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**Original Article**

# Efficacy of angiotensin receptor neprilysin inhibitor in hypertension management: A systematic review and meta-analysis of clinical trials

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## Abstract

Dysregulation of renin-angiotensin-aldosterone system (RAAS) often leads to hypertension and severe cardiorenal complications. Although RAAS-targeted therapies have proven effective, it remains yet optimal in reducing cardiovascular events. The aim of this study was to evaluate the efficacy and safety of angiotensin receptor neprilysin inhibitor (ARNI) compared to control in patients with hypertension. The primary outcomes were systolic and diastolic blood pressure (BP) control, along with the incidence of adverse events. A systematic review and meta-analysis was conducted according following PRISMA guidelines. A comprehensive literature search was performed across five databases: PubMed, ScienceDirect, EBSCO, Cochrane, and ProQuest, with studies identified up until October 3, 2024. The study included nine clinical trials that met the predefined eligibility criteria: (1) randomized clinical trials; (2) adult patients diagnosed with hypertension; and (3) comparison of ARNI versus control, reporting either BP control or adverse events. Quality appraisal using RoB 2.0 revealed that eight studies had a low risk of bias, and one had a high risk of bias. The pooled analysis demonstrated that ARNI is significantly more efficacious in achieving targeted systolic BP as compared to the control group (OR: 1.80; 95%CI: 1.41–2.30; $p<0.001$; $I^2=0\%$), and there was no statistical difference for the efficacy on diastolic BP compared to control (OR: 0.92; 95%CI: 0.75–1.13; $p=0.45$; $I^2=75\%$). The incidence of adverse events was not associated with ARNI (OR: 1.07; 95%CI: 0.90–1.27; $p=0.46$; $I^2=72\%$). In conclusion, ARNI demonstrated a favorable outcome only in systolic BP, but in diastolic BP which could be associated with inadequate duration of observation. Further studies are warranted to assess BP-lowering effect and safety profile of ARNI in a longer observation time.

**Keywords**: Antihypertensive, angiotensin receptor neprilysin inhibitor, efficacy, safety, therapy

## Introduction

Hypertension is a significant contributor to the risk factor for cardiovascular disease (CVD), which plays a pivotal role in global mortality and morbidity. Approximately one billion adults are



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affected by this condition, with the prevalence expected to escalate reaching 1.5 billion by 2025 [1]. The World Health Organization (WHO) identifies hypertension as the majority (77%) of non-communicable diseases to hypertension [2]. Moreover, hypertension acts both as a cause and a complication of chronic kidney disease (CKD), leading to functional and structural alterations in the kidney [3,4]. Given the close association between the progression of renal disease and increases in blood pressure (BP), effective hypertension management becomes crucial in mitigating the risk of further renal function decline and reducing the development of cardiovascular complications [5]. Unfortunately, current therapies are still considered to be unable to yield optimal efficacy and address the challenge of achieving BP targets.

BP regulation and the maintenance of body fluid balance are essential functions performed by the renin-angiotensin-aldosterone system (RAAS). Dysregulation of RAAS can initiate a series of events leading to elevated BP, often resulting in hypertension and subsequent fatal cardiovascular and renal complications [6]. To improve dysregulated RAAS, several inhibitors (such as ACE inhibitors, angiotensin II receptor blockers, renin inhibitors, and mineralocorticoid receptor blockers are commonly prescribed as first-line therapies [7]. Despite significant advancements achieved by these agents in impeding the progression of the established cardiorenal disease, ACE inhibitors, and ARBs only yield a 20% reduction in the relative risk of cardiovascular disease progression when compared to therapies not specifically targeting RAAS [8]. This effect is primarily observed in patients with controlled blood pressure. For clarity, controlled blood pressure in this context is defined as <130/80 mmHg, as recommended by the latest guidelines for hypertension management, particularly in patients at high cardiovascular risk [7]. As the results, researchers and clinicians have investigated angiotensin receptor neprilysin inhibitor (ARNI) as a new class of drug in achieving the treatment targets [9,10].

Based on previous studies, ARNI therapy has demonstrated efficacy in slowing the progression of hypertension [9,10]. Moreover, ARNI have also been incorporated into heart failure (HF) management guidelines [11]. ARNIs combine the inhibition of RAAS via angiotensin receptor blockade with the augmentation of natriuretic peptides through neprilysin inhibition. This double inhibitory mechanism addresses multiple pathophysiological pathways implicated in hypertension and heart failure, offering superior efficacy compared to traditional monotherapy, Nevertheless, a notable research gap persists in terms of assessing ARNI's direct comparative efficacy with standard therapy and also in terms of assessing its safety, including the possible post-administration adverse events [12].

Considering its efficacy in reducing blood pressure levels, ameliorating target organ damage, and improving cardiovascular outcomes, ARNI emerges as a beacon of hope, offering not merely symptomatic relief but transformative disease-modifying effects [13]. These strategies hold the promise of not only addressing the dysregulation of RAAS but also potentially surpassing the efficacy limitations associated with current treatments. Therefore, this study seeks to evaluate the comparative efficacy and safety profiles of therapies, including ARNI in managing hypertension. Through a comprehensive assessment of ARNI, the aim of this study was to contribute valuable insights that may reshape the landscape of antihypertensive strategies, moving towards more effective and personalized approaches to cardiovascular and renal disease.

## Methods

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [14]. The protocol of this study was registered in PROSPERO with registration number CRD42024517047 on March 6, 2024.

### Search strategy and selection of studies

The literature search was conducted using five databases such as PubMed, ScienceDirect, EBSCO, Cochrane, and ProQuest, up until October 3, 2024. The literature search was carried out with keywords using Boolean operators 'AND' and 'OR' as presented in **Table 1**. Three independent reviewers (R.N.R., D.D.C.H.R., and S.E.W.) were responsible for the article search, retrieval, and screening. Any discrepancies that arise during this process will be resolved through consensus. Articles with relevant titles and abstracts will be included for full-text assessment based on this process.

Table 1. Literature search terms for included studies

| Database | Keywords |
|---|---|
| PubMed | #1 antihypertensive therapy [MeSH Terms]<br>#2 ((“antihypertensive therapy”[Title/Abstract]) OR (“RAAS-targeted therapy"[Title/Abstract]))<br>#3 #1 OR #2<br>#4 "angiotensin receptor neprilysin inhibitor" [Supplementary Concept]<br>#5 ((“angiotensin receptor neprilysin inhibitor"[Title/Abstract]) OR ("ARNI" [Title/Abstract]) OR ("sacubitril/valsartan"[Title/Abstract]))<br>#6 #4 OR #5<br>#6 ((“safety"[Title/Abstract]) OR (“efficacy”[Title/Abstract]) OR (“effectiveness”[Title/Abstract])<br>#7 #3 AND #6<br>#8 #7, Filter: Clinical Trial |
| ScienceDirect | (“antihypertensive therapy” OR “RAAS-targeted therapy”) AND (“ARNI” OR “angiotensin receptor neprilysin inhibitor” OR “sacubitril/valsartan”) AND (“safety” OR “efficacy” OR “effectiveness”) |
| EBSCO | (“antihypertensive therapy” OR “RAAS-targeted therapy”) AND (“ARNI” OR “angiotensin receptor neprilysin inhibitor” OR “sacubitril/valsartan”) AND (“safety” OR “efficacy” OR “effectiveness”) |
| Cochrane | #1 MeSH descriptor: [antihypertensive therapy] explode all trees<br>#2 (“antihypertensive therapy" OR “RAAS-targeted therapy”):ti,ab,kw<br>#3 #1 OR #2<br>#4 ("angiotensin receptor neprilysin inhibitor" OR “ARNI” OR “sacubitril/valsartan”):ti,ab,kw<br>#5 #3 AND #4<br>#6 (“safety” OR “efficacy” OR “effectiveness”):ti,ab,kw<br>#7 #5 AND #6<br>#8 #7 AND (“clinical trial”) |
| ProQuest | #1 mesh.Exact(“antihypertensive therapy”)<br>#2 noft(“antihypertensive therapy" OR “RAAS-targeted therapy")<br>#3 noft("angiotensin receptor neprilysin inhibitor" OR “ARNI” OR “sacubitril/valsartan”)<br>#4 noft(“safety” OR “efficacy” OR “effectiveness”)<br>#5 noft(“cllinical trial”)<br>#6 (#1 OR #2) AND #3 AND #4 AND #5 |

## Inclusion and exclusion criteria

Inclusion and exclusion criteria were predefined to ensure consistency in the selection of studies. The inclusion criteria were: (1) studies published in English; (2) clinical trials; (3) studies involving patients diagnosed with hypertension; (4) studies comparing ARNI intervention to a control; and (5) studies reporting at least one parameter of interest, such as systolic BP (SBP) control, diastolic BP (DBP) control, or adverse event rates. Studies were excluded if they: (1) involved non-human samples; (2) were not peer-reviewed; (3) lacked adequate data on ARNI intervention or the relevant outcome measures; (4) did not include hypertension as a primary diagnosis; (5) were reviews, editorials, or opinion pieces, or (6) included duplicate data or overlapping patient populations. No restrictions were placed on the publication date. The authors independently assessed the eligibility of each study, and any disagreements were resolved through discussion.

## Outcome measures

The efficacy and safety of ARNI as one of the RAAS-based antihypertensive therapies was examined. Efficacy was evaluated by analyzing the control of SBP and DBP, which was determined by the attainment rate of target blood pressure levels according to the American Heart Association (AHA) or local hypertension practice guidelines in each included study [15-17]. Conversely, safety was assessed based on the incidence of adverse events absent before medical treatment or pre-existing events that intensified in either intensity or frequency after treatment, as defined by treatment-emergent adverse events (TEAEs) [11,17,18]. The quantitative analysis involved independent extraction of results from the included papers by each author, and any disparities were resolved through discussion.

### Screening and selection

Following automatic duplicate removal in EndNote 19, screening was performed in two phases: first by evaluating titles and abstracts and then by reviewing full texts. Two independent review authors (R.N.R. and I.P.) conducted each stage, resolving disagreements through consensus; if consensus was not reached, a third reviewer (S.D.S.) was consulted for clarification.

### Quality assessment

All studies were critically appraised by five authors (R.N.R., D.D.C.H.R., S.E.W., and I.P.), with disagreements resolved through discussion with the referee (S.D.S). The assessment of bias risk in the included studies was conducted using The Revised Tool for Risk of Bias in Randomized Trials (RoB 2.0) [19]. Subsequently, the assessment findings were recorded in the "bias" section of a Microsoft Excel 2021 spreadsheet. Following this, the spreadsheet was uploaded to the ROBVIS website, where the results of the assessment were visually presented using a traffic light system [20].

### Data extraction

After identifying and screening relevant studies according to established inclusion and exclusion criteria, two independent reviewers (S.E.W. and I.P.) conducted the data extraction. The extracted data from each study included the first author's name, publication year, country, study design, and sample size. This process gathered essential information about study characteristics and outcomes, covering ARNI intervention in hypertension. Demographic data such as age (in months), gender (male/female), and clinical characteristics relevant to ARNI intervention were also collected. Specific outcomes, including SBP, DBP, and adverse events were documented. To ensure data accuracy, the second reviewer verified the data initially collected by the primary reviewer, with any discrepancies addressed through discussion and consensus.

### Quantitative analysis

The meta-analysis was conducted using Review Manager version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen) [31]. All outcome measures were assessed as dichotomous data with a 95% confidence interval (CI) of 0.05. The inverse variance model was utilized as the statistical method, with either fixed or random effects models applied depending on the heterogeneity of each outcome. Heterogeneity was analyzed using $I^2$ statistics, with cut-off values of 0%, 25%, 50%, and 75% representing insignificant, low, moderate, and high heterogeneity, respectively. Begg's funnel plot for publication bias identification would be constructed if the number of included studies was at least 10.

## Results

### Search results

A total of 633 records were retrieved by applying the search strategies across five databases (**Figure 1**). Following this, 146 duplicates were removed due to duplication, ineligible by automation tools, and non-research articles (such as editorials, commentaries, expert opinions, and conference abstracts), as well as studies with inappropriate population, intervention, control, or insufficient outcome reporting. The screening of titles and abstracts further narrowed the records from 46 to 26, which were then assessed for full-text retrieval. Six full-text articles could not be retrieved, and the remaining 20 articles underwent eligibility evaluation. Of these, 11 were excluded due to irrelevant data and insufficient detail for thorough evaluation. This process eventually identified nine studies eligible for inclusion in the network meta-analysis [21-29] **Figure 1**).

### Characteristics of the included studies

The key characteristics of studies evaluating the efficacy of ARNI in hypertension management are summarized in **Table 2**. It includes data from multiple countries with varying sample sizes, age ranges, gender distribution, interventions, controls, and follow-up periods. The studies span across various countries, including Argentina, Guatemala, the Philippines, Russia, Spain, the United States of America (USA), Japan, and several Asian and European nations [21-29]. The

total number of participants in these studies ranged from 46 to 950, with male and female participants fairly represented. The mean age of participants generally fell between the mid-50s to late 60s [21-29], with the oldest participants averaging 70.5 years [26]. The intervention groups typically received ARNI treatment, while the control groups were given standard hypertension treatment (angiotensin II receptor blocker (ARB)). Follow-up durations varied across the studies, from 4 [27] to 52 weeks [29]. The primary outcomes measured included SBP and DBP levels and adverse events related to the intervention. The results indicated notable differences in blood pressure outcomes, with some studies focusing on SBP and DBP improvements, while others prioritized the assessment of adverse events linked to ARNI use. The summaries of demographic and clinical characteristics of each study are presented in **Table 2**.

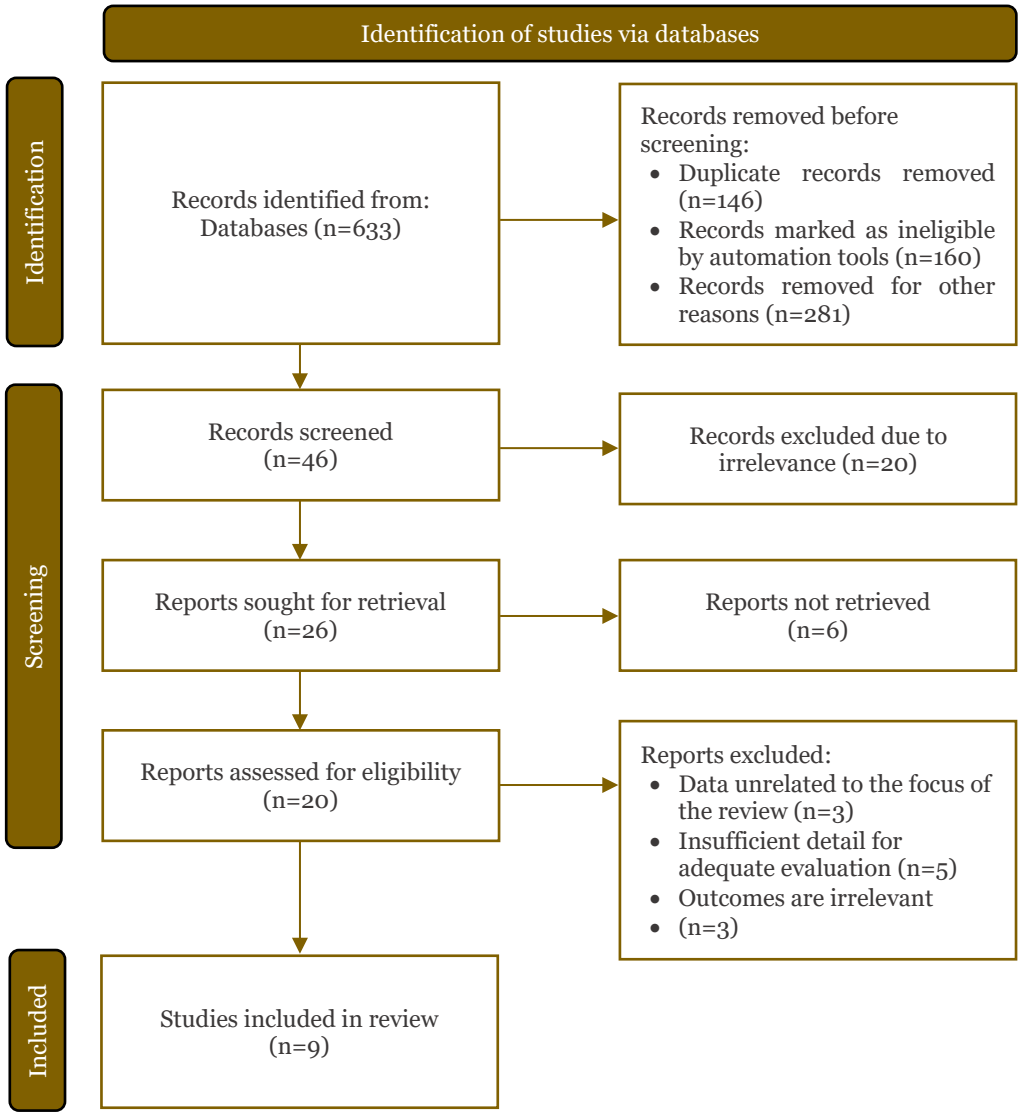


Figure 1. The identification and selection of studies followed the PRISMA flowchart for systematic reviews and meta-analyses.

## Risk of bias assessment

The risk of bias in the included studies was evaluated using the Revised Tool for Risk of Bias in Randomized Trials (RoB 2.0). The assessment results indicated that the majority of the randomized controlled trials (RCTs) had a low risk of bias across all five domains. Specifically, 90% of the studies demonstrated a low risk of bias in all assessed domains, including bias from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.

Table 2. The demography and clinical characteristics of each study

| Author, year | Country | Age (years) | Total | Male | Female | Intervention | Control | Follow-up (weeks) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | mean±SD | n | n | n | n | n | | |
| Cheung *et al.*, 2017 [21] | Argentina, Guatemala, the Philippines, Russia, Spain, and the United States | 57.6±9.65 | 375 | 192 | 183 | 188 | 187 | 8 | DBP, Adverse event |
| Huo *et al.*, 2018 [22] | China, Hong Kong, South Korea, Philippines, Singapore, Taiwan, Thailand | 57.7±10 | 950 | 495 | 455 | 469 | 481 | 8 | SBP, DBP |
| Kario *et al.*, 2014 [23] | China, Japan, Taiwan, South Korea, Thailand | 52.5 ±10.03 | 128 | 128 | 60 | 96 | 92 | 13 | Adverse event |
| Kario *et al.*, 2023 [24] | Japan | 58.7±10.8 | 700 | 439 | 261 | 470 | 230 | 8 | Adverse event |
| Ruilope *et al.*, 2010 [25] | Argentina, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Russia, Slovakia, Spain, Sweden, Taiwan, and USA | 53 ±10·2 | 509 | 229 | 280 | 336 | 173 | 7 | SBP, DBP |
| Supasyndh *et al.*, 2017 [26] | Thailand, Taiwan, Philippines, South Korea, Japan, China | 70.5 ± 4.67 | 294 | 294 | 294 | 296 | 292 | 14 | Adverse event |
| Wang *et al.*, 2017 [27] | China, Japan, South Korea, Malaysia, Philippines, Taiwan | 55.4 ± 9.3 | 156 | 110 | 110 | 130 | 136 | 8 | Adverse event |
| Wang *et al.*, 2017 [28] | USA, Hong Kong, South Korea, Singapore, Taiwan | 57.3 ±10.3 | 46 | 26 | 26 | 36 | 36 | 4 | Adverse event |
| Williams *et al.*, 2017 [29] | Argentina, Colombia, France, Germany, Greece, Italy, Japan, Korea, Russia, Spain, Taiwan, and the United States | 67.7±5.85 | 237 | 217 | 217 | 229 | 225 | 52 | Adverse event |

DBP: diastolic blood pressure**;** SBP: systolic blood pressure

However, one study exhibited a high risk of bias in the domain related to missing outcome data, which raises some concerns about the reliability of its conclusions [30]. The detailed results of risk of bias assessment on the included studies are summarized and presented in **Figure 2**.

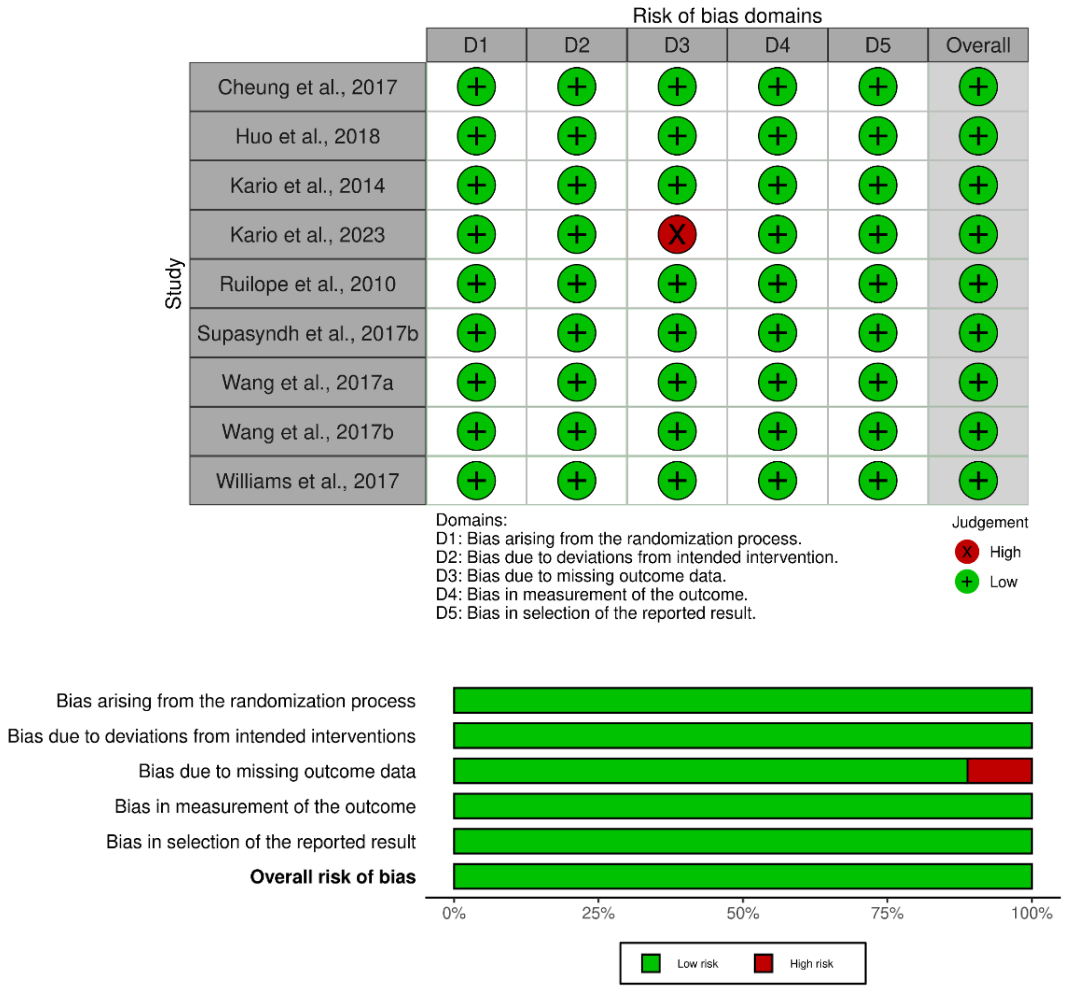


Figure 2. Risk of bias summary using the Cochrane Risk of Bias 2.0 tool for randomized-controlled trial studies. The green region represents studies with low risk of bias, the yellow region shows studies with unclear risk of bias, and the red region shows studies with high risk of bias.

## Efficacy and safety analysis of angiotensin receptor neprilysin inhibitor (ARNI)

The pooled estimates for the efficacy and safety of ARNI in managing hypertension are presented in **Figure 3**. The efficacy analysis for systolic blood pressure (SBP) control was conducted with 1,458 patients across two eligible studies [22,25]. As compared to the control, ARNI was found to be more efficacious in SBP control (OR:1.80; 95%CI: 1.41–2.30; $p<0.001$; $I^2=0\%$). For diastolic blood pressure (DBP) control, the pooled estimate was calculated based on three studies recruiting a total of 1,833 patients [21-22,25]. There was no statistical difference for the efficacy on DBP control between ARNI and control (OR: 0.92; 95%CI: 0.75–1.13; $p=0.45$; $I^2=75\%$).

The pooled effects for adverse events were estimated from eight studies (n=2,442 patients). There was no significant association between adverse event and ARNI administration, with OR of 1.07 (95%CI: 0.90–1.27) and $p$-value of 0.46. The heterogeneity for the adverse event was high, with $I^2=72\%$.

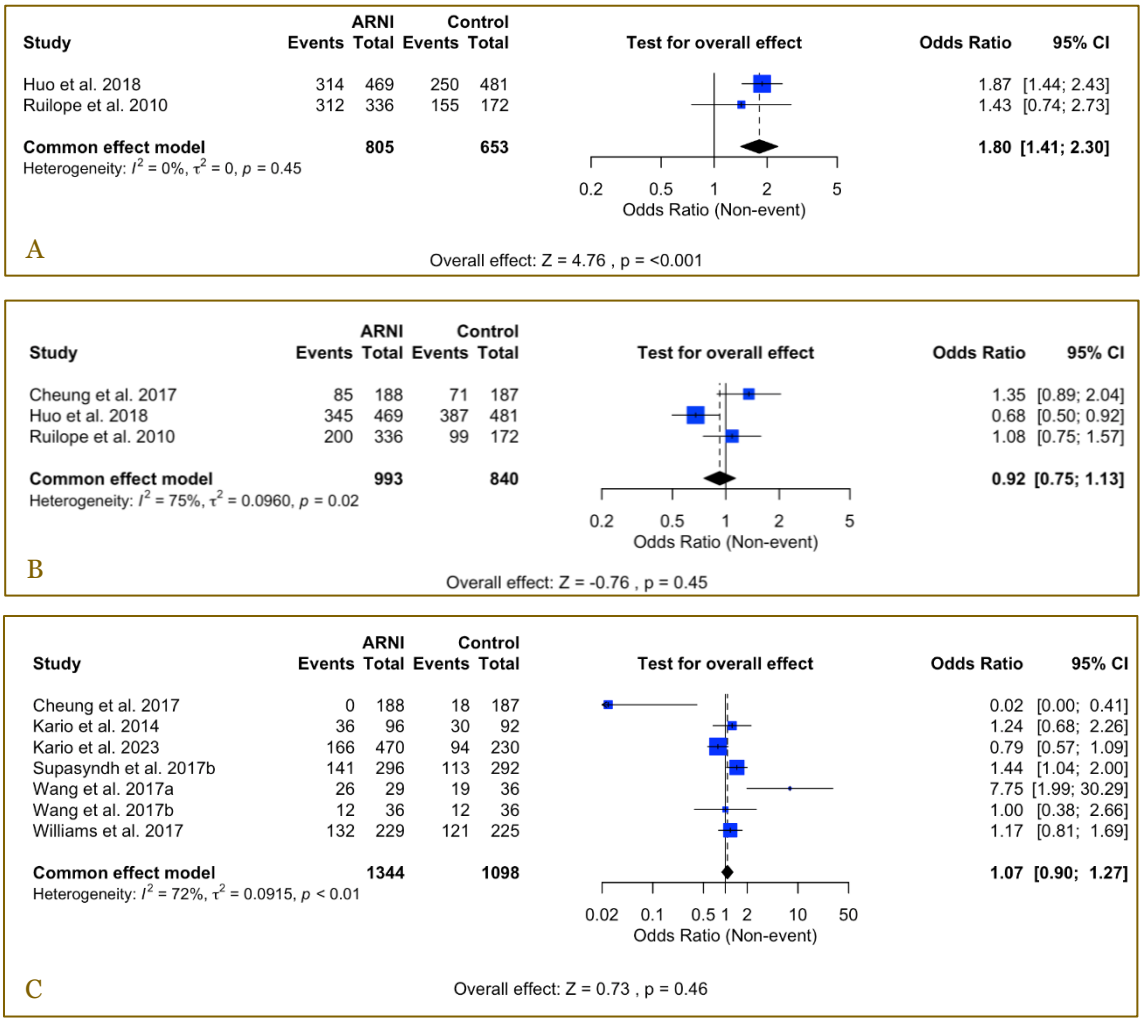


Figure 3. Forest plot of the pooled odd ratios for systolic blood pressure (A) and diastolic blood pressure controls (B) in angiotensin receptor neprilysin inhibitor compared to control. Forest plot of the pooled odd ratios for adverse events in angiotensin receptor neprilysin inhibitor group compared to control (C). The blue square and solid lines represent the odds ratio with 95%CI. The size of the squares indicates the weight of each study. The black rhombus indicates the pooled estimate with 95%CI.

## Discussion

The pooled estimates suggested that ARNI demonstrated a higher efficacy in controlling SBP compared to the control group. However, there was no significant differences observed regarding the efficacy in controlling DBP among the ARNI and control group. Previous studies found ARNI was proven to be effective in addressing myocardial remodeling by expanding blood vessels, facilitating sodium and urine excretion, and inhibiting myocardial remodeling [31]. Sacubitril/valsartan, the first agent in the ARNI class, enhances the effects of natriuretic peptides (NPs), promoting myocardial relaxation, reducing hypertrophy, and offering potential antifibrotic and sympatho-inhibitory effects [32]. The efficacy of ARNI in improving BP profiles is thought to be associated with its ability to reduce SBP by promoting vasodilation and lowering vascular resistance [33].

In the present systematic review, the efficacy of ARNI in achieving SBP control was observed in a study involving an Asian population but not in a non-Asian population. Previous finding highlighted that this therapy was reported to be effective in treating hypertension, especially in the dominantly Asian population [34]. Neprilysin inhibition leads to the augmentation of NPs, which facilitates enhanced excretion of sodium in urine and suppression of sympathetic activity. The combination of ARB and neprilysin inhibitor in ARNIs results in vasodilation, decreased vascular resistance, and enhanced fluid excretion, all of which contribute to the lowering of blood

pressure and systolic pressure [34]. A previous study found that the reduction of SBP was significantly higher in sacubitril/valsartan group as compared to olmesartan group [16]. Another study found that sacubitril/valsartan at 200 mg displayed greater reductions in 24-hour mean ambulatory SBP compared to a 20 mg dosage of olmesartan [21]. Approximately 40.4% of patients in the sacubitril/valsartan group achieved blood pressure control, compared to only 27.8% in the olmesartan group [9].

Additionally, in the present study, the incidence of adverse event was not associated with ARNI. Previously, no instances of angioedema were observed in ARNI group, which could be attributed to the limited role of neprilysin in the metabolic breakdown of bradykinin [35]. However, some disadvantages and safety precautions regarding the use of ARNI should also be considered. One such concern is hypotension, which can occur, especially during the initiation and up-titration phases of therapy [17,36]. Additionally, ARNIs may lead to hyperkalemia, particularly in patients with pre-existing kidney problems or those taking potassium-sparing diuretics [17,36]. Other than the efficacy and safety, socioeconomic factors should be considered, as they can impact both the financial burden and adherence to medication regimens [37].

This study succeeded in developing an understanding on the safety and efficacy of ARNI in treating hypertension. Nevertheless, to facilitate more homogenous and less biased systematic reviews and meta-analyses, future clinical trials are deemed necessary. The overall quality of the evidence is high with only one of the included studies exhibiting bias in one domain. Further RCTs with standardized protocols and longer follow-up remain required.

## Conclusion

ARNI is efficacious in managing systolic hypertension, although its pooled efficacy is variable across studies. Further, its effect on DBP control requires further studies with longer follow-up duration. The safety profile appears acceptable, with few treatment-emergent adverse events reported. However, further rigorous studies are needed to fully establish the safety and long-term efficacy of ARNI. Additionally, cost-effectiveness analyses are needed to substantiate its broader clinical utility in hypertensive populations.

### Ethics approval

Not required.

### Acknowledgments

None declared.

### Competing interests

The authors declare that they have no competing interests.

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### Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

## How to cite

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