviews that include hypertension  
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24  
25 89 patients and related comorbid populations.

27 90 **Intervention:** This umbrella review will include systematic reviews that focus on aliskiren  
28  
29  
30 91 combination with other anti-hypertension medicine, such as ARBs, ACEIs, HCTZs.

32 92 **Comparators:** Aliskiren monotherapy or aliskiren combined with another medicine.

### 34 93 **Outcomes**

36 94 We will assess the following outcomes: The primary efficacy outcomes were cardiovascular  
37  
38  
39 95 outcomes such as mortality rate, the composite of death and major adverse events, the  
40  
41  
42 96 incidence of stroke and myocardial infarction. Secondary efficacy outcomes were rates of  
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45 97 therapeutic response and BP control, reduction from baseline to the end of treatment in mean  
46  
47 98 clinical SBP ( $\Delta$ mSBP) and DBP ( $\Delta$ mDBP). The safety of drug was assessed by incidence of  
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50 99 some adverse events such as hyperkalaemia, acute kidney injury. The tolerability of the drug  
51  
52 100 was assessed by considering overall rates of any adverse events and withdrawal from a study  
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55 101 due to adverse events. Reviews with any of the above outcomes will be included.

57 102 **Type of studies:** Systematic reviews, meta-analyses or pooled analyses

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4 103 The reviews that were out of date will be excluded. Meta-analyses that did not provide  
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6 104 specific study data (number of incident events, number of study population, follow-up period,  
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8  
9 105 relative risks and 95% confidence intervals (CI)) and in which the missing data was not  
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11  
12 106 retrievable from the original studies will be excluded.

### 14 107 **Search Strategy**

17 108 We will search the following databases from inception of databases to August 2020: Pubmed,  
18  
19 109 Embase, Cochrane Library and CNKI. Additionally, we will manually search all reference  
20  
21  
22 110 lists of the included studies to identify additional reviews of relevance.

24 111 We developed this search strategy using keywords, MeSH (Medical Subject Headings) terms  
25  
26  
27 112 and text words, which will be searched in combination (aliskiren OR direct renin inhibitor  
28  
29  
30 113 OR renin-angiotensin inhibition OR spp100 OR takturna) AND (systematic review OR  
31  
32  
33 114 meta-analysis OR pooled analysis). We will modify the database-specific controlled  
34  
35 115 vocabulary and key terms to suit the above mentioned databases.

### 37 116 **Study screening**

39  
40 117 Electronic search results will be down loaded into Endnote software, and duplicates will be  
41  
42  
43 118 removed automatically and manually based on an exact match of the title, date, author and  
44  
45  
46 119 result. Two reviewers will independently screen titles and abstracts of retrieved articles  
47  
48  
49 120 according to the inclusion and exclusion criteria. When the reviewers cannot decide the  
50  
51 121 eligibility of a study through title or abstract screening, full-texts will be screened.  
52  
53 122 Disagreements between reviewers will be resolved using consensus, and by a third reviewer  
54  
55  
56 123 if necessary. The outline of the study selection procedure will be shown in a flow chart  
57  
58 124 (Figure 1).  
59  
60

## 125 **Data Extraction**

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

## 138 **Assessment of methodological quality of included reviews**

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

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4 146 disagreements between reviewers will be resolved among themselves through discussion and  
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6 147 by a third reviewer if being unable to achieve consensus.  
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#### 9 148 **Data synthesis and statistical analysis**

10  
11 149 Statistical analysis will be conducted using RevManV.5.3 software and StataV.14.0 software.

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14 150 In our analysis, when possible, we will stratify the comparisons into several groups according  
15  
16  
17 151 to the characteristics of our targeted population. We will divide patients into three groups:  
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19 152 simple hypertension patients, patients with hypertension and diabetes; and patients who are  
20  
21  
22 153 suffering from hypertension, diabetes and nephropathy or albuminuria at the same time.

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25 154 When evaluating antihypertensive effects, we will divide patients into three groups: young  
26  
27 155 patients (<50years), early elderly patients (50-70years), elderly patients (>70years).

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30 156 For each outcome, if the random model was already used, we will extract the pooled  
31  
32 157 effect sizes of included systematic review. If not, we will extract original data and reanalyze  
33  
34  
35 158 them with the random effect methods to get the pooled effect size and its related 95% CI. We  
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37  
38 159 will also estimate the 95% prediction interval (95% PI) for the summary estimate based on  
39  
40 160 the random-effect model, to represent the range in which the effect estimates of future studies  
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42  
43 161 will lie. The Q and I<sup>2</sup> test statistics will be calculated to determine the degree of heterogeneity.  
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46 162 For the Q statistic, p<0.05 will be considered significant. We will classify the degree of  
47  
48 163 heterogeneity into substantial heterogeneity (I<sup>2</sup>>50%) and considerable heterogeneity  
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50 164 (I<sup>2</sup>>75%). We will conduct a Bayesian network meta-analysis to estimate relative combination  
51  
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53 165 therapy effects based on a synthesis of direct and indirect evidence.  
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56 166 Where no quantitative pooling of effect sizes was reported or where outcomes were  
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58 167 reported descriptively by single studies, we will provide these results by using standardized  
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4 168 language indicating direction of effect and statistical significance.

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6 169 If an outcome is examined at least 3 articles, we will use Egger's test (conducted using  
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9 170 StataV.14.0) to evaluate if the reporting bias exists. Values of  $p < 0.1$  will be interpreted as  
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11 171 statistically significant [16].

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13  
14 172 All included systematic reviews and meta-analyses will be screened for over lapping of  
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17 173 included original studies. We will explore this through the use of The Cochrane Handbook's  
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19 174 template for mapping individual primary studies contained within included systematic  
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22 175 reviews [17]. If reviews are reporting the same outcomes from the same study, we will  
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25 176 highlight this overlap. To assess the degree of overlap, we will calculate the corrected  
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27 177 covered area (CCA)[18]. A CCA score of 0-5 indicates slight overlap, 6-10 moderate, 11-15  
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30 178 high and  $>15$  very high. We will consider overlap when interpreting results of the overview.

### 31 32 179 **Patient and public involvement**

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34  
35 180 Patients and/or the public were involved in the design, or conduct, or reporting, or  
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37 181 dissemination plans of this research. The results of this work will be disseminated to the  
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40 182 public via conferences, publications and presentations.

### 41 42 43 183 **DISCUSSION**

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45 184 Aliskiren is an orally administered, direct renin inhibitor approved in numerous  
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48 185 countries, including the US and the EU for the management of hypertension. The clinical  
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51 186 efficacy and tolerability of aliskiren-based therapy in hypertension have been previously  
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53 187 reviewed by many systematic reviews, while the evidence about aliskiren combination  
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56 188 therapy has not been appraised holistically. Umbrella review is a review of systematic  
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59 189 reviews and meta-analyses, which is viewed as one of the four next-generation  
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4 190 meta-analyses<sup>[19]</sup>.

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6 191 For this umbrella review, we will (1) identify and synthesize existing review and  
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9 192 meta-analysis studies on aliskiren combination therapies; (2) critically evaluate the available  
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11 193 evidence both narrative and quantitative; and (3) identify the most prominent aliskiren  
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14 194 combination treatment used to manage hypertension. We will use qualitative methods and  
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17 195 quantitative methods to synthesizing the review literatures. We plan to evaluate the  
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20 196 credibility of included evidences. We will create the summary of findings tables and report a  
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22 197 summary of findings from all included reviews based on data synthesis, presenting a  
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25 198 comprehensive overview of what is known in the literatures about the efficacy, safety and  
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27 199 tolerability of different aliskiren combination therapies.

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30 200 This is the first umbrella review about aliskiren combination therapy. Summarizing  
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32 201 these evidences will be an asset to clinicians and researchers aiming to improve the scientific  
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35 202 of aliskiren combine use. Anticipated limitations of our study are the heterogeneity and quality  
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38 203 of the included reviews. To address the limitations, we will reanalyze each outcome using the  
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41 204 random effects model and evaluate the quality of included studies. Furthermore, these two  
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43 205 factors will be carefully considered when interpreting the results. Another limitation of this  
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46 206 overview will be the potential for study overlap across reviews. Considering this potential  
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49 207 bias, we will examine and report on any overlap in the overview. Despite anticipated  
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52 208 limitations, this umbrella review will be conducted using the most systematic procedures  
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55 209 available at this time. Adhering to these guidelines helps ensure that we produce a  
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58 210 high-quality umbrella review, which will be a useful and trustworthy resource for interested  
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60 211 parties.

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4 **212 Ethics and dissemination**

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6 213 Ethical approval is not required for the study, as we only collected data from available  
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9 214 materials. This umbrella review will be also submitted to a peer-reviewed journal for  
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12 215 publication.

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14 **216 Authors' contributors**

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17 217 Jiantong Shen and Wenming Fen carried on the conception and construction of this protocol.  
18  
19 218 Yike Wang developed the search strategy. Qiyuan Zhao and Jingya Lu compared and found  
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21  
22 219 the best tools for assessing possible bias and evaluating quality of included reviews. Jiantong  
23  
24  
25 220 Shen wrote the protocol. BILLONG Laura Flavorta added grammar editing and conceptual  
26  
27 221 clarification. All authors read and approved of the final manuscript.

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35 224 numbers Y201635273] and Chinese Academic Degree and Postgraduate Education Society  
36  
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38 225 Medical Science Working Committee [Grant numbers B3-YX20190302-18]

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40 **226 Competing interests**

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43 227 None declared

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45 **228 Patient and public involvement**

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48 229 No patients and public are involved in developing plans for project and implementation of  
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51 230 this study. None of them are asked to advise on interpretation of results. The results will be  
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54 231 disseminated to the general population through public presentations by the authors.

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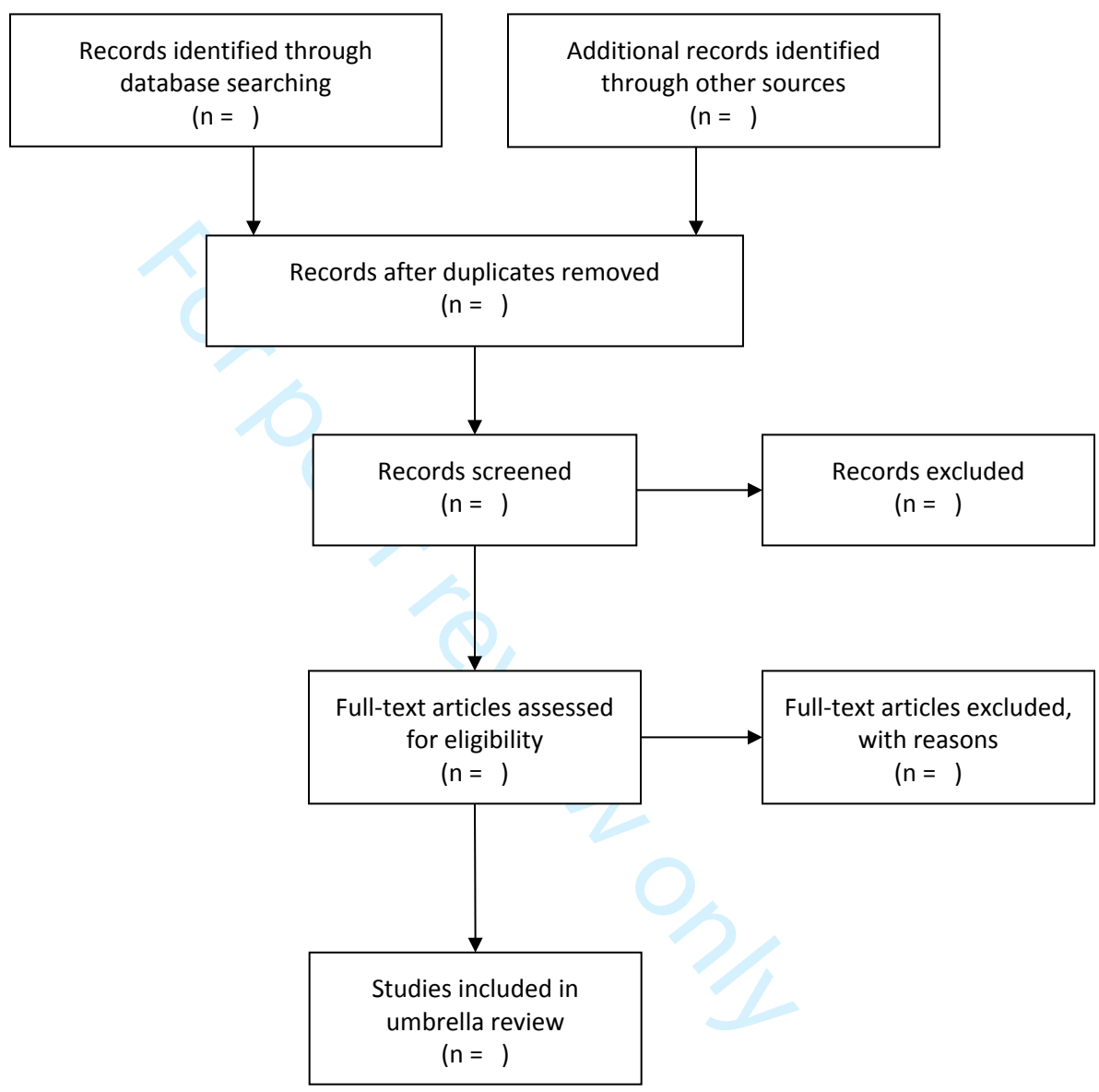
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Identification

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# BMJ Open

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

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<b>Primary Subject Heading</b>:	Cardiovascular medicine
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Keywords:	Hypertension < CARDIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, VASCULAR MEDICINE

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6 2 Efficacy and Safety of Aliskiren Combination Therapy: A Protocol for An Umbrella Review  
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- 27 **Word count: 2870**

For peer review only

## 28 **ABSTRACT**

### 29 **Introduction**

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

### 37 **Methods and analysis**

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

### 46 **Ethics and dissemination**

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



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50 **Trial Registration**

51 Our study has been registered in PROSPERO (CRD42020192131)

52 **Keywords: Aliskiren; combination therapy; clinical outcome**

For peer review only

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4 53 **Strengths and limitations of this study**

- 5  
6 54 • This will be the first study that systematically summarizes the effectiveness, safety and  
7  
8  
9 55 tolerability of aliskiren combination therapy.  
10  
11 56 • When sufficient data are available, we will compare clinical outcomes of different  
12  
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14 57 aliskiren combination therapies.  
15  
16 58 • If the included reviews in our study are not of high quality, we will re-analyze each  
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18  
19 59 outcome using the random effects model.  
20  
21  
22 60 • Anticipated limitations of our study are the heterogeneity and quality of the included  
23  
24  
25 61 reviews. Another limitation of this overview will be the potential for study overlap across  
26  
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28 62 reviews.  
29  
30 63 • The results of this umbrella review are an asset to patients, clinicians and researchers,  
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33 64 help them to better acknowledge the scientific value of aliskiren combined use.  
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## 66 INTRODUCTION

67 Aliskiren is the first in a new class of oral, non-peptide, low molecular weight direct renin  
68 inhibitor (DRI). It has been approved by the US Food and Drug Administration (FDA) for the  
69 management of hypertension in 2007<sup>[1]</sup>. As studies revealed, aliskiren was effective in  
70 controlling blood pressure as monotherapy<sup>[2,3]</sup>. Furthermore, researchers found that aliskiren  
71 could provide more anti-hypertension efficacy when combined with other kinds of blood  
72 pressure medicines <sup>[4-8]</sup>. An increasing number of clinical trials and systematic reviews have  
73 assessed the anti-hypertension efficacy and tolerability of aliskiren combination therapies  
74 <sup>[4,9,10]</sup>. However, there has yet to be a comprehensive evidence map that summarizes the wide  
75 array of health benefits and safety of aliskiren combination treatments. As noted above,  
76 existing systematic reviews on aliskiren combination treatments focused on single health  
77 outcomes, and most reviews evaluated only one type of combination treatment rather than  
78 exploring the multiple combination treatments. In addition, due to the diversity in settings,  
79 types and outcomes of aliskiren combination treatments, the quality of these reviews were  
80 varied. Umbrella reviews can systematically appraise evidence in the published literature by  
81 evaluating meta-analyses of multiple combination treatment on multiple outcomes<sup>[11]</sup>. We  
82 would perform an umbrella review of systematic reviews to holistically evaluate and  
83 summarize existing systematic reviews that assess the efficacy, safety and tolerability of  
84 aliskiren combination therapy.

## 85 METHODS

86 Protocol development

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4 87 This umbrella review protocol follows the Joanna Briggs Institute Methodology for Umbrella  
5  
6 88 Reviews [12]. This protocol was also reported align with the Preferred Reporting Items for  
7  
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9 89 Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement [13] and has  
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11  
12 90 been registered with the PROSPERO database for systematic reviews (CRD42020192131).

### 91 **Eligibility criteria**

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

94 **Population:** This umbrella review will include systematic reviews that include hypertension  
95 patients and related comorbidity populations. Hypertension define as blood pressure  $\geq 140/90$   
96 mmHg for office measurement.

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

99 **Comparators:** Aliskiren monotherapy or aliskiren combined with another medicine.

### 100 **Outcomes**

101 We will assess the following outcomes: The primary efficacy outcomes were cardiovascular  
102 outcomes such as mortality rate, the composite of death and major adverse events, the  
103 incidence of stroke and myocardial infarction, any acute coronary syndrome. Secondary  
104 efficacy outcomes were rates of therapeutic response and BP control (audit standard of <  
105 140/90 mmHg for office measurement), reduction from baseline to the end of treatment in  
106 mean clinical SBP ( $\Delta$ mSBP) and DBP ( $\Delta$ mDBP). We will use clinic blood pressure. The  
107 safety of drug was assessed by incidence of some adverse events such as hyperkalaemia,  
108 acute kidney injury, angioedema and postural hypotension. The tolerability of the drug was  
109 assessed by considering overall rates of any adverse events and withdrawal from a study due

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4 110 to adverse events. Reviews with any of the above outcomes will be included. We will also  
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6 111 consider cost- effectiveness results such as incremental cost- effectiveness ratios, average  
7  
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9 112 cost-effectiveness ratio, benefit–cost ratio and unit costs.  
10

11  
12 113 **Type of studies:** Systematic reviews, meta-analyses or pooled analyses  
13

14 114 The reviews that were out of date will be excluded. Meta-analyses that did not provide  
15  
16  
17 115 specific study data (number of incident events, number of study population, follow-up period,  
18  
19 116 relative risks and 95% confidence intervals (CI)) and in which the missing data was not  
20  
21  
22 117 retrievable from the original studies will be excluded.  
23

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25 118 **Search Strategy**

26  
27 119 We will search the following databases from inception of databases to August 2020: Pubmed,  
28  
29  
30 120 Embase, Cochrane Library and CNKI. Additionally, we will manually search all reference  
31  
32 121 lists of the included studies to identify additional reviews of relevance.  
33

34  
35 122 We developed this search strategy using keywords, MeSH (Medical Subject Headings) terms  
36  
37 123 and text words, which will be searched in combination (aliskiren OR direct renin inhibitor  
38  
39 124 OR renin-angiotensin inhibition OR spp100 OR takturna OR Rasilez) AND (systematic  
40  
41 125 review OR meta-analysis OR pooled analysis) (see Supplementary 1). We will modify the  
42  
43 126 database-specific controlled vocabulary and key terms to suit the above mentioned databases.  
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48 127 **Study screening**

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50 128 Electronic search results will be down loaded into Endnote software, and duplicates will be  
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52  
53 129 removed automatically and manually based on an exact match of the title, date, author and  
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56 130 result. Two reviewers will independently screen titles and abstracts of retrieved articles  
57  
58 131 according to the inclusion and exclusion criteria. When the reviewers cannot decide the  
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4 132 eligibility of a study through title or abstract screening, full-texts will be screened.  
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6 133 Disagreements between reviewers will be resolved using consensus, and by a third reviewer  
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8  
9 134 if necessary. The outline of the study selection procedure will be shown in a flow chart  
10  
11  
12 135 (Figure 1).  
13

#### 14 136 **Data Extraction**

15  
16  
17 137 Standardized abstraction forms will be established in Microsoft EXCEL, and the data from  
18  
19 138 each eligible systematic review will be extracted by two reviewers independently.  
20  
21

22 139 Ambiguities related to data extraction will be resolved by discussion or by a third reviewer if  
23  
24 140 the reviewers are unable to achieve consensus. The following information will be extracted:  
25  
26 141 characteristics of included reviews (e.g. first author, publication year, number and type of  
27  
28 142 studies included in each review, total sample size), population (disease conditions),  
29  
30 143 intervention and control (medicine of intervention or control, sample size of each group and  
31  
32 144 details of treatment, dosing of treatment, follow-up period) and outcomes (name and  
33  
34 145 definition of outcome, summary effect size and its related 95% CI and the number of  
35  
36 146 participants included in the outcome assessment). When the data are only provided through  
37  
38 147 plots, we will use Ycasd to determine the effect size and its 95% CI<sup>[14]</sup>. We will contact the  
39  
40 148 corresponding authors to ask for data, when necessary data were not provided in the article.  
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#### 48 149 **Assessment of methodological quality of included reviews**

49  
50 150 The quality of the included studies will be appraised by using the Assessment of Multiple  
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52 151 Systematic Reviews 2 tool (AMSTAR2, an updated version of AMSTAR), which is updated  
53  
54 152 to allow for both randomized and observational studies. Unlike its predecessor, AMSTAR 2  
55  
56 153 has the capacity to identify critical weaknesses that reduce confidence in the findings of a  
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4 154 review<sup>[15]</sup>. AMSTAR 2 consists of 16 items with the following response options: Yes, Partial  
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6 155 Yes and No. Two reviewers will independently rate the quality of each systematic review as  
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8  
9 156 high, moderate, low and critically low based on the overall score of the AMSTAR2. Any  
10  
11 157 disagreements between reviewers will be resolved among themselves through discussion and  
12  
13  
14 158 by a third reviewer if being unable to achieve consensus.

### 159 **Data synthesis and statistical analysis**

160 Statistical analysis will be conducted using RevManV.5.3 software and StataV.14.0 software.  
161 In our analysis, when possible, we will stratify the comparisons into several groups according  
162 to the characteristics of our targeted population. We will divide patients into three groups:  
163 simple hypertension patients, patients with hypertension and diabetes; and patients who are  
164 suffering from hypertension, diabetes and nephropathy or albuminuria (an eGFR < 60  
165 mL/min/1.73 m<sup>2</sup> or The Kidney Disease Improving Global Outcomes (KDIGO) GFR stages  
166 3 to 5) at the same time. In order to be consistent with changes in the classification and  
167 diagnostic criteria for diabetes over the years, the diagnosis should be established using the  
168 standard criteria valid at the time of the trial commencing (for example ADA 2003; ADA  
169 2008; WHO 1998). Ideally, the diagnostic criteria should have been described. We will use  
170 the trial authors' definition of diabetes mellitus if necessary. We plan to subject diagnostic  
171 criteria to a sensitivity analysis. When evaluating antihypertensive effects, we will divide  
172 patients into three groups: young patients (<50years), early elderly patients (50-70years),  
173 elderly patients (>70years).

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

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4 176 them with the random effect methods to get the pooled effect size and its related 95% CI. We  
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6 177 will also estimate the 95% prediction interval (95% PI) for the summary estimate based on  
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9 178 the random-effect model, to represent the range in which the effect estimates of future studies  
10  
11 179 will lie. The Q and  $I^2$  test statistics will be calculated to determine the degree of heterogeneity.  
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14 180 For the Q statistic,  $p < 0.05$  will be considered significant. We will classify the degree of  
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17 181 heterogeneity into substantial heterogeneity ( $I^2 > 50\%$ ) and considerable heterogeneity  
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19 182 ( $I^2 > 75\%$ ). We will conduct a Bayesian network meta-analysis to estimate relative  
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22 183 combination therapy effects based on a synthesis of direct and indirect evidence.  
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25 184 Where no quantitative pooling of effect sizes was reported or where outcomes were  
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27 185 reported descriptively by single studies, we will provide these results by using standardized  
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30 186 language indicating direction of effect and statistical significance.  
31

32 187 If an outcome is examined at least 3 articles, we will use Egger's test (conducted using  
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35 188 StataV.14.0) to evaluate if the reporting bias exists. Values of  $p < 0.1$  will be interpreted as  
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38 189 statistically significant [16].  
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40 190 All included systematic reviews and meta-analyses will be screened for over lapping of  
41  
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43 191 included original studies. We will explore this through the use of The Cochrane Handbook's  
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46 192 template for mapping individual primary studies contained within included systematic  
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48 193 reviews [17]. If reviews are reporting the same outcomes from the same study, we will  
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51 194 highlight this overlap. To assess the degree of overlap, we will calculate the corrected  
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54 195 covered area (CCA)[18]. A CCA score of 0-5 indicates slight overlap, 6-10 moderate, 11-15  
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56 196 high and  $> 15$  very high. We will consider overlap and do sensitivity analyses when  
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59 197 interpreting results of the overview.  
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4 **198 Patient and public involvement**

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6 199 No patients and public are involved in developing plans for project and implementation of  
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9 200 this study. None of them are asked to advise on interpretation of results. The results will be  
10  
11 201 disseminated to the general population through public presentations by the authors.

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14 **202 DISCUSSION**

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17 203 Aliskiren is an orally administered, direct renin inhibitor approved in numerous  
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19 204 countries, including the US and the EU for the management of hypertension. The clinical  
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21 205 efficacy and tolerability of aliskiren-based therapy in hypertension have been previously  
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23 206 reviewed by many systematic reviews, while the evidence about aliskiren combination  
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25 207 therapy has not been appraised holistically. Umbrella review is a review of systematic  
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27 208 reviews and meta-analyses, which is viewed as one of the four next-generation meta-analyses  
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32 209 [19].

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35 210 For this umbrella review, we will (1) identify and synthesize existing review and  
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37 211 meta-analysis studies on aliskiren combination therapies; (2) critically evaluate the available  
38  
39 212 evidence both narrative and quantitative; and (3) identify the most prominent aliskiren  
40  
41 213 combination treatment used to manage hypertension. We will use qualitative methods and  
42  
43 214 quantitative methods to synthesizing the review literatures. We plan to evaluate the  
44  
45 215 credibility of included evidences. We will create the summary of findings tables and report a  
46  
47 216 summary of findings from all included reviews based on data synthesis, presenting a  
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49 217 comprehensive overview of what is known in the literatures about the efficacy, safety and  
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51 218 tolerability of different aliskiren combination therapies.

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58 219 This is the first umbrella review about aliskiren combination therapy. Summarizing  
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4 220 these evidences will be an asset to clinicians and researchers aiming to improve the scientific  
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6 221 of aliskien combine use. Anticipated limitations of our study are the heterogeneity and quality  
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9 222 of the included reviews. To address the limitations, we will reanalyze each outcome using the  
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11 223 random effects model and evaluate the quality of included studies. Furthermore, these two  
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14 224 factors will be carefully considered when interpreting the results. Another limitation of this  
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17 225 overview will be the potential for study overlap across reviews. Considering this potential  
18  
19 226 bias, we will examine and report on any overlap in the overview. Despite anticipated  
20  
21 227 limitations, this umbrella review will be conducted using the most systematic procedures  
22  
23  
24 228 available at this time. Adhering to these guidelines helps ensure that we produce a  
25  
26  
27 229 high-quality umbrella review, which will be a useful and trustworthy resource for interested  
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30 230 parties.

### 31 32 231 **Ethics and dissemination**

33  
34  
35 232 Ethical approval is not required for the study, as we only collected data from available  
36  
37 233 materials. This umbrella review will be also submitted to a peer-reviewed journal for  
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39  
40 234 publication.

### 41 42 43 235 **Authors' contributors**

44  
45 236 Jiantong Shen and Wenming Feng carried on the conception and construction of this protocol.  
46  
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48 237 Yike Wang developed the search strategy. Qiyuan Zhao and Jingya Lu compared and found  
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50 238 the best tools for assessing possible bias and evaluating quality of included reviews. Jiantong  
51  
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53 239 Shen wrote the protocol. BILLONG Laura Flavorta added grammar editing and conceptual  
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56 240 clarification. All authors read and approved of the final manuscript.  
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14 245 National Social Science Fund of China[Grant numbers 20BTQ042].

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17 246 **Competing interests**

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19 247 None declared

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4 305 Figure 1 Flow diagram of study selection process  
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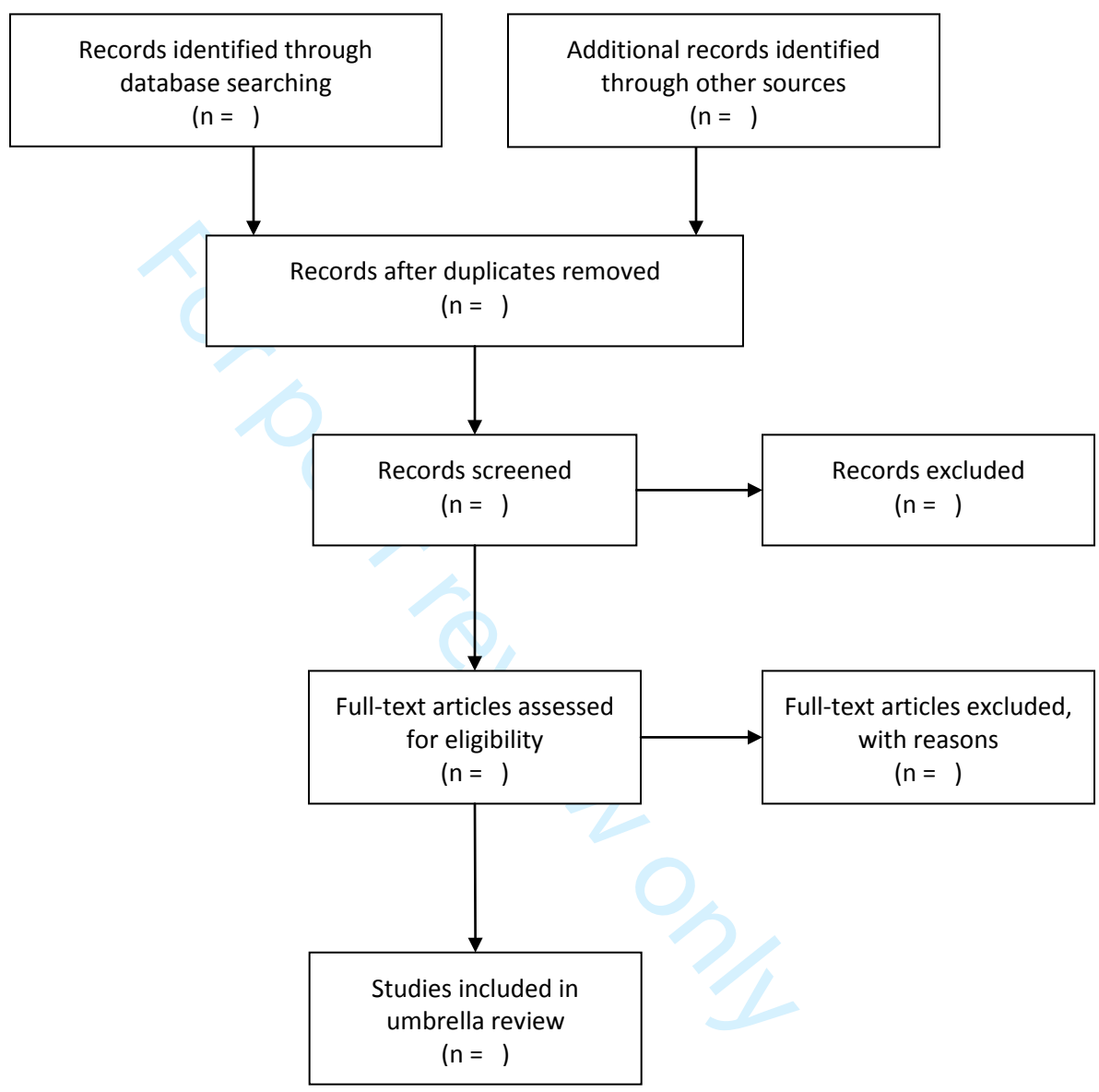
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Identification

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8 #1 "aliskiren"[Supplementary Concept]  
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10 #2 "Rasilez"[Title/Abstract]

11 #3 "tekturna"[Title/Abstract]

12 #4 "spp100"[Title/Abstract]

13 #5 "renin angiotensin inhibition"[Title/Abstract]

14 #6 "direct renin inhibitor"[Title/Abstract]

15 #7 "aliskiren"[Title/Abstract]

16 #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7  
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18 Filters: Meta-Analysis, Systematic Review  
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