

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Efficacy and Safety of Aliskiren Combination Therapy: A Protocol for An Umbrella Review
<b>AUTHORS</b>	Shen, Jiantong; Feng, Wenming; Wang, Yike; Zhao, Qiyuan; Flavorta, BILLONG Laura; Lu, Jingya

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Dr James Coulson School of Medicine, Cardiff University, Cardiff, United Kingdom.
<b>REVIEW RETURNED</b>	21-Sep-2020

<b>GENERAL COMMENTS</b>	<p>Thank you for allowing me to review the study protocol for an umbrella review of the antihypertensive, aliskiren, in combination with other antihypertensives. I have the following suggestions and comments:</p> <ol style="list-style-type: none"><li>(1) Please clarify the major adverse cardiac events that you will record as part of the composite primary outcome, for example would any acute coronary syndrome be included or will you limit to ST-elevation MIs only?</li><li>(2) Recommend that you consider achievement of blood pressure control (e.g "audit standard of &lt; 140/90 mmHg for office measurement).</li><li>(3) Please clarify if you will record clinic ("office") blood pressure measurement, 24 ambulatory blood pressure measurement or home blood pressure monitoring?</li><li>(4) Recommend including the incidence of angioedema and postural hypotension to the advise effects data collection.</li><li>(5) Recommend including "Rasilez" in the search terms.</li><li>(6) Please provide brief details on how patients and/or the public were involved in the study design?</li><li>(7) Please clarify that you will be collecting dosing data for aliskiren and the other antihypertensives.</li><li>(8) Please clarify the diagnostic criteria that will be used to determine the hypertensive; diabetic and nephrotic patient populations.</li><li>(9) Recommend you consider including health economic data in the secondary outcomes.</li></ol>
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	(10) The manuscript needs to be checked for typographical errors to bring it up to publication standard. There are word spacing errors and tense disagreements in sections of the manuscript.
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<b>REVIEWER</b>	Stefano Omboni Italian Institute of Telemedicine,. Italy
<b>REVIEW RETURNED</b>	26-Sep-2020

<b>GENERAL COMMENTS</b>	<p>In this protocol paper, the authors describe the methodology for an umbrella review of aliskiren-based studies.</p> <p>Abstract. I recommend making clear in the abstract that this is an umbrella review of previously published systematic reviews and meta-analyses (add this information on page 2, line 29).</p> <p>Since the main target population for these studies is hypertension, I do not understand why BP control or BP reduction is not the primary target of this umbrella review. I expect that this would be the most commonly available endpoint.</p> <p>I expect a heterogeneity of studies designs with some RCTs, some uncontrolled, some observational, etc. How do the authors plan to deal with this?</p> <p>The possible overlapping of the same studies in multiple meta-analyses is dealt with by the authors (page 10). If the number of systematic reviews is high, some sensitivity analyses may be planned.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

(1) Please clarify the major adverse cardiac events that you will record as part of the composite primary outcome, for example would any acute coronary syndrome be included or will you limit to ST-elevation MIs only?

Thanks for suggestion. We will include any acute coronary syndrome.

(2) Recommend that you consider achievement of blood pressure control (e.g "audit standard of < 140/90 mmHg for office measurement).

Thanks for suggestion. We will take standard of < 140/90 mmHg for office measurement. We have added this in our manuscript.

(3) Please clarify if you will record clinic ("office") blood pressure measurement, 24 ambulatory blood pressure measurement or home blood pressure monitoring?

Thanks for suggestion. We have added this in our manuscript.

(4) Recommend including the incidence of angioedema and postural hypotension to the advise effects data collection.

Thanks for suggestion. We have added.

(5) Recommend including "Rasilez" in the search terms.

Thanks for suggestion. We have added.

(6) Please provide brief details on how patients and/or the public were involved in the study design?  
We have made a typing mistake. No patients and public are involved in developing plans for project.  
We have revised.

(7) Please clarify that you will be collecting dosing data for aliskiren and the other antihypertensives.  
Thanks for suggestion. We have added this in our manuscript.

(8) Please clarify the diagnostic criteria that will be used to determine the hypertensive; diabetic and nephrotic patient populations.  
Thanks for suggestion. We have added this in our manuscript.

(9) Recommend you consider including health economic data in the secondary outcomes.

Thanks for suggestion. We have added this in our manuscript.

(10) The manuscript needs to be checked for typographical errors to bring it up to publication standard. There are word spacing errors and tense disagreements in sections of the manuscript.

Thanks for suggestion. We have checked the manuscript and do revised

Reviewer: 2

Abstract. I recommend making clear in the abstract that this is an umbrella review of previously published systematic reviews and meta-analyses (add this information on page 2, line 29).  
Thanks for suggestion. We have added this in abstract.

Since the main target population for these studies is hypertension, I do not understand why BP control or BP reduction is not the primary target of this umbrella review. I expect that this would be the most commonly available endpoint.

BP control or BP reduction was used as primary target in most studies. However, it is an intermediate indicator. Cardiovascular event is the patient-related end outcome of hypertension. We hope to evaluate based on end outcomes.

I expect a heterogeneity of studies designs with some RCTs, some uncontrolled, some observational, etc. How do the authors plan to deal with this?

We will include systematic reviews and meta-analysis only. The results of systematic reviews based on different type studies will be described separately. Also we will grade the evidence use GRADE tool.

The possible overlapping of the same studies in multiple meta-analyses is dealt with by the authors (page 10). If the number of systematic reviews is high, some sensitivity analyses may be planned.  
Thanks for suggestion. We have added sensitivity analyses about overlapping.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Dr James Coulson Cardiff University Wales, United Kingdom
<b>REVIEW RETURNED</b>	28-Nov-2020

<b>GENERAL COMMENTS</b>	Thank you for addressing my comments. I have no further comments at this time.
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<b>REVIEWER</b>	Stefano Omboni Italian Institute of Telemedicine Italy
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<b>REVIEW RETURNED</b>	01-Dec-2020
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<b>GENERAL COMMENTS</b>	I am satisfied with the changes made to the paper. I recommend revising English style and grammar.
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