

# Effect of aliskiren on cardiovascular outcomes in patients with prehypertension: a meta-analysis of randomized controlled trials

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**Background:** Aliskiren is a widely used therapy for patients with hypertension, however, the effect of aliskiren on major cardiovascular outcomes is a matter of debate. The aim of this study is to evaluate the effects of aliskiren therapy on major cardiovascular outcomes by this meta-analysis of randomized controlled trials.

**Methods:** We searched PubMed, EmBase, and the Cochrane Central Register of Controlled Trials for relevant literature. All eligible studies were randomized controlled trials assessing the effect of aliskiren therapy compared with patients without aliskiren therapy. Relative risks (RRs) with 95% confidence intervals (CIs) were used to measure the effect of aliskiren therapy on major cardiovascular outcomes with a random-effect model.

**Results:** We included six trials reporting data on 12,465 patients. These studies reported 1,886 occurrences of major cardiovascular events, 1,074 events of total mortality, 739 events of cardiac death, 366 events of myocardial infarction, and 319 events of stroke. Aliskiren therapy had no effect on major cardiovascular events (RR, 0.93; 95% CI: 0.77–1.13;  $P=0.47$ ), total mortality (RR, 1.00; 95% CI: 0.77–1.29;  $P=1.00$ ), cardiac death (RR, 1.01; 95% CI: 0.79–1.29;  $P=0.95$ ), myocardial infarction (RR, 0.71; 95% CI: 0.36–1.38;  $P=0.31$ ), or stroke (RR, 0.87; 95% CI: 0.48–1.58;  $P=0.64$ ).

**Conclusion:** Aliskiren therapy does not have an effect on the incidence of major cardiovascular events, total mortality, cardiac death, myocardial infarction, or stroke.

**Keywords:** aliskiren, cardiovascular disease, stroke, systematic review, meta-analysis

## Introduction

Hypertension is the leading cause of premature morbidity for both men and women. It raises considerable public concern, because it increases the prevalence of severe cardiovascular disease, stroke, diabetes, and other systemic diseases, causing great costs and burden to both society and families.<sup>1</sup> Around 73 million adults in the US have hypertension, and approximately 30% of these patients have stage 2 hypertension.<sup>2</sup> These patients are at increased cardiovascular risk compared to the risk for those with smaller elevations in blood pressure (BP). Therefore, achieving BP control in these patients is necessary to reduce cardiovascular risk. However, in approximately 30% of patients, BP returns to pretreatment levels or higher during ongoing treatment.<sup>3,4</sup> Thus, it is necessary to develop additional effective treatment schemes.

Inhibition of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has proved to be a successful strategy for the treatment of hypertension.<sup>5–7</sup> Aliskiren is the latest addition to drugs that block the RAS. Its primary indication is as an antihypertensive

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agent, in combination with ACEIs or ARBs for BP control.<sup>8</sup> The clinical efficacy of these drugs when used individually for BP control has been shown in several randomized controlled trials.<sup>5–11</sup> However, the effect of aliskiren therapy on cardiovascular outcomes has not been confirmed by any trials. A previous meta-analysis<sup>12</sup> showed the efficacy and safety of dual blockade of the RAS. Although this treatment showed a slight beneficial effect on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events, such as hyperkalemia, hypotension, and renal failure. Furthermore, although the study incorporated aliskiren, it also included other therapies for dual blockade of the RAS. This leads to uncertainty regarding the cardiovascular protective effects of aliskiren therapy. Therefore, we conducted a meta-analysis of pooled data from randomized controlled trials, including the latest evidence of the effects of aliskiren therapy on the risk of cardiovascular outcomes.

## Methods

### Data sources, search strategy, and election criteria

Randomized controlled trials of aliskiren therapy in English language literature were eligible for inclusion in our research, regardless of publication status (published, in press, or in progress). We performed our search in PubMed (inception to September 2013), EmBase (inception to March 2013), and the Cochrane Library (inception to September 2013) by using selected common keywords pertaining to aliskiren in randomized controlled trials. We searched the bibliographies of relevant articles in order to identify additional studies of interest. For studies that did not directly report the efficacy and safety of aliskiren, we also contacted the authors in the field for any unpublished data. However, they did not have any available data to use in our meta-analysis. Studies were eligible for inclusion when they met the following requirements: 1) the study was a randomized controlled trial; 2) the study investigated the effects of aliskiren therapy; and 3) the study reported at least one of the following outcomes: major cardiovascular events, total mortality, cardiac death, myocardial infarction, and stroke.

The literature search was undertaken independently by two authors with a standardized approach, and any disagreement between these two authors was settled by a third author until a consensus was reached. This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement issued in 2009.<sup>13</sup>

## Data collection and quality assessment

All studies retrieved from databases and bibliographies were independently evaluated by two authors of this paper. Of the articles found in the three databases, duplicate articles and those that did not meet the selection criteria were excluded. We extracted the following data from the remaining studies: first author or study group name, year of publication, number of patients, mean age, percentage male, disease status, intervention, study duration, and reported outcomes. Data abstraction was also performed in duplicate, as was study selection. We measured the quality of the trials included in this study with the Jadad score<sup>14</sup> based on randomization, concealment of treatment allocation, blinding, completeness of follow-up, and the use of intention-to-treat analysis.

## Statistical analysis

We allocated the results of each randomized controlled trial as dichotomous frequency data. Individual study relative risks (RRs) and 95% confidence intervals (CIs) were calculated from event numbers extracted from each trial before data pooling. Both fixed-effects and random-effects models were used to evaluate the pooled RR for aliskiren therapy. Although both models yielded similar findings, results from the random-effects model presented here assume that the true underlying effect varies among included trials.<sup>15,16</sup> Heterogeneity of the treatment effects between studies was investigated visually using a scatter plot analysis as well as statistically using the heterogeneity  $I^2$  statistic.<sup>17,18</sup> Subsequently, subgroup analyses were conducted for major cardiovascular events and total mortality on the basis of current disease status, control, and the duration of follow-up. We also performed a sensitivity analysis by removing each individual trial from the meta-analysis. Visual inspection of funnel plots for major cardiovascular events and total mortality was conducted, and Egger<sup>19</sup> and Begg<sup>20</sup> tests were used to assess publication bias statistically and quantitatively. All reported  $P$ -values are two-sided, and  $P$ -values of less than 0.05 were regarded as statistically significant for all included studies. Statistical analyses were performed using STATA software (version 10.0) (StataCorp LP, College Station, TX, USA).

## Results

A total of 311 articles were identified by searching the three databases and relevant bibliographies. We excluded 272 articles that did not satisfy the selection criteria. After the full text for the remaining 39 articles was reviewed, 33 articles were excluded. As a result, we included six randomized controlled trials,<sup>9,11,21–24</sup> which ultimately met our

inclusion criteria (Figure 1). Table 1 summarizes the characteristics of these trials and the important baseline information of the included 12,758 individuals. The follow-up periods for participants ranged from 8 weeks to 32.9 months, and the number of individuals included in each trial ranged from 550 to 8,561. The primary outcomes were major cardiovascular events available in five trials,<sup>9,11,22–24</sup> total mortality in six trials,<sup>9,11,21–24</sup> cardiac death in four trials,<sup>9,11,22,24</sup> myocardial infarction in four trials,<sup>9,11,22,24</sup> and stroke in three trials.<sup>9,11,24</sup> Although the included trials rarely reported on the key indicators of trial quality, the quality of the trials was also assessed by the Jadad score.<sup>13</sup> Overall, three trials<sup>11,21,24</sup> had a Jadad score of 5, and the remaining three trials<sup>9,22,23</sup> had a score of 4.

Data for the effect of aliskiren therapy on major cardiovascular events included 12,155 individuals and reported 1,886 major cardiovascular events. Overall, aliskiren therapy reduced the risk of major cardiovascular events by 7%, but this difference was not statistically significant (RR, 0.93; 95% CI: 0.77–1.13;  $P=0.47$ ; Figure 2A). Although substantial heterogeneity was observed in the magnitude of the effect across the trials included ( $I^2=67\%$ ;  $P=0.02$ ) a sensitivity analysis indicated that the results were not affected by sequential exclusion of any particular trial from all pooled analysis.

Data for the effect of aliskiren therapy on total mortality included 12,758 individuals and 1,074 death events. There were no differences observed between patients receiving aliskiren therapy versus those receiving ACEI or ARB therapy for total mortality (RR, 1.00; 95% CI: 0.77–1.29;

$P=1.00$ ; Figure 2B). Although there was some evidence of heterogeneity across the studies included, the results were not affected by exclusion of any specific trial ( $I^2=47\%$ ;  $P=0.09$ ).

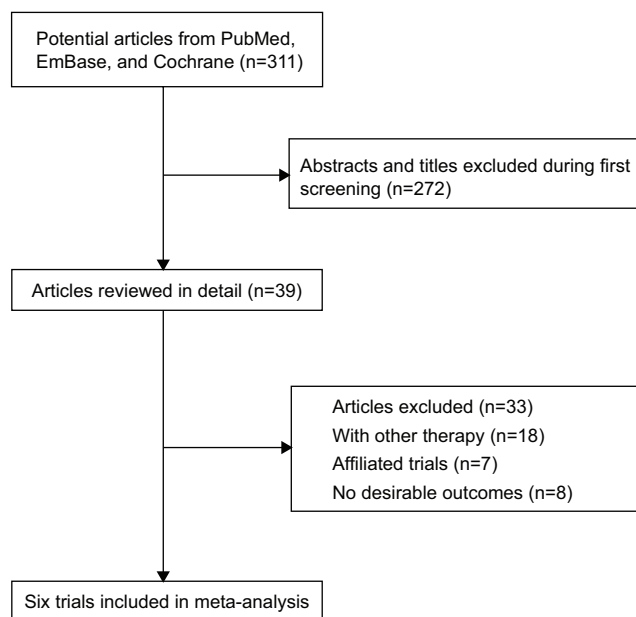
Data for the effect of aliskiren therapy on cardiac death included 11,335 individuals and 739 events of cardiac death. We noted that aliskiren therapy did not have an effect on cardiac death (RR, 1.01; 95% CI: 0.79–1.29;  $P=0.95$ ; Figure 3A). Moderate heterogeneity was observed across included trials, after sequential exclusion of each trial from all pooled analysis, the results were not affected by exclusion of any specific trial ( $I^2=43\%$ ;  $P=0.15$ ).

Data for the effect of aliskiren therapy on myocardial infarction included 11,335 individuals and 366 events of myocardial infarction. We noted that aliskiren therapy showed a 29% reduction in myocardial infarction; however, there was no supporting evidence to show it protected against myocardial infarction risk (RR, 0.71; 95% CI: 0.36–1.38;  $P=0.31$ ; Figure 3B). Heterogeneity was observed in the magnitude of the effect across the trials ( $I^2=72\%$ ;  $P=0.01$ ). However, after sequential exclusion of each trial from all pooled analyses, the conclusion was not affected by the exclusion of any specific trial.

Data for the effect of aliskiren therapy on stroke included 10,789 individuals and 319 events of stroke. We noted that aliskiren therapy reduced the risk of stroke by 13%, but this decrease was not statistically significant (RR, 0.87; 95% CI: 0.48–1.58;  $P=0.64$ ; Figure 3C). Heterogeneity was observed in the magnitude of the effect across the included trials ( $I^2=61\%$ ;  $P=0.08$ ); however, after sequential exclusion of each trial from all pooled analyses, the results were not affected by exclusion of any specific trial.

Subgroup analyses were also performed for major cardiovascular events and total mortality to evaluate the effect of aliskiren therapy in a specific population. However, no significant differences were observed in predefined factors between those who received aliskiren therapy or other therapy (Table 2).

A review of funnel plots could not rule out the potential for publication bias for major cardiovascular events (Figure 4A) and total mortality (Figure 4B). In addition, Egger<sup>19</sup> and Begg<sup>20</sup> tests showed no evidence of publication bias for major cardiovascular events ( $P$ -value for Egger, 0.322;  $P$ -value for Begg, 0.462), total mortality ( $P$ -value for Egger, 0.430;  $P$ -value for Begg, 0.260), cardiac death ( $P$ -value for Egger, 0.348;  $P$ -value for Begg, 0.308), myocardial infarction ( $P$ -value for Egger, 0.381;  $P$ -value for Begg, 0.734), and stroke ( $P$ -value for Egger, 0.240;  $P$ -value for Begg, 1.000).



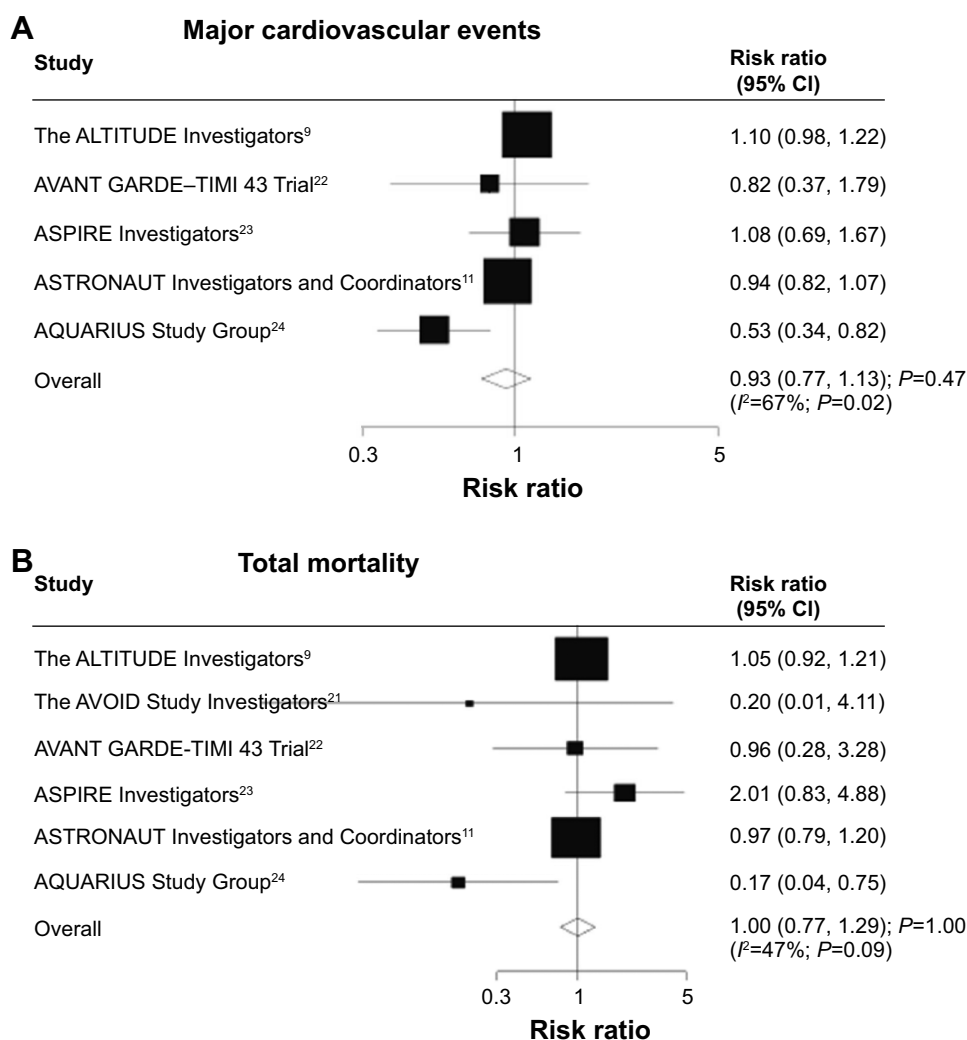
**Figure 1** Flow diagram of the literature search and trial selection process.

**Table 1** Design and characteristic of trials included in our meta-analysis

Source	Publication year	No of patients	Mean age, y	Percentage male	Disease status	Intervention	Control	Study duration	Primary endpoint	Entry BP	Jadad score
The ALTITUDE Investigators <sup>9</sup>	2012	8,561	64.5	68.1	Type 2 diabetes	Aliskiren 300 mg plus ACE inhibitor or an ARB	Placebo plus ACE inhibitor or an ARB	32.9 months	Death from CV cause	137±16.2/71.4±9.8	4
The AVOID Study Investigators <sup>21</sup>	2008	599	60.8	71.3	Hypertension and type 2 diabetes with nephropathy	Aliskiren 300 mg plus losartan 100 mg daily	Losartan 100 mg daily	6 months	Albumin to creatinine ratio	135±12/78±8	5
AVANT GARDE-TIMI 43 Trial <sup>22</sup>	2010	550	63.4	71.1	Acute coronary syndromes	Aliskiren 300 mg plus valsartan 320 mg daily	Valsartan 320 mg daily	8 weeks	CV death, myocardial infarction	125±16.92/74.9±9.58	4
ASPIRE Investigators <sup>23</sup>	2011	820	60.2	83.0	Myocardial infarction with systolic dysfunction	Aliskiren 300 mg plus ACE inhibitor or an ARB	Placebo plus ACE inhibitor or an ARB	36 weeks	Composite of CV death	121.6±16.1/75.2±9.4	4
ASTRONAUT Investigators and Coordinators <sup>11</sup>	2013	1,615	64.6	77.2	Heart failure	Aliskiren 300 mg plus diuretics, digoxin, ACE inhibitors, ARBs, β-blockers, and MRAs	Placebo plus diuretics, digoxin, ACE inhibitors, ARBs, β-blockers, and MRAs	11.3 months	CV death, HF re-hospitalization	>110 mmHg/ >80 mmHg	5
AQUARIUS Study Group <sup>24</sup>	2013	613	59.7	76.2	Coronary artery disease	Aliskiren 300 mg	Placebo	25 months	CV death, nonfatal myocardial infarction	132.0±5.03/77.5±6.8	5

**Notes:** Entry criteria: participants aged 18 years or older, with systolic blood pressure between 110 and 139 mmHg, and diastolic blood pressure between 70 and 89 mmHg.

**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; CV, cardiovascular; y, years; MRAs, mineralocorticoid receptor antagonists; BP, blood pressure.



**Figure 2** Effects of aliskiren therapy on the risk of major cardiovascular events (A) and total mortality (B).

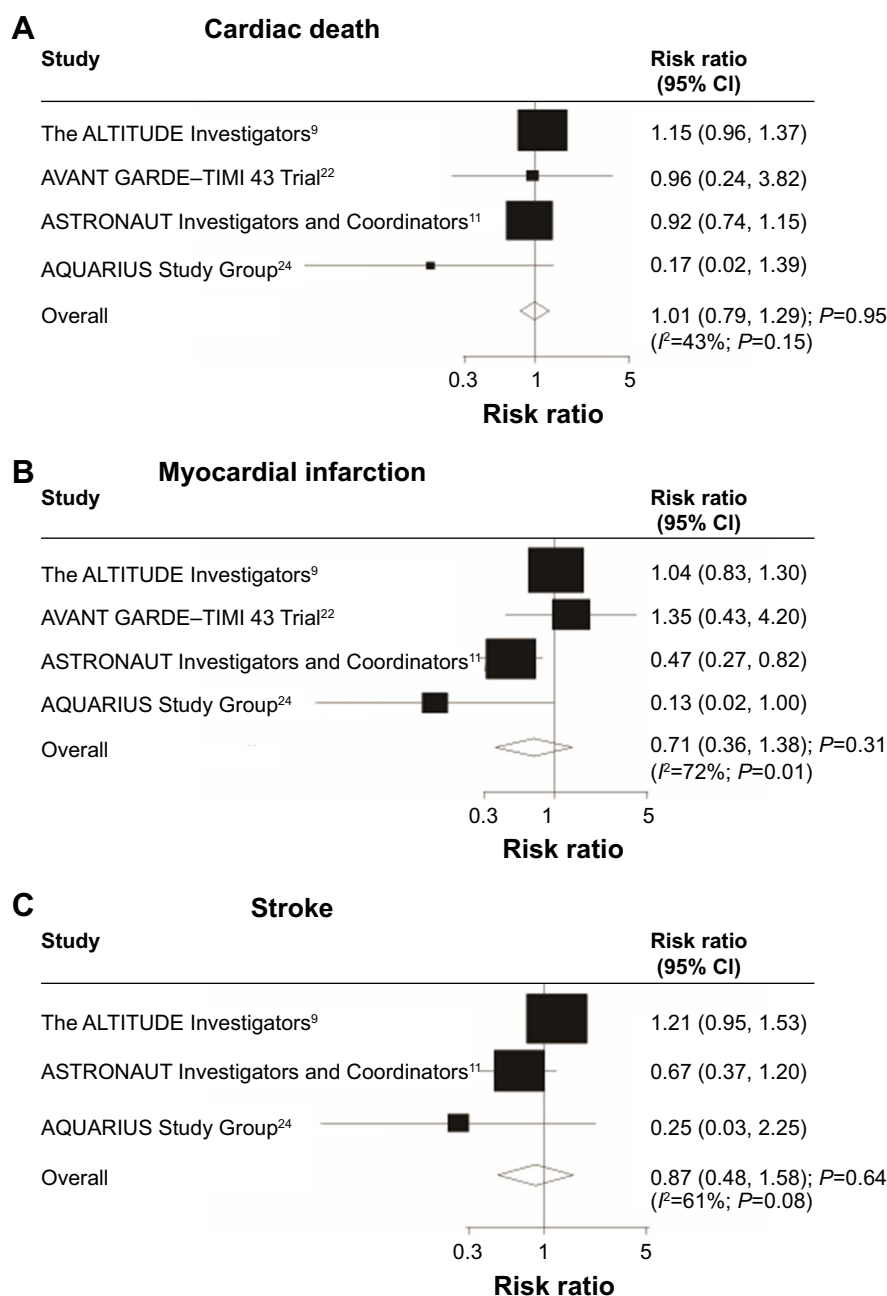
**Abbreviation:** CI, confidence interval.

## Discussion

Several previous trials<sup>5–7</sup> have suggested that ACEI or ARB monotherapy provides an antihypertensive effect in hypertension patients, but certain patients with refractory hypertension are intolerant to ACEI or ARB therapy alone. It is necessary to find additional effective preventive therapies. Pool et al<sup>25</sup> performed a randomized controlled trial of aliskiren, and indicated that aliskiren and valsartan in combination may provide additive BP-lowering effects with maintained tolerance. However, the ALTITUDE Investigators' trial<sup>9</sup> concluded that the addition of aliskiren to standard therapy has no effect on cardiovascular outcomes; but the proportion of patients with hyperkalemia (11.2% versus [vs] 7.2%), or hypotension (12.1% vs 8.3%) was significantly higher in the aliskiren group than in the placebo group, respectively. A previous review<sup>26</sup> has evaluated the benefits and harms of aliskiren therapy versus ARB therapy in patients with

hypertension on the basis of randomized controlled trials and suggested that combination therapy was superior to ARBs in controlling BP, and did not differ from ARB in risk of adverse events. Another important study<sup>27</sup> encompassed a large body of literature spanning numerous cohorts, with different demographic characteristics, and concluded that combination therapy is associated with an increased risk for hyperkalemia. Our study was based on randomized controlled trials and explored the effect of aliskiren therapy on major cardiovascular outcomes.

Our comprehensive, quantitative study included 12,758 patients from six trials with a broad range of baseline characteristics. Although the studies included clinically diverse populations (different disease status), the results were consistent when subjected to various sensitivity analyses. The results of our meta-analysis suggest that aliskiren therapy has no effect on the incidence of major cardiovascular events,



**Figure 3** Effects of aliskiren therapy on the risk of cardiac death (A), myocardial infarction (B), and stroke (C).

**Abbreviation:** CI, confidence interval.

total mortality, cardiac death, myocardial infarction, and stroke.

There were no significant differences between aliskiren therapy and ACEIs or ARBs alone for the RR of major cardiovascular events, total mortality, cardiac death, myocardial infarction, or stroke. Three large-scale randomized controlled trials of aliskiren therapy have been conducted recently. The ALTITUDE Investigators Study<sup>9</sup> compared aliskiren therapy with ACEI or ARB therapy, and concluded that aliskiren therapy had no effect on cardiovascular and renal events, and it may even be harmful in patients with

type II diabetes. Furthermore, ASTRONAUT Investigators and Coordinators' trial<sup>11</sup> suggested that aliskiren plus standard therapy did not reduce major cardiovascular events (35.0% vs 37.3%), death from any cause (17.8% vs 18.3%), cardiac death (15.6% vs 17.0%), and stroke (2.2% vs 3.3%), but had given the significant advantage in myocardial infarction (2.2% vs 4.7%). The AQUARIUS Randomized Clinical Trial indicated that aliskiren therapy did not result in improvement or slowing of progression of coronary atherosclerosis, and has no significant effect on the risk of major cardiovascular outcomes.<sup>24</sup> The possible reason for



**Table 2** Subgroup analysis for the effect of aliskiren therapy on major cardiovascular events and total mortality

Outcomes	Subgroup	Number of included studies	RR and 95% CI	P-value	Heterogeneity (%)	P-value for heterogeneity
Major cardiovascular events	<b>Current disease status</b>					
	CVD	4	0.84 (0.63–1.12)	0.23	55	0.08
	Without CVD	1	1.10 (0.98–1.22)	0.09	–	–
	<b>Control</b>					
	ACE inhibitor	2	0.94 (0.82–1.06)	0.31	0	0.73
	Both	3	0.88 (0.58–1.35)	0.56	80	0.007
	<b>The duration of follow-up</b>					
Total mortality	12 months or more	2	0.78 (0.38–1.61)	0.51	90	0.002
	<12 months	3	0.95 (0.84–1.07)	0.37	0	0.79
	<b>Current disease status</b>					
	CVD	4	0.91 (0.45–1.81)	0.78	62	0.05
	Without CVD	2	0.93 (0.40–2.19)	0.87	14	0.28
	<b>Control</b>					
	ACE inhibitor	3	0.96 (0.79–1.18)	0.73	0	0.59
	Both	3	0.89 (0.36–2.20)	0.80	75	0.02
	<b>The duration of follow-up</b>					
	12 months or more	2	0.49 (0.08–2.90)	0.43	83	0.02
	<12 months	4	1.06 (0.73–1.54)	0.77	16	0.31

**Notes:** Entry criteria: participants aged 18 years or older, with systolic blood pressure between 110 and 139 mmHg, and diastolic blood pressure between 70 and 89 mmHg.

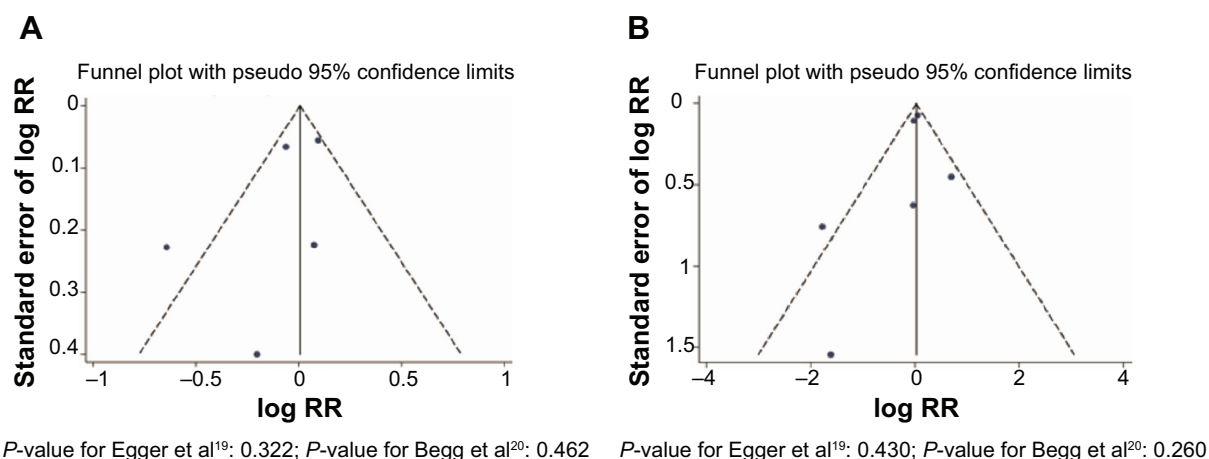
**Abbreviations:** ACE, angiotensin-converting enzyme; CVD, cardiovascular disease; RR, relative risk; CI, confidence interval.

this lack of significant effect could be that relatively few trials reported these outcomes, contributing to broad CIs. Furthermore, the trials always reported cardiovascular outcomes that needed more than 12 months follow-up, but only two of six included trials had greater than 12 months follow-up periods.

Previous meta-analysis<sup>27,28</sup> suggested that aliskiren therapy was associated with an increased risk for hyperkalemia. However, the study did not observe the efficacy of combination therapy on cardiovascular events. In the present study, we observed the efficacy of aliskiren therapy on major cardiovascular outcomes. The results of our meta-analysis

suggested that aliskiren therapy does not have an effect on the risk of major cardiovascular events, total mortality, cardiac death, myocardial infarction, and stroke. Subgroup analysis also supports that aliskiren therapy has no significant effect on the risk of major cardiovascular events and total mortality. Hence, clinicians should be cautioned about the use of aliskiren in patients with high BP recognizing that there are no benefits for the use of this drug to prevent cardiovascular events.

The limitations of our study include the inherent assumptions made for any meta-analysis, because the analysis uses pooled data from published papers and original data were not

**Figure 4** Funnel plot for major cardiovascular events (A) and total mortality (B).

**Abbreviation:** RR, relative risk.

available. Furthermore, data on major cardiovascular outcomes were available from few trials, which made the conclusions potentially unreliable. We therefore provided a relative result by comparing aliskiren therapy and ACEI or ARB therapy, and provided a synthetic and comprehensive review.

## Conclusion

In conclusion, the findings of our study suggest that aliskiren therapy has no beneficial effect on major cardiovascular events, total mortality, cardiac death, myocardial infarction, and stroke. Though the use of aliskiren could control BP effectively, there are no benefits for the use of this drug to prevent cardiovascular events. For future study, promising interventions should be tested, including dosage, duration of treatment, or combination with other ARB or ACE inhibitors. We suggest that ongoing trials should be improved in the following ways: 1) it will be important to focus on the patients' baseline characteristics, especially for current disease status. 2) The role of treatment duration and dosage should be taken into consideration before evaluating clinical outcomes.

## Disclosure

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