


BMJ Open Clinical efficacy, safety and tolerability of aliskiren monotherapy: a protocol for an umbrella review

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ABSTRACT

Introduction Aliskiren is a newly developed medicine. As one of the effective renin–angiotensin–aldosterone system inhibitors, its role in lowering blood pressure has been recognised. However, its safety and tolerability still remain controversial. The aim of the paper is to systematically summarise the published studies about the clinical efficacy and side effects of aliskiren monotherapy.

Methods and analysis A comprehensive review of PubMed, Embase and Cochrane Library databases published from inception until June 2019 will be conducted. The selected articles are meta-analyses that integrated the randomised controlled studies, which evaluated efficacy, safety and tolerability of aliskiren monotherapy. Two people will select eligible articles and extract data 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 AMSTAR 2 tool. Study selection process will be presented using a flowchart. We will re-analyse each outcome with the random effect methods if necessary. If possible, we will also calculate 95% prediction intervals for each random effect estimate, by using Egger's test to evaluate if the reporting bias existed.

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

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INTRODUCTION

Description of the condition

Hypertension is a highly prevalent disease and its treatment and control are less than satisfactory. The prevalence of hypertension in the USA (defined as taking antihypertensive medication or having a systolic pressure of ≥ 140 mm Hg and/or a diastolic pressure of ≥ 90 mm Hg) was approximately 32% and had remained relatively constant since 1999.^{1–3} Given its high prevalence, hypertension will increase the risk for heart disease and stroke, which are two of the leading causes of death of Americans.⁴

Heart failure (HF) is a rapidly growing public health problem. The estimated

Strengths and limitations of this study

- This will be the first study that systematically summarises the effectiveness, safety and tolerability of aliskiren monotherapy clinically.
- When sufficient data are available, we will stratify our comparisons by dosage or specific categories of the medications.
- If more than one meta-analysis evaluates the same outcome when comparing aliskiren with the same drug, we will incorporate all the original trials from those meta-analyses, without including duplicates.
- If the included reviews in our study are not of high quality, we will re-analyse each outcome using the random effects model.
- The methodological quality of the eligible reviews will be evaluated using AMSTAR 2 for assessing risk of bias.

prevalence of it is >37.7 million individuals globally, imposing a great burden to society.⁵ HF is also a leading cause of hospitalisation among adults and the elderly. In the USA, medical expenses for patients with HF are expected to rise from US\$20.9 billion in 2012 to US\$53.1 billion by 2030.⁶ HF is usually associated with diabetes and patients, with both conditions having a progressive chronic disease trajectory.⁷ Renin–angiotensin–aldosterone system (RAAS) inhibitors are used for treatment of cardiovascular and renal diseases.

Description of the intervention

RAAS blockade is an effective approach to interfere with the pathogenesis of hypertension, cardiovascular disease and chronic renal failure.^{8,9} RAAS inhibitors fall into five distinctive drug classes: beta blockers, renin inhibitors, angiotensin receptor enzyme inhibitors (ACEIs), angiotensin receptors (ARBs) and aldosterone inhibitors.¹⁰

Aliskiren is the first in a new class of oral, non-peptide, low molecular weight direct renin inhibitor. Because of its mechanism of decreasing Ang I, aliskiren can lower blood



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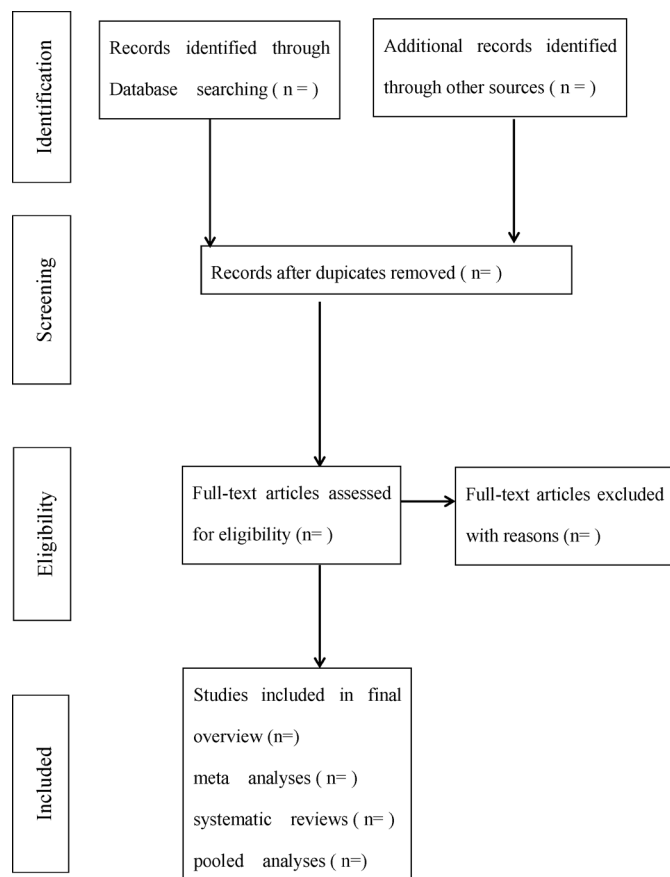


Figure 1 Flow diagram of study selection process.

pressure (BP).¹¹ It had already been approved by the US Food and Drug Administration for the management of hypertension by 2007.¹⁰ Furthermore, aliskiren has been proven to be beneficial in the management of congestive HF and proteinuria either as monotherapy,^{12 13} or in combination with ACEIs or ARBs.^{14 15}

Several systematic reviews,^{16 17} meta-analyses^{18–20} and pooled analyses²¹ have evaluated the clinical outcomes of aliskiren treatment. Some articles reported favourable clinical outcomes,^{18 21} whereas many others^{16 17 19 20} reported that aliskiren had no significant outcomes. For instance, in Bangalore's review,¹⁶ when compared with placebo, the ARBs or aldosterone antagonist, aliskiren did not result in significant changes in the rate of efficacy outcomes (the outcome of death, cardiovascular death, composite outcome of cardiovascular death or heart failure hospitalisation). Furthermore, when compared with placebo, aliskiren increased the risk of hypotension. In Zhang's¹⁹ review, aliskiren monotherapy had no effect on major cardiovascular events, death, cardiac death, myocardial infarction or stroke. An umbrella review evaluating the clinical effectiveness, safety and tolerability of aliskiren is required to weigh the pros and cons of aliskiren monotherapy in the literature.

Aim

The aim of the study is to systematically overview the published articles about the clinical efficacy and side effects of aliskiren monotherapy.

METHODS

Stage 1: identifying relevant studies

At this stage, authors will establish a team and discuss the eligibility criteria, electronic databases and search strategy.

Eligibility criteria

The selected articles will meet the following requirements: published in English; meta-analysis, systematic review or pooled analysis; meta-analyses that integrated the randomised controlled studies, which evaluated efficacy, tolerability or safety of aliskiren treatment and meta-analyses that had substantial data and were up-to-date.

The articles meeting the following requirements will be excluded: observational studies, conference briefs, editorials or overview articles; meta-analyses in which the intervening measures only included aliskiren combination therapy. Meta-analyses that did not provide specific study data (number of incident events, number of study population, follow-up period, relative risks and 95% CIs) and in which the missing data was not retrievable from the original studies will be excluded.

Databases

The identification of studies relevant to this overview will be gained by searching of the published reviews from inception of databases until June 2019 which are listed below: PubMed, Embase and Cochrane Library. We will also manually search all reference lists of the included studies to identify additional reviews of relevance.

Search strategy

We will use the search strategy with those specified keywords: (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 search strategy to suit all three databases.

Stage 2: study selection

We will import our search results into Endnote software and then start selection. The review process consists of two levels of screening: (1) a title and abstract review and (2) a full-text review. In the first phase of screening, the titles and abstracts of the retrieved articles will be browsed through and analysed by two independent investigators to identify potential eligibility. In the second phase, the two investigators will then independently evaluate the full-text articles to decide whether each should be included/excluded. Any discrepancies in the two phases will be reconsidered, and unresolved disagreements will be further discussed with a third investigator, until a full

consensus is reached. The outline of the study selection procedure will be shown in a flowchart (figure 1).

Stage 3: data extraction

Data extraction tables will be established in Microsoft software and the data from selected articles will be extracted independently by two people. Disputes will be resolved by discussion or the arbitration of a third person if necessary. The following categories of data will be extracted: the first author, year of publication, number of trials included, main population, comparative drugs, follow-up period and the investigated clinical outcomes.

Population

Hypertension or patients with HF, some of them suffered from diabetes and/or nephropathy or albuminuria at the same time.

Intervention

Including aliskiren monotherapy.

Comparators

Conventional anti-hypertension and HF medications, such as ARBs, ACEIs, hydrochlorothiazide.

Type of studies

Systematic reviews, meta analyses or pooled analyses that integrated randomised controlled trials

Outcomes

Primary outcomes

Cardiovascular outcomes such as mortality rate, the composite of death and major adverse events, the incidence of stroke and myocardial infarction.

Secondary outcomes

Changes of surrogate markers such as NT-proBNP, BNP levels, plasma renin activity, plasma renin concentration.

Renal outcomes such as the incidence of hyperkalemia, changes of serum creatinine or estimated glomerular filtration rate, changes of urinary albumin creatinine ratio, urinary albumin excretion ratio, urinary protein creatinine rate and urinary protein excretion rate.

Antihypertensive effects such as BP reduction, BP response rate, BP control rate, the incidence of some adverse events.

Cost-effectiveness results such as incremental cost-effectiveness ratios, average cost-effectiveness ratio, benefit–cost ratio and unit costs.

The study of specific risk estimations will also be included: risk ratio, OR, weighted mean difference, standard mean difference together with their 95% CI and number of incident events and total events in each study. If more than one meta-analysis evaluates the same outcome when comparing aliskiren with the same drug, we will incorporate all the original trials from those meta-analyses, without including duplicates. We will summarise all the available data to get a more comprehensive and objective result.

Stage 4: data synthesis and statistical analysis

Statistical analysis will be conducted with RevMan V.5.3 software provided by Cochrane Collaboration and Stata V.14.0 software. In our analysis, when possible, we will stratify the comparisons into several groups according to the dose, such as initial group, initial to high group, high group. In each group, the doses of aliskiren and control drug are comparable. We will also stratify the comparisons according to the categories of control drugs. For example, we will divide ARBs into three specific drugs: losartan, valsartan and irbesartan.

Given the totally different characteristics of our targeted population, we would also do subgroup analysis. For example, when evaluating cardiovascular effects, we will divide heart failure patients into three groups: normotensive, hypertensive and mixed population. We can also divide patients into: patients with no diabetes, patients with diabetes, patients with diabetes and high cardiovascular risk or established cardiovascular disease. When evaluating renal outcomes, we will divide patients into three groups: simple hypertension patients, patients with hypertension and diabetes mellitus type 1 or type 2; 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 (<50 years), early elderly patients (50–70 years), elderly patients (>70 years).

For each outcome, if the random model was already used, we will record the results. If not, we will extract original data and reanalyse them with the random effect methods to get a new 95% CI, to increase credibility. We will also calculate 95% PI for each random effect estimate, 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 amount of heterogeneity. For the Q statistic, $p < 0.05$ will be considered to indicate significant differences. An I^2 statistic, $I^2 > 50\%$, indicates substantial heterogeneity, and $I^2 > 75\%$ indicates considerable heterogeneity.

If sufficient studies are included and they covered relevant information, we will also do the cost-effectiveness analysis, compared between the intervention and the control group. We will extract common outcome results such as incremental cost-effectiveness ratios, average cost-effectiveness ratio, benefit–cost ratio and unit costs from the included studies. We will report outcome measures as presented in the original studies and, for comparison, we will convert the original values to international dollars using purchasing power parity for the country where the study is conducted.

Stage 5: identifying possible publication bias

If an outcome is examined in at least three articles, we will use Egger's test (conducted using Stata V.14.0) to evaluate if the reporting bias exists. Values of $p < 0.1^{22}$ will be interpreted as statistically significant.



Stage 6: evaluating quality of included studies

The methodological quality of the eligible studies will be evaluated using the AMSTAR 2 tool for assessing risk of bias. AMSTAR 2 is a major revision of the original AMSTAR instrument, which was designed to appraise systematic reviews that included randomised controlled trials. AMSTAR 2, like its predecessor, has an important role as a convenient teaching aid and a brief checklist for those conducting systematic reviews. AMSTAR 2, unlike its predecessor, has the capacity to identify critical weaknesses that reduce confidence in the findings of a review.²³

Patient and public involvement

No patients 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

In the systematic reviews and meta-analyses that focused on clinical outcomes after using aliskiren alone, some of the results are widely divergent. To the best of our knowledge, this is the first study that systematically summarises the effectiveness, safety and tolerability of aliskiren monotherapy clinically. When sufficient data are available, we will stratify our comparisons by dosage or specific categories of the medications. We will also calculate 95% PI in order to provide more unbiased and convincing results.

The limitations of our study are the heterogeneity and quality of the selected reviews. To address the limitations, we will reanalyse each outcome using the random effects model. We will also use AMSTAR 2 to evaluate quality of studies that we will include. Furthermore, these two factors will be carefully considered when interpreting the results.

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.

Contributors JS carried on the conception and construction of this protocol. JL developed the search strategy. QJ and YW compared and found the best tools for assessing possible bias and evaluating quality of included reviews. QZ wrote the protocol. JS reviewed and amended the draft of the protocol. FL added grammar editing and conceptual clarification. All authors read and approved of the final manuscript.

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