# Cardiorenal safety and efficacy of angiotensin receptor-neprilysin inhibitors in heart failure across the ejection fraction spectrum: A meta-analysis and meta-regression of RCTs with 28,001 patients

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**Abstract.** Angiotensin receptor-neprilysin inhibitors (ARNIs), including sacubitril/valsartan, exert blood pressure-lowering and organ-protective effects in patients with heart failure (HF). However, differences of these effects across HF phenotypes and their impact on renal outcomes remain unclear. The present systematic review aimed to evaluate the antihypertensive efficacy, safety and cardiorenal benefits of ARNIs vs. angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) in patients with HF with reduced, mildly reduced, and preserved ejection fractions. Data were extracted from PubMed, Scopus, Cochrane, ProQuest and Google Scholar up to July 2025. Risk of bias was evaluated using the Cochrane Risk of Bias 2 tool. Meta-analyses were performed using risk ratios (RRs) with 95% confidence intervals (CIs). Data analyses were conducted using RevMan version 5.4 and STATA version 16.0. Outcomes encompassed all-cause mortality, cardiovascular mortality, HF-related hospitalization, major adverse cardiovascular events (MACEs) and adverse events. A total of 18 randomized control trials involving 28,001 patients were included. Compared with ACE-I/ARB, ARNI decreased all-cause (RR=0.67; 95% CI=0.83-0.97) and cardiovascular mortality (RR=0.84; 95% CI=0.77-0.92), HF hospitalization (RR=0.87; 95% CI=0.81-0.93) and MACE (RR=0.89; 95% CI=0.85-0.94), but increased symptomatic hypotension (RR=1.54; 95% CI=1.43-1.65). Subgroup analysis by left ventricular ejection fraction category did not reveal any significant effect modification across outcomes. Meta-regression identified N-terminal prohormone of brain natriuretic peptide (P=0.02) and body mass index (P<0.0001) as predictors of cardiovascular mortality. Estimated glomerular filtration rate was associated with all-cause mortality (P=0.001) and hypotension (P=0.03), while sex (P=0.001) predicted hospitalization. Systolic blood pressure (P=0.001) was linked to renal outcomes. Overall, ARNIs confer consistent cardiorenal benefits across the HF spectrum, particularly in patients with elevated systolic blood pressure and decreased renal function, though hypotension requires careful monitoring. The present study was registered in PROSPERO (registration no. CRD42024569374).

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## Introduction

Heart failure (HF), a progressive clinical syndrome, is characterized by impaired cardiac output and/or elevated intracardiac pressure, resulting in systemic hypoperfusion and congestion (1). It encompasses a broad spectrum of hemodynamic and structural abnormalities, frequently associated with the dysregulation of neurohormonal pathways, particularly the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (2). The incidence of HF is increasing, causing an escalating burden on healthcare systems (3). In a population-based study from Spain in 2012, 30.8% of patients with heart failure were hospitalized within one year of follow-up, and the all-cause mortality rate during that period was 14.3% (4). In the United States, it is one of the most costly medical disorders, with a total annual cost of $30.7 billion (5).

The classification of HF based on ejection fraction (EF) has advanced to support more precise therapeutic decisions. HF is classified on the basis of the left ventricular EF (LVEF) into reduced (HFrEF, ≤40%), mildly reduced (HFmrEF, 41-49%), preserved (HFpEF, ≥50%), and improved ejection fraction (HFimpEF), defined as a baseline LVEF of <40% with an increase of ≥10 percentage points to >40% on follow-up (6). This classification based on LVEF, is currently endorsed by the 2021 European Society of Cardiology (ESC) Guidelines on Heart Failure. This is a positive change compared with the 2016 ESC Guidelines, which reassigned patients with an exact LVEF of 40% to HFrEF rather than HFmrEF, and improves alignment between management strategies and clinical trial evidence (7).

The revised classification has informed contemporary treatment guidelines, particularly regarding the use of angiotensin receptor-neprilysin inhibitors (ARNIs). The 2022 the American Heart Association/American College of Cardiology/Heart Failure Society of America (HFSA) Guideline for the Management of HF recommend replacing angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) with ARNIs, including sacubitril/valsartan, in patients with symptomatic HFrEF (New York Heart Association classes II-III) and initiating ARNI therapy before discharge in patients hospitalized with acute HF. Furthermore, to decrease the risk of hospitalization, ARNIs may be considered in select patients with HFmrEF or HFpEF (1). Previous landmark trials, including PARADIGM-HF and PARAGON-HF, have demonstrated the superiority of ARNIs by achieving a substantial decrease in cardiovascular-associated mortality, HF-related hospitalization and complication rates compared with the use of either ACE-Is or ARBs alone (8,9).

In parallel with advancements in neurohormonal modulation therapies such as ARNI, diuretic strategies remain a key component in the symptomatic management of congestive HF, particularly in patients presenting with volume overload. Recently, interest has grown in combinatorial diuretic regimens to overcome diuretic resistance and improve decongestive outcomes (10-12). A meta-analysis by Duta *et al* (10) demonstrated that the combination of acetazolamide with loop diuretics significantly enhances natriuresis and fluid removal compared with loop diuretics alone. This approach targets both proximal and distal renal tubular sites, optimizing diuretic response and offering promising adjunctive benefits in acute and chronic HF settings (10). Incorporating evolving strategies into the broader HF treatment paradigm reflects the growing recognition of the need for individualized, phenotype-based interventions beyond guideline-directed medical therapy.

Although prior meta-analyses have demonstrated the clinical benefits of ARNIs, particularly in decreasing mortality, hospitalization and improving functional outcomes, these have primarily focused on patients with rEF, with limited exploration of its effects across the full spectrum of HF phenotypes (13,14). The generalizability is further limited by the heterogeneity in study populations, outcome definitions and reporting standards. Therefore, the present systematic review and meta-analysis aimed to evaluate the efficacy, safety and BP-associated outcomes of ARNIs across populations with HFrEF, HFmrEF and HFpEF while accounting for key clinical modifiers, including age, sex, anthropometric profile, laboratory parameters, hemodynamic factors and cardiac and renal function. By integrating a large body of evidence and applying meta-regression to key hemodynamic and renal parameters, the present study aimed to offer clinically relevant insights to inform more individualized and hypertension-conscious HF management.

## Materials and methods

*Study design and protocol registration*. The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (15). The study protocol was registered in the International Prospective Register of Systematic Reviews with registration no. CRD42024569374 (crd.york.ac.uk/PROSPERO/view/CRD42024569374).

*Search strategies*. A systematic search of the relevant studies was conducted across five databases, including PubMed (pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/), Cochrane (https://www.cochranelibrary.com/), ProQuest (https://www.proquest.com/) and Google Scholar (https://scholar.google.com/). Databases were searched from inception to July 7, 2025; data extraction and all derived estimations were completed on July 29, 2025, after which no additional updates were incorporated. The following main keywords, combined with Boolean operators 'AND' and 'OR', were initially established: ('Angiotensin Receptor Neprilysin Inhibitor' OR 'ARNI' OR 'Sacubitril/Valsartan' OR 'LCZ696' OR 'Entresto') AND ('Heart Failure' OR 'Congestive Heart Failure' OR 'CHF' OR 'Cardiac Insufficiency' OR 'Left Ventricular Dysfunction') AND ('Reduced Ejection Fraction' OR 'Reduced EF' OR 'HfrEF' OR 'Heart Failure with Reduced Ejection Fraction' OR 'Systolic Heart Failure') AND ('Preserved Ejection Fraction' OR 'Preserved EF' OR 'HfpEF' OR 'Heart Failure with Preserved Ejection Fraction' OR 'Diastolic Heart Failure'). No publication date and language restrictions were set.

*Selection of studies*. The search results from each database were collected and managed using Google Sheets (Google LLC). After removing duplicates, the remaining articles were screened based on title and abstract. Full-text studies that were available and published were assessed according to the pre-specified eligibility criteria by four investigators. Any disagreements were resolved through a group discussion.

Exclusion criteria were as follows: i) Wrong study design (single-arm or non-comparative reports); ii) wrong population (not chronic HF); iii) wrong comparator (not ACE-I/ARB or guideline-directed therapy); iv) wrong outcomes (no extractable data for prespecified endpoints); and v) overlapping populations (for multiple publications from the same trial, the most complete primary report was retained). When outcome data were unavailable, author contact was attempted; studies with unresolved missing data were excluded from quantitative synthesis.

*Eligibility criteria*. Population, Intervention, Comparison, Outcome (PICO) framework (Table SI) designed for systematic reviews was used to establish the eligibility criteria as follows:

i) Study population consisted of patient with various stages of EF HF (HFmEF, HFpEF, HFrEF); ii) used ARNI as intervention; iii) used ACE-I/ARB as control therapy; iv) evaluated efficacy [all-cause and cardiovascular-related mortality, major adverse cardiac events (MACE) and HF hospitalization] and safety (hypotension, hyperkalemia, angioedema and renal impairment); and v) randomized control trial design. Exclusion criteria were as follows: i) Title or abstract was irrelevant; ii) full-text was irretrievable and iii) the study was a review article, case report, case series or conference abstract. Titles or abstracts were considered irrelevant if they did not pertain to the predefined PICO framework.

*Data extraction*. A total of two investigators extracted data from each included study. The data extracted included the first author and year of publication, study location (country), HF type, age, sample size, sex (% of males), type of intervention and control (drug administration and dosing regimens), follow-up duration (months), efficacy (all-cause and cardiovascular-related mortality, MACEs and HF-related hospitalization), and safety (hypotension, hyperkalemia, angioedema and renal impairment). Adverse events (AEs) were classified using the Common Terminology Criteria for AEs (CTCAE) developed by developed by the US National Cancer Institute of the National Institute of Health, with severity graded from 1 (mild) to 5 (death) (16).

*Quality assessment of individual studies*. To evaluate the risk of bias of each eligible study, two investigators independently conducted a methodological quality assessment using the Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool (17). The RoB 2 is a revised tool comprising five bias domains designed to consider the risk of bias of randomized trials arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement and selecting the reported results. The risk of bias on each domain was rated as low or high risk, or some concerns (unclear). A study was considered to have a low risk of bias when all domains exhibited low risk. A study was judged to have some concerns when at least one domain was rated unclear. A study was considered to be at a high risk of bias when at least one domain presented a high risk or some concerns in multiple domains that may lower the confidence in the results.

*Statistical analysis*. The present study performed a meta-analysis with fixed- or DerSimonian-Laird random effect to compute the risk ratio (RR) for all dichotomous outcomes using Review Manager version 5.4 (The Cochrane Collaboration), STATA version 16.0 (StataCorp LLC) and meta package in RStudio version 4.4.1 (Posit PBC). The data are presented as RR and 95% confidence interval. A random effect was used when heterogeneity was detected ($I^2$>50%). Heterogeneity was assessed using Higgins' $I^2$ statistic. To interpret the degree of heterogeneity, $I^2$ values of 0, 1-24, 25-49, 50-74 and ≥75% were considered to indicate no, very low, low, moderate and high heterogeneity, respectively (18). P<0.05 was considered to indicate a statistically significant difference.

Subgroup analyses and meta-regression were performed to explore heterogeneity. Subgroups were prespecified by LVEF ≤40% vs. >40%, with pooled effects estimated within strata and between-group differences assessed using an interaction P-value. Meta-regression employed the DerSimonian-Laird random-effects approach to evaluate continuous study-level covariates, including mean age, proportion of female patients, N-terminal pro-B-type natriuretic peptide (NT-proBNP), LVEF, heart rate, systolic (S)BP, body mass index (BMI) and renal impairment as estimated by glomerular filtration rate (eGFR). Where the same construct appeared in both frameworks, it was modeled categorically in subgroup analyses and continuously in meta-regression.

Funnel plots were constructed for each outcome. For outcomes with ≥10 studies, Egger's regression test (primary) and Begg's rank-correlation test (sensitivity) were performed, using $\alpha$=0.10 (two-sided) to flag potential asymmetry; outcomes with <10 studies were not tested.

## Results

*Study selection and identification*. The initial database search yielded 20,856 studies. Before screening, 7,288 articles were removed, including 138 duplicates and 7,150 identified as ineligible. Following the title and abstract screening, 13,340 articles were excluded. A total of 228 articles were assessed for retrieval, with 29 removed. The remaining 199 articles underwent eligibility assessment, leading to the inclusion of 18 studies for quantitative and qualitative analyses (8,9,19-34). The PRISMA flowchart detailing the study selection process is depicted in Fig. 1.

*Characteristics of the included studies*. A total of 18 RCTs were eligible for inclusion in the analysis, involving 28,001 HF patients from nine studies conducted in the United States (9,19-21,27,28,31,33,34), one each from the United Kingdom (8), Canada (28), Italy (29), South Korea (25), Japan (32) and Bangladesh (23) and two each from Germany (24,30) and China (22,26) (Table I). The mean patient age was 59.4-72.8 years, with most participants being male (64.18%). The patient population comprised individuals with three types of HF, categorized by LVEF: Preserved (six studies) (9,20,28,30,31,34), mildly reduced (one study) (30) and reduced (12 studies) (8,19,21-27,27,32,33),. A total of 13,876 patients received ARNI intervention, with doses of 50, 100 and 200 mg, taken twice daily. Conversely, 14,125 patients received control treatments, consisting of ARB in 10 studies (6,704 patients) (9,20,22,23,26-28,30,31,33) and ACE-I in eight studies (7,204 patients) (8,19,21,24,26,29,32,33). The follow-up time ranged from 2 to 36 months. The most frequently reported CTCAE-graded AEs were hypotension, worsening renal function, hyperkalemia, angioedema and acute kidney injury.

*Quality assessment of studies*. Studies were assessed for bias using the Cochrane RoB 2.0 tool (Fig. 2). A total of two studies (26,34) were rated as having some concerns, while one study (22) was judged to have a high risk of bias. Gao *et al* (22) was rated high risk in the domains of deviation from intended interventions and selection of the reported result, primarily due to the absence of blinding procedures and lack of trial registration. This omission raises concern about selective outcome reporting, particularly in the context of exploratory or post hoc analyses. Additionally, outcome measurement in

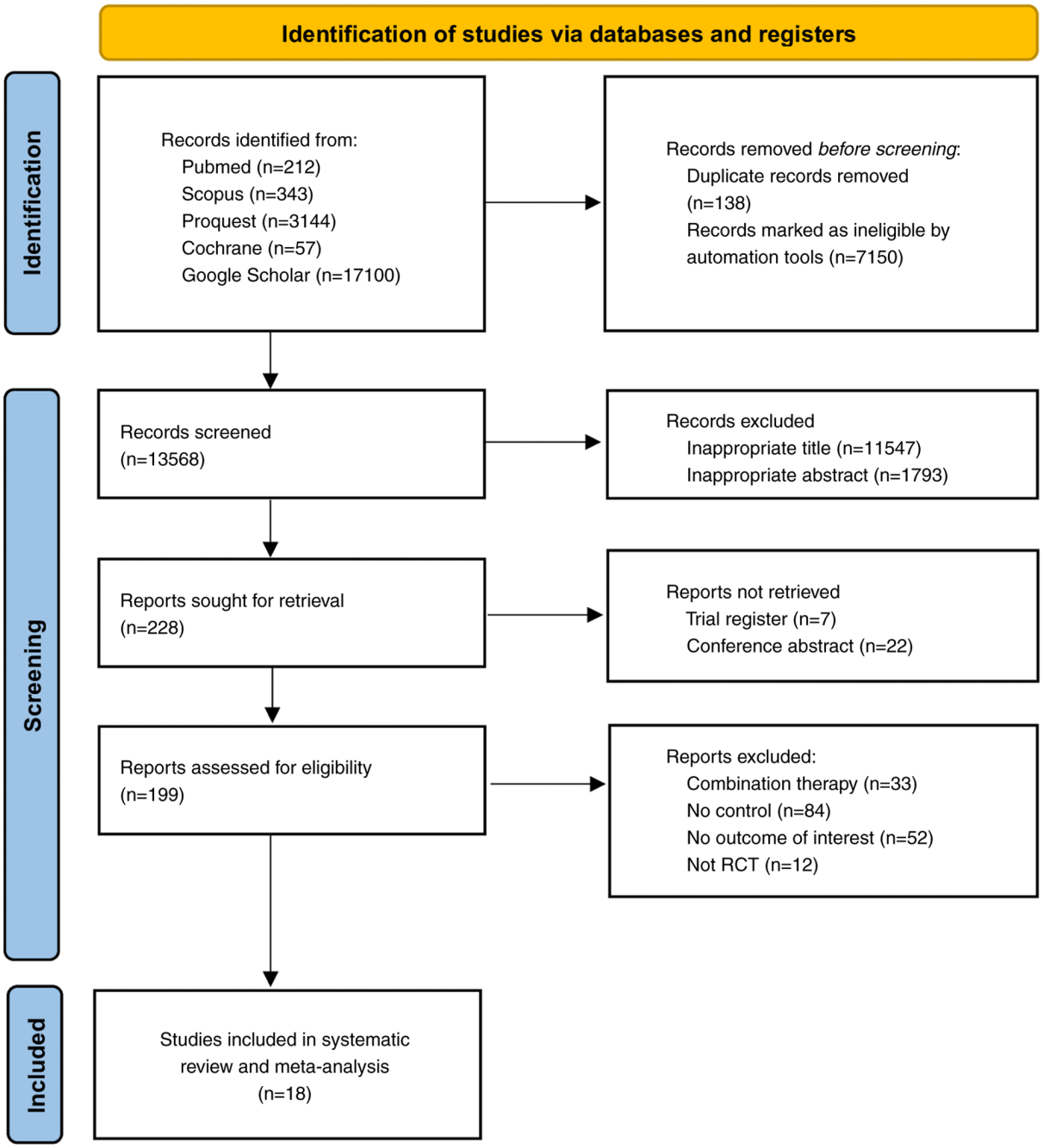


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. RCT, randomized control trial.

the aforementioned study was graded as some concerns due to unblinded assessment of endpoints. Li *et al* (26) demonstrated some concerns in the domains of randomization and outcome measurement, as the allocation concealment process was not clearly reported and there was insufficient detail regarding blinding of outcome assessors. Voors *et al* (34) was also rated as having some concerns in the domain of missing outcome data, due to incomplete reporting of renal endpoints from a post hoc analysis. Despite these exceptions, the overall risk of bias across trials was low, indicating generally high methodological quality.

*Efficacy of ARNI*. The clinical outcomes regarding the efficacy and safety of ARNI compared with the control group are summarized in Table II. The analysis of the included studies highlighted favorable results associated with ARNI use (Figs. S1 and S2).

*All-cause mortality*. A total of six studies (8,9,27,30,31,33) with 17,276 patients with HF, including 8,630 patients who received ARNI and 8,646 patients who received control, were included in the meta-analysis of all-cause mortality (Fig. 3). ARNI in patients with HF significantly decreased all-cause mortality (RR=0.67; 95% CI=0.83-0.97). No outlier was detected based on the funnel plot (Fig. S1). The level of heterogeneity was low ($I^2$=25.1%).

*Cardiovascular-associated mortality*. A cumulative total of 14,319 participants, including 7,155 participants treated with ARNI and 7,164 participants in the control group from six

Table I. Characteristics of studies.

| First author, year | Country | Number of patients | Male patients (%) | Mean age, years | Type of HF | Control | | Intervention | | Follow-up duration, months | CTCAE (grade) | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Type | n | Type | n | | | |
| McMurray *et al*, 2014 | United Kingdom | 8,399 | 6,567 (78.2) | 63.80±11.40 | HFrEF | Sacubitril/valsartan, 200 mg twice daily | 4,187 | Enalapril, 10 mg twice daily | 4,212 | 4 | Hyperkalemia (G1-2), worsening renal function (G2-3), symptomatic hypotension (G2-3), angioedema (G2-3), hospitalization (G3-4), cardiovascular-associated mortality (G5) | (8) |
| Solomon *et al*, 2019 | United States of America | 4,796 | 2,317 (48.3) | 72.75±8.40 | HFpEF | Sacubitril/valsartan, 97/103 mg twice daily | 2,407 | Valsartan, 160 mg twice daily | 2,389 | 35 | Hypotension (G2-3), worsening renal function (G2-3), hyperkalemia (G1-2), angioedema (G3), cough (G1-2), dizziness (G1-2), acute kidney injury (G2-3), elevated creatinine (G2-3), syncope (G2-3) | (9) |
| Vardeny *et al*, 2016 | United States of America | 3,549 | 2,785 (78.5) | 63.85±11.48 | HFrEF | Sacubitril/valsartan, 200 mg twice daily | 1,755 | Enalapril, 10 mg twice daily | 1,794 | 27 | Hyperkalemia (G1-2), hypotension (G2-3), worsening renal function (G2-3), acute kidney injury (G2-3), angioedema (G3), cough (G1-2), dizziness (G1-2) | (19) |
| Chandra *et al*, 2022 | United States of America | 4,476 | 2,192 (48.9) | 72.60±8.50 | HFpEF | Sacubitril/valsartan, 97/103 mg twice daily | 2,226 | Valsartan, 160 mg twice daily | 2,250 | 36 | NA | (20) |

Table I. Continued.

| First author, year | Country | Number of patients | Male patients (%) | Mean age, years | Type of HF | Control | | Intervention | | Follow-up duration, months | CTCAE (grade) | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Type | n | Type | n | | | |
| Desai *et al*, 2019 | United States of America | 464 | 355 (76.5) | 71.70±10.30 | HFrEF | Sacubitril/valsartan, 97/103 mg twice daily | 231 | Enalapril, 10 mg twice daily | 233 | 3 | Hypotension (G2-3); no significant CTCAE-graded differences in renal dysfunction (G2-3), hyperkalemia (G1-2), or angioedema (G3) | (21) |
| Gao *et al*, 2020 | China | 120 | 88 (73.3) | 70.30±7.30 | HFrEF | Sacubitril/valsartan, 50 mg twice daily | 60 | Valsartan, 80 mg once daily | 60 | 18 | Hyperkalemia (G1-2), worsening renal function (G2-3), acute kidney injury (G2-3), hypotension (G2-3), all-cause morality (G5), cardiovascular-associated mortality (G5), discontinuation due to AEs (G3) | (22) |
| Ghafur *et al*, 2020 | Bangladesh | 100 | 67 (67) | 61.40±11.90 | HFrEF | Sacubitril/valsartan, 100 mg twice daily | 50 | Valsartan, 80 mg twice daily | 50 | 4 | Cardiovascular-associated mortality (G5), hospitalization due to HF (G3), elevated serum creatinine (G2-3), hyperkalemia (G1-2), hyperglycemia (G1-2) | (23) |
| Halle *et al*, 2021 | Germany | 201 | 163 (81.1) | 66.90±10.40 | HFrEF | Sacubitril/valsartan, 97/103 mg twice daily | 103 | Enalapril, 10 mg twice daily | 98 | 3 | Hyperkalemia (G1-2), worsening renal function (G2-3), hypotension (G2-3), angioedema (G3), acute kidney injury (G2-3) | (24) |
| Kang *et al*, 2019 | South Korea | 118 | 72 (61) | 62.60±11.20 | HFrEF | Sacubitril/valsartan, 97/103 mg twice daily | 60 | Valsartan, 80 mg once daily | 58 | 6 | Hyperkalemia (G1-2), hypotension (G2-3), worsening renal function (G2-3), dizziness (G1-2), cough (G1-2) | (25) |

Table I. Continued.

| First author, year | Country | Number of patients | Male patients (%) | Mean age, years | Type of HF | Control | | Intervention | | Follow-up duration, months | CTCAE (grade) | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Type | n | Type | n | | | |
| Li *et al*, 2020 | China | 80 | 47 (58.8) | 63.00±5.70 | HFrEF | Sacubitril/valsartan, 200 mg twice daily | 40 | Perindopril tert-butylamine, 4 mg once daily | 40 | 3 | NA | (26) |
| Mann *et al*, 2022 | United States of America | 335 | 245 (73.1) | 59.40±13.50 | HFrEF | Sacubitril/valsartan, 97/103 mg twice daily | 167 | Valsartan, 160 mg twice daily | 168 | 6 | Hyperkalemia (G1-2), worsening renal function (G2-3), hypotension (G2-3), hospitalization (G3-4), cardiovascular-associated mortality (G5) | (27) |
| Mentz *et al* , 2023 | United States of America and Canada | 466 | 224 (48.1) | 71.40±3.10 | HFpEF | Sacubitril/valsartan, 97/103 mg twice daily | 233 | Valsartan, 160 mg twice daily | 233 | 2 | Hyperkalemia (G1-2), hypotension (G2-3), worsening renal function (G2-3), acute kidney injury (G2-3), dizziness (G1-2), cough (G1-2), fatigue (G1-2) | (28) |
| Piepoli *et al*, 2020 | Italy | 619 | 487 (78.7) | 66.90±10.70 | HFrEF | Sacubitril/valsartan, 97/103 mg twice daily | 309 | Enalapril, 10 mg twice daily | 310 | 3 | Hyperkalemia (G1-2), hypotension (G2-3), worsening renal function (G2-3), cough (G1-2), dizziness (G1-2) | (29) |
| Pieske *et al*, 2021 | Germany | 2,572 | 1,271 (49.4) | 72.60±8.50 | HFpEF, HFmrEF | Sacubitril/valsartan, 97/103 mg twice daily | 1,288 | Valsartan, 160 mg twice daily | 1,284 | 6 | Hypotension (G2-3), albuminuria (G1-2), hyperkalemia (G1-2) | (30) |
| Solomon *et al*, 2012 | United States of America | 301 | 131 (43.5) | 71.00±9.10 | HFpEF | Sacubitril/valsartan, 200 mg twice daily | 149 | Valsartan, 160 mg twice daily | 152 | 26 | Hypotension (G2-3), albuminuria (G1-2), hyperkalemia (G1-2), hypotension (G2-3), elevated serum creatinine (G2-3), hyperkalemia (G1-2), angioedema (G3), liver-related AEs (G1-2). | (31) |

Table I. Continued.

| First author, year | Country | Number of patients | Male patients (%) | Mean age, years | Type of HF | Control | | Intervention | | Follow-up duration, months | CTCAE (grade) | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Type | n | Type | n | | | |
| Tsutsui *et al*, 2021 | Japan | 223 | 192 (86.1) | 67.85±10.36 | HFrEF | Sacubitril/valsartan, 100 mg twice daily | 111 | Enalapril, 10 mg twice daily | 112 | 12 | Hypotension (G2-3), hyperkalemia (G1-2), worsening renal function (G2-3), cough (G1-2), dizziness (G1-2), angioedema (G3), acute kidney injury (G2-3) | (32) |
| Velazquez *et al*, 2018 | United States of America | 881 | 635 (72.1) | 62.00±3.42 | HFrEF | Sacubitril/valsartan, 97/103 mg twice daily | 440 | Enalapril, 5 mg twice daily | 441 | 2 | Hypotension (G2-3), hyperkalemia (G1-2), worsening renal function (G2-3), acute kidney injury (G2-3), angioedema (G3), cough (G1-2), dizziness (G1-2), elevated creatinine (G2-3) | (33) |
| Voors *et al*, 2015 | United States of America | 301 | 131 (43.5) | 70.73±9.01 | HFpEF | Sacubitril/valsartan, 50 mg twice daily | 60 | Valsartan, 80 mg once daily | 60 | 8.3 | Hypotension (G2-3), hyperkalemia (G1-2), worsening renal function (G2-3), acute kidney injury (G2-3), cough (G1-2), dizziness (G1-2), angioedema (G3) | (34) |

CTCAE, Common Terminology Criteria for Adverse Events; HFmrEF, heart failure with mildly reduced ejection fraction; p, preserved; NA, not available.

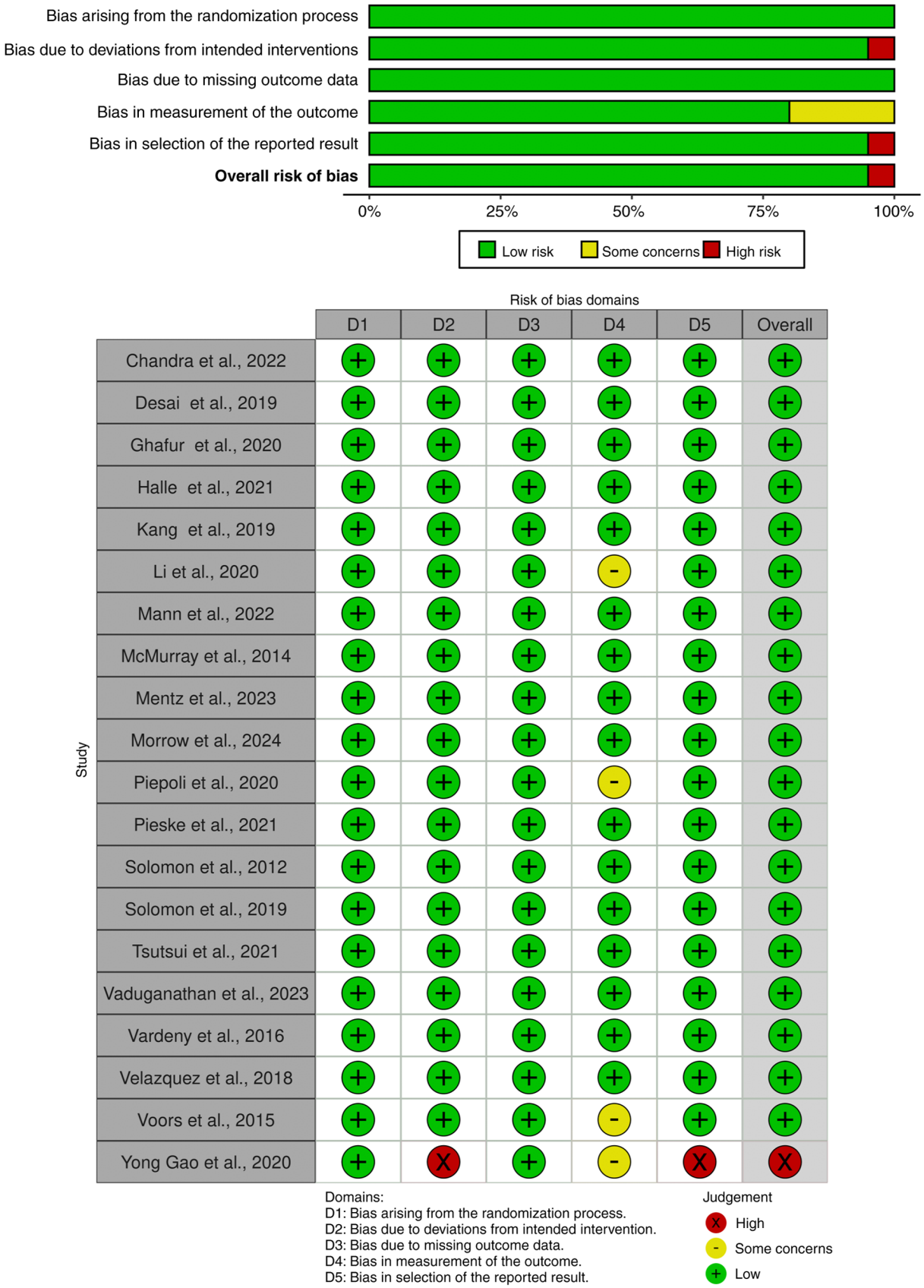


Figure 2. Quality assessment using the Cochrane Risk of Bias 2.0 tool. (A) Domain-specific quality assessment. (B) Quality assessment summary.

studies (8,9,23,27,28,32), were included in the meta-analysis of cardiovascular-related mortality (Fig. 4A). The use of ARNI for various types of HF was associated with a significantly lower risk of cardiovascular-associated mortality (RR=0.84; 95% CI=0.77-0.92). No outlier was detected based on the funnel plot (Fig. S1). The degree of heterogeneity was low ($I^2$=41%).

Table II. Effectiveness and safety of ARNI vs. control.

A, Effectiveness

| Outcome | ARNI (n/total) | Control (n/total) | RR (95%CI) | $I^2$ value,% | Favours ARNI | Favours control | Significant |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 1,100/8,630 | 1,226/8,646 | 0.67 (0.83-0.97) | 25.1 | Yes | No | Yes |
| Cardiovascular-associated mortality | 800/7,165 | 952/7,164 | 0.84 (0.77-0.92) | 41 | Yes | No | Yes |
| HF hospitalization | 1,079/7,488 | 1,234/7,497 | 0.87 (0.81-0.93) | 60 | Yes | No | Yes |
| MACE | 1,981/8,413 | 2,241/8,471 | 0.89 (0.85-0.94) | 57 | Yes | No | Yes |

B, Safety

| Outcome | ARNI (n/total) | Control (n/total) | RR (95%CI) | $I^2$ value,% | Favours ARNI | Favours control | Significant |
|---|---|---|---|---|---|---|---|
| Renal impairment | 719/11,588 | 798/11,648 | 0.91 (0.83-1.00) | 46.4 | Yes | No | No |
| Hyperkalaemia | 796/7,395 | 804/7,422 | 0.99 (0.90-1.09) | 47 | Yes | No | No |
| Angioedema | 41/11,389 | 28/11,446 | 1.44 (0.90-2.29) | 4.9 | No | Yes | No |
| Symptomatic hypotension | 1,759/11,492 | 1,150/11,544 | 1.54 (1.43-1.65) | 54.2 | No | Yes | Yes |

RR, risk ratio; CI, confidence interval; ARNI, angiotensin receptor-neprilysin inhibitor; MACE, major adverse cardiovascular event; HF, heart failure.

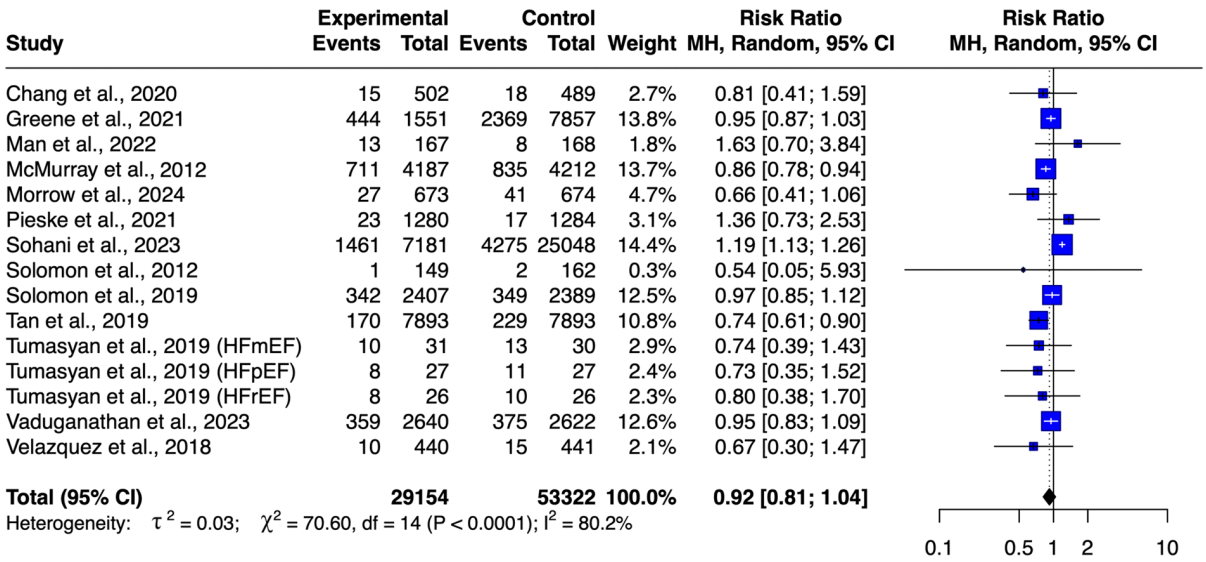


Figure 3. Effect of angiotensin receptor-neprilysin inhibitor vs. control on all-cause mortality. Square represents the study weights; diamond shape represents the overall effect. MH, Mantel-Haenszel; df, degrees of freedom.

*HF-associated hospitalization*. A total of seven studies (8,9,22,23,28,32,33), with 14,985 patients, including 7,488 patients who received ARNI and 7,497 patients in the control, were included in the meta-analysis of HF-related hospitalization (Fig. 4B). ARNI resulted in a significant decrease in the risk of HF-related hospitalization (RR=0.87; 95% CI=0.81-0.93). No outlier was detected on the basis of the funnel plot (Fig. S1). The level of heterogeneity was moderate ($I^2$=60%).

*MACEs*. A total of eight studies (8,20,22,27,28,30-32) with 16,884 patients, including 8,413 patients who received ARNI and 8,471 patients in the control group, were included in the meta-analysis of MACE (Fig. 4C). Treatment with ARNI significantly decreased the risk of MACEs in the pooled analysis (RR=0.89; 95% CI=0.85-0.94). No outlier was detected on the basis of the funnel plot (Fig. S1). The level of heterogeneity was moderate ($I^2$=57%).

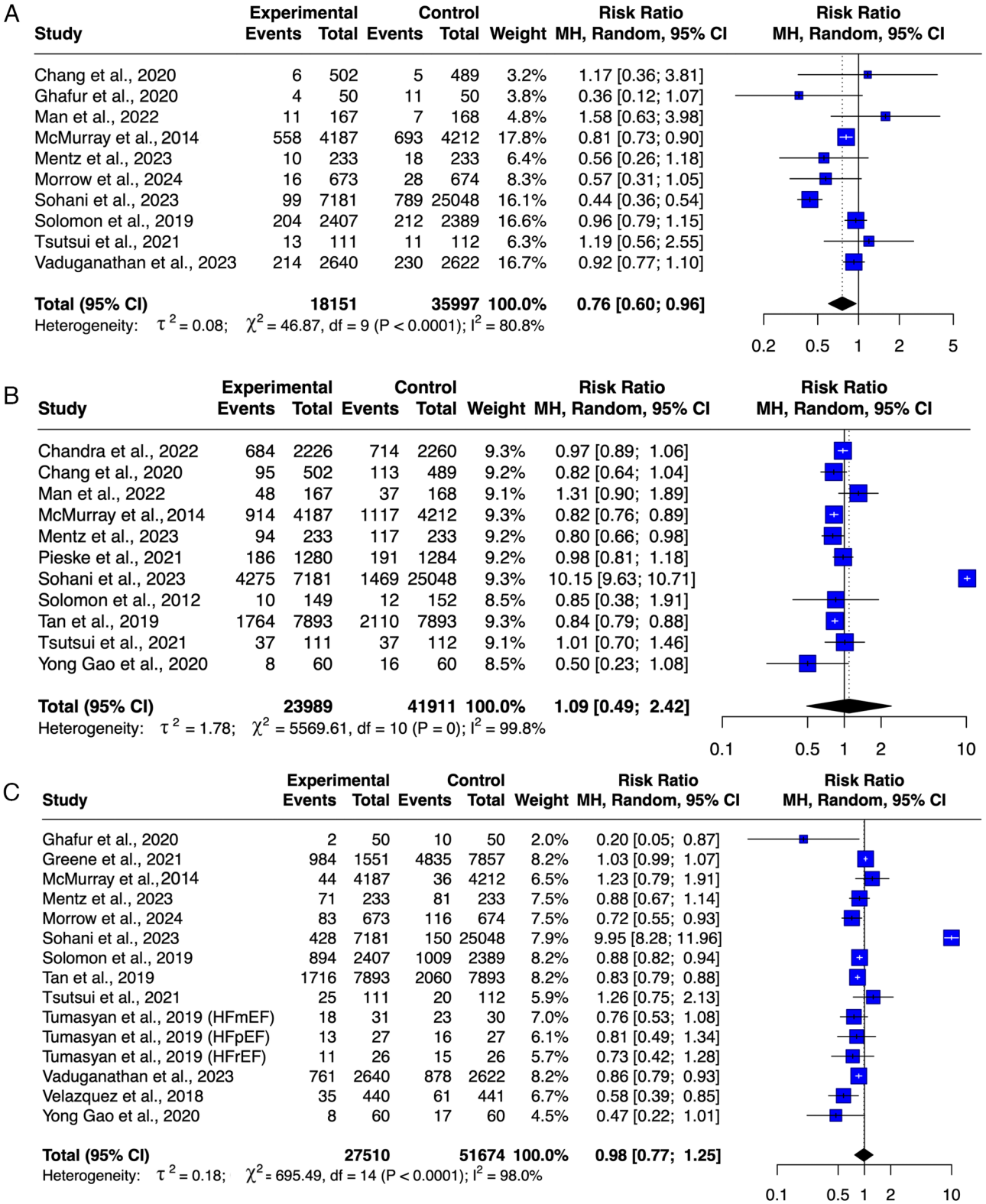


Figure 4. Effect of ARNI vs. control on (A) cardiovascular-related mortality, (B) heart failure hospitalization and (C) major adverse cardiovascular event. The blue square represents the study weights; the black diamond, overall effect. ARNI, angiotensin receptor-neprilysin inhibitor; MH, Mantel-Haenszel; df, degrees of freedom.

*Safety outcome of ARNI*

*Renal impairment*. A total of 23,236 participants from 15 studies (8,9,19,21-23,25,27-34) were included in the meta-analysis of renal impairment outcomes, comprising 11,588 participants in the ARNI group and 11,648 participants in the control group (Fig. 5A). ARNI use was associated with decreased risk of renal impairment (RR=0.91; 95% CI: 0.83-1.00), although this was not significant. No publication bias was observed based on the funnel plot, and heterogeneity was low ($I^2$=46.4%).

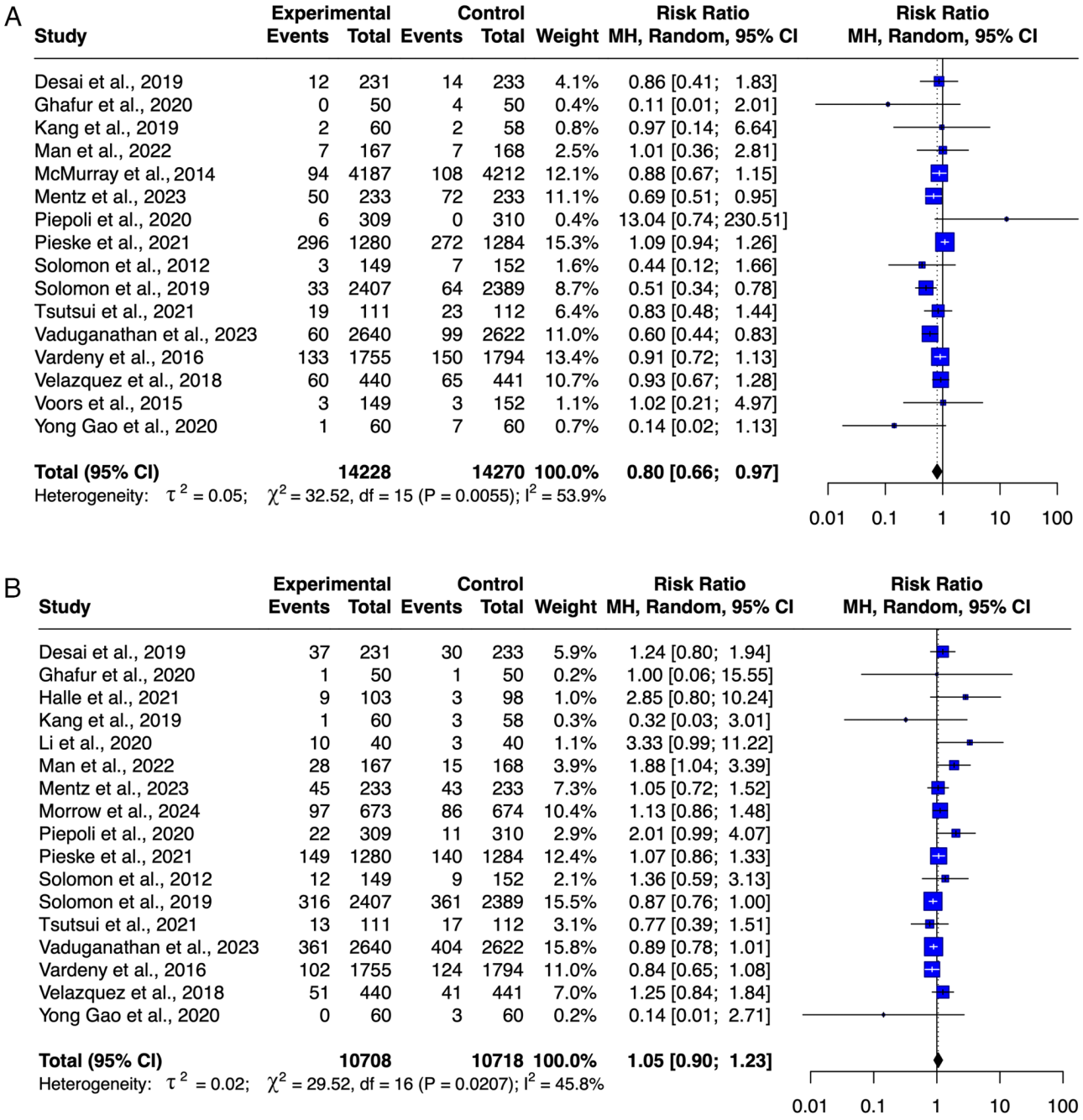


Figure 5. Safety outcome analysis related to renal function and electrolyte imbalance. Analysis of (A) renal impairment and (B) hyperkalemia incidence in the angiotensin receptor-neprilysin inhibitor vs. control group. MH, Mantel-Haenszel; df, degrees of freedom.

*Hyperkalemia*. A total of 14,817 participants, consisting of 7,395 participants treated with ARNI and 7,422 participants in the control group from 15 studies (9,19,21-33), were included in the meta-analysis of hyperkalaemia (Fig. 5B). The use of ARNI in HF interventions showed a lower risk of hyperkalaemia but this was not significant (RR=0.99; 95% CI=0.90-1.09). No outlier was detected based on the funnel plot (Fig. S2). The degree of heterogeneity was low ($I^2$=47%).

*Angioedema*. A total of 13 studies (8,9,19,21,22,25,27,28-33) with a total sample of 22,835 patients, consisting of 11,389 patients who received ARNI and 11,446 patients who received control, were included in the meta-analysis of angioedema (Fig. 6A). The meta-analysis showed no significant difference between the ARNI and the control groups in decreasing the risk of angioedema (RR=1.44; 95% CI=0.90-2.29). No outlier was detected based on the funnel plot (Fig. S2). The level of heterogeneity was very low ($I^2$=4.9%).

*Symptomatic hypotension*. A total of 23,036 participants, comprising 11,492 participants treated with ARNI and 11,544 participants in the control group from 14 studies (8,9,19,21, 22,24,25,27-33) was included in the meta-analysis of symptomatic hypotension (Fig. 6B). ARNI was associated with a significantly increased risk of symptomatic hypotension

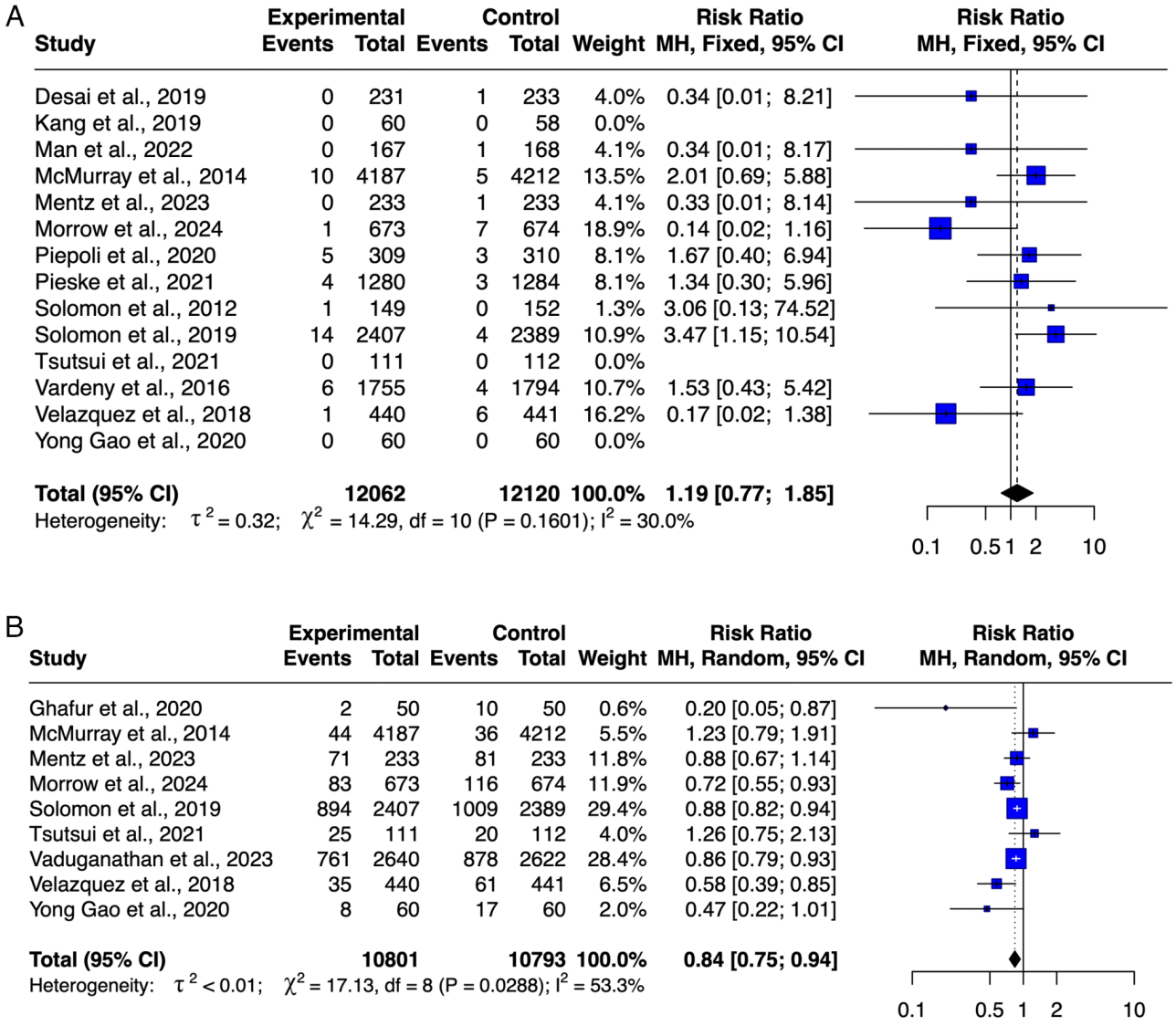


Figure 6. Saferty outcome analysis related to angioedema and hypotension. Analysis of (A) angioedema and (B) symptomatic hypotension incidence in the angiotensin receptor-neprilysin inhibitor vs. control group. MH, Mantel-Haenszel; df, degrees of freedom.

(RR=1.54; 95% CI=1.43-1.65). No outlier was detected based on the funnel plot (Fig. S2). The degree of heterogeneity was moderate ($I^2$=54.2%).

*Subgroup analysis*. Subgroup analyses stratified by LVEF (≤40 vs. >40%) demonstrated no significant interaction between LVEF category and the effect of ARNI across all assessed outcomes (Table III). The decrease in all-cause and cardiovascular-related mortality, MACEs and HF hospitalization was consistent between subgroups. Hypotension risk was increased in both LVEF subgroups, whereas hyperkalemia risk showed a non-significant trend towards elevation in LVEF ≤40% but not in LVEF >40%. Notably, angioedema risk was higher in the LVEF >40% subgroup, though the difference was not statistically significant. The incidence of renal impairment was lower in the LVEF >40% subgroup; however, no significant subgroup effect was detected. Heterogeneity across most comparisons was minimal, except for hyperkalemia and angioedema, which showed moderate variability.

*Meta-regression analysis*. Meta-regression analysis revealed significant study-level predictors across outcomes (Table IV). Higher eGFR was associated with a lower risk of all-cause mortality [standard error (SE)=0.06]. Higher NT-proBNP increased risk (SE=0.06), whereas higher BMI decreased risk of cardiovascular-associated mortality (SE=0.05). Hypotension was less common in females (SE=0.15) but more likely with higher eGFR (SE=1.07). Female sex was the only factor associated with a decreased risk of HF hospitalization (SE=0.15). Hyperkalemia risk was greater with older age (SE=0.84), female sex (SE=0.11) and lower LVEF (SE=0.29). Angioedema risk increased with higher heart rate (SE=1.46), diastolic BP (SE=2.40) and NT-proBNP (SE=0.77). Higher SBP was the only significant predictor of renal impairment (SE=1.60). All other covariates were not significantly associated with these outcomes.

## Discussion

The present meta-analysis confirmed the superior efficacy of ARNI therapy in reducing all-cause and cardiovascular

Table III. Subgroup analysis.

| Outcome | LVEF, % | Number of studies | RR | 95% CI | P-value | $I^2$ value, % | (Refs.) |
|---|---|---|---|---|---|---|---|
| All-cause mortality | ≤40 | 3 | 0.89 | 0.67-1.19 | 0.52 | 0.0 | (8,27,33) |
| | >40 | 3 | 0.99 | 0.86-1.13 | | | (9,30,31) |
| Cardiovascular-associated mortality | ≤40 | 4 | 0.88 | 0.58-1.32 | 0.86 | 0.0 | (8,23,27,32) |
| | >40 | 2 | 0.83 | 0.52-1.32 | | | (9,28) |
| MACE | ≤40 | 4 | 0.92 | 0.70-1.21 | 0.85 | 0.0 | (8,22,27,32) |
| | >40 | 4 | 0.95 | 0.88-1.02 | | | (20,28,30,31) |
| Hypotension | ≤40 | 11 | 1.48 | 1.25-1.75 | 0.73 | 0.0 | (8,19,21-25,27,29,32,33) |
| | >40 | 4 | 1.62 | 1.16-2.28 | | | (9,28,30,31) |
| Hospitalization | ≤40 | 5 | 0.73 | 0.44-1.21 | 0.48 | 0.0 | (8,22,23,32,33) |
| | >40 | 2 | 0.88 | 0.82-1.94 | | | (9,28) |
| Hyperkalemia | ≤40 | 11 | 1.10 | 0.94-1.30 | 0.11 | 60.0 | (17,21-27,29,32,33) |
| | >40 | 4 | 0.94 | 0.84-1.05 | | | (9,28,30,31) |
| Angioedema | ≤40 | 9 | 1.10 | 0.61-1.99 | 0.16 | 48.2 | (8,19,21,22,25,27,29,32,33) |
| | >40 | 4 | 2.22 | 1.01-4.87 | | | (9,28,29,31) |
| Renal impairment | ≤40 | 10 | 0.89 | 0.77-1.03 | 0.23 | 31.4 | (8,19,21-23,25,27,29,32,33) |
| | >40 | 5 | 0.67 | 0.44-1.04 | | | (9,28,30,31,34) |

RR, risk ratio; CI, confidence interval; MACE, major adverse cardiac events; LVEF, left ventricular ejection fraction.

mortality, HF-associated hospitalization and MACE across HF phenotypes. The magnitude of risk reduction observed in cardiovascular outcomes supports the pharmacological rationale of neprilysin-angiotensin receptor pathway dual inhibition (33). These findings align with those of earlier trials, including PARADIGM-HF, and meta-analyses, but include a broader range of HF subtypes and integrated meta-regression analyses to elucidate outcome modifiers (13,14,36).

The present findings support previous studies that showed the efficacy of ARNI in HF (8,13,34,35). Nielsen *et al* (36) demonstrated that sacubitril/valsartan significantly decreased all-cause mortality and serious AEs in HFrEF compared with ACE-Is/ARBs. Similarly, Park *et al* (13) reported a reduction in all-cause and cardiac-associated mortality and MACEs with ARNI therapy. However, both the aforementioned studies reported an increased risk of hypotension. The present analysis emphasizes the robust mortality benefit of ARNIs and confirms its association with hypotension, potentially due to enhanced NP activity, RAAS suppression and sympathetic inhibition, which promote vasodilation and natriuresis (8). Despite this hypotension risk, ARNI also substantially mitigated renal impairment, reinforcing its net clinical benefit. Its superior antihypertensive effect arises from early sodium diuresis and sustained vasodilation, making it more effective than traditional RAS inhibitors, even as natriuretic effects wane with prolonged use (37).

The present meta-analysis provides a broader evaluation of ARNI therapy across the full spectrum of HF phenotypes, including HFrEF, HFmrEF and HfpEF, which have been underrepresented or inconsistently analyzed in earlier reviews (13,38). While landmark trials such as PARADIGM-HF and PARAGON-HF have established the basis for ARNIs in HF management, previous meta-analyses have largely centered on patients with rEF, limiting their relevance to more diverse clinical presentations (17,18). By contrast, the present study integrated findings from a wider range of HF subtypes and incorporated meta-regression techniques to explore how key clinical and hemodynamic variables such as blood pressure, renal function and NT-proBNP levels modify ARNI effects. This approach not only enhances the generalizability of findings but also allows for more personalized, phenotype-specific interpretations of efficacy and safety. The present study complements recent comprehensive reviews, such as Tromp *et al* (39) and van Essen *et al* (40), and focused analysis on BP-associated outcomes and renal parameters, which are relevant to daily clinical decision-making. The present analysis support more precise and hypertension-conscious use of ARNIs in routine practice, aligning with the growing emphasis on individualized treatment in HF care.

Meta-regression analysis revealed that a lower eGFR was associated with an increased risk of all-cause mortality, supporting the findings of Khan *et al* (41), which linked a rapid decrease in eGFR (>15 ml/min/year) with a higher mortality rate. Consistent with the results of a previous study, the present analysis demonstrated that higher SBP was associated with worsening renal impairment (42). RAAS upregulation, increased sympathetic nervous system activity, elevated pro-inflammatory factors and left ventricular hypertrophy progression are potential mechanisms underlying these findings, all contributing to difficulties in volume handling, pump failure and mortality (41). Additionally, female sex was associated with a lower risk of HF-associated hospitalization, potentially due to the effect of estrogen on vascular function, inflammatory response, metabolism, cardiac myocytes and

Table IV. Random-effects univariate regression analysis of ARNI therapeutic outcomes by sociodemographic and clinical characteristics.

A, All-cause mortality

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | -0.05 | 0.15 | 0.719 |
| Female | -0.18 | 0.27 | 0.511 |
| NT-proBNP | -0.01 | 0.08 | 0.857 |
| LVEF | -0.03 | 0.08 | 0.693 |
| HR | -0.12 | 0.08 | 0.116 |
| SBP | 0.52 | 0.47 | 0.266 |
| BMI | -0.04 | 0.25 | 0.868 |
| eGFR | -0.21 | 0.06 | 0.001 |
| sCr | -0.10 | 0.06 | 0.102 |

B, Cardiovascular-associated mortality

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | 0.46 | 0.56 | 0.416 |
| Female | -0.30 | 0.24 | 0.211 |
| NT-proBNP | -0.14 | 0.06 | 0.015 |
| LVEF | -0.07 | 0.18 | 0.687 |
| HR | -1.18 | 0.62 | 0.059 |
| SBP | 0.46 | 0.48 | 0.335 |
| BMI | -0.20 | 0.05 | <0.001 |
| eGFR | -1.01 | 0.55 | 0.065 |
| sCr | -0.17 | 0.10 | 0.081 |

C, Major adverse cardiovascular event

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | 0.36 | 1.40 | 0.799 |
| Female | -0.06 | 0.64 | 0.925 |
| NT-proBNP | -0.04 | 0.06 | 0.427 |
| LVEF | -0.15 | 0.20 | 0.460 |
| HR | -0.05 | 0.30 | 0.877 |
| SBP | 0.36 | 0.29 | 0.212 |
| BMI | -0.03 | 0.24 | 0.918 |
| eGFR | -0.40 | 0.29 | 0.163 |
| sCr | -1.98 | 2.47 | 0.423 |

D, Hypotension

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | 0.84 | 0.55 | 0.127 |
| Female | -0.38 | 0.15 | 0.009 |
| NT-proBNP | -0.02 | 0.10 | 0.839 |
| LVEF | 0.05 | 0.37 | 0.897 |
| HR | 0.59 | 1.77 | 0.738 |
| SBP | -0.12 | 0.17 | 0.469 |
| DBP | -0.04 | 0.06 | 0.486 |

Table IV. Continued.

D, Hypotension

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| BMI | 0.75 | 1.36 | 0.581 |
| eGFR | -2.29 | 1.07 | 0.033 |
| sCr | -2.76 | 0.99 | 0.242 |

E, Hospitalization

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | -0.68 | 0.26 | 0.948 |
| Female | -0.49 | 0.15 | 0.001 |
| NT-proBNP | 0.22 | 0.47 | 0.635 |
| LVEF | -0.21 | 0.52 | 0.683 |
| HR | -0.43 | 1.61 | 0.948 |
| SBP | 0.17 | 0.57 | 0.971 |
| BMI | -1.08 | 2.03 | 0.596 |
| eGFR | -0.97 | 0.88 | 0.273 |
| sCr | 2.74 | 0.19 | 0.375 |

F, Hyperkalemia

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | 2.61 | 0.84 | 0.002 |
| Female | 0.35 | 0.11 | 0.001 |
| NT-proBNP | -0.14 | 0.18 | 0.453 |
| LVEF | 0.81 | 0.29 | 0.005 |
| HR | -2.15 | 3.05 | 0.481 |
| SBP | 4.55 | 1.63 | 0.084 |
| BMI | 0.58 | 2.52 | 0.818 |
| Egfr | -0.52 | 1.40 | 0.710 |
| sCr | -2.71 | 1.24 | 0.028 |

G, Angioedema

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | -8.16 | 2.33 | 0.126 |
| Female | -0.57 | 0.43 | 0.188 |
| NT-proBNP | 1.67 | 0.77 | 0.031 |
| LVEF | -0.36 | 0.92 | 0.695 |
| HR | 5.59 | 1.46 | 0.016 |
| SBP | -10.02 | 1.71 | 0.349 |
| DBP | 11.94 | 2.40 | 0.007 |
| BMI | 4.18 | 2.03 | 0.077 |
| eGFR | -5.44 | 1.84 | 0.488 |
| sCr | 11.94 | 1.40 | 0.007 |

H, Renal impairment

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Age | 1.81 | 1.51 | 0.230 |

Table IV. Continued.

H, Renal impairment

| Covariate | Estimate | Standard error | P-value |
|---|---|---|---|
| Female | -0.16 | 0.14 | 0.271 |
| NT-proBNP | -0.23 | 0.18 | 0.193 |
| LVEF | 0.30 | 0.20 | 0.122 |
| HR | -0.64 | 1.80 | 0.723 |
| SBP | 5.22 | 1.60 | 0.001 |
| DBP | 8.05 | 2.83 | 0.239 |
| BMI | 1.39 | 0.89 | 0.121 |
| eGFR | -0.84 | 1.29 | 0.516 |
| sCr | -0.61 | 1.43 | 0.670 |

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVEF, left ventricular ejection fraction; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; sCr, serum creatinine.

the development of hypertrophy yielding better outcomes. Lastly, elevated NT-proBNP levels were associated with cardiovascular-associated mortality; previous findings showed that NT-proBNP indicates increased cardiac stress (43,44).

ARNI exerts its therapeutic effect in HF through a dual mechanism that enhances beneficial pathways and suppresses maladaptive neurohormonal activation (Fig. 7). Sacubitril inhibits neprilysin, preventing the degradation of NPs (atrial, brain and C-type), causing vasodilation, natriuresis, diuresis and attenuation of myocardial fibrosis and hypertrophy. Simultaneously, valsartan blocks the angiotensin 1 receptor, counteracting the effects of angiotensin II and decreasing vasoconstriction, BP, aldosterone secretion and cardiac remodeling (17).

The mechanisms of ARNI vary across different HF stages with distinct EF profiles. In HfrEF (LVEF <40%), ARNI improves cardiac output by decreasing preload and afterload and improving ventricular contractility. In HfmrEF (LVEF, 40-49%), ARNI targets both systolic and diastolic dysfunction, stabilizing LVEF and decreasing vascular resistance. In HFpEF (LVEF ≥50%), ARNI mitigates diastolic dysfunction by lowering left ventricular filling pressure and relieving systemic congestion, with potential antifibrotic effects that improve myocardial compliance (45). These phenotype-specific actions highlight the versatility of ARNI across the HF spectrum.

ARNI therapy has become a transformative option in HF management, particularly for patients with HFrEF who remain symptomatic despite optimal treatment. By combining angiotensin II receptor blockade and neprilysin inhibition, ARNI provides a dual mechanism that attenuates the harmful effects of the RAAS and improves the protective NP system (19,46). This causes significant decreases in all-cause mortality, HF-related hospitalization and improvements in the quality of life, including enhanced exercise capacity and symptom control (8,19,44). Additionally, the decrease in hospitalizations lessens the healthcare system burden and mitigates costs (34). Although the benefits of ARNI in HFpEF remain poorly understood, its potential role in this subgroup emphasizes the need for further research to identify its influence across all HF phenotypes.

Beyond ARNI therapy, the management of congestive HF continues to evolve with optimizing volume control strategies. Duta *et al* (10) demonstrated the use of acetazolamide in combination with loop diuretics to enhance decongestive therapy. This combinatorial approach not only augments natriuresis but also addresses diuretic resistance, which is a challenge in HF management. Although ARNI has demonstrated beneficial effects on hemodynamics and renal function, residual congestion remains a clinical concern in a subset of patients. Therefore, integrating ARNI therapy with advanced decongestive regimens may offer synergistic benefits, particularly in patients with persistent volume overload. Future research should explore how ARNI and adjunctive diuretic strategies can be co-optimized to maximize clinical outcomes while minimizing renal and hemodynamic complications.

The effective use of ARNI necessitates precise dosing and careful patient monitoring to optimize outcomes and minimize risks. Initial therapy typically starts with 49/51 mg sacubitril/valsartan twice daily, with a lower dose of 24/26 mg twice daily recommended for patients with significant renal impairment or hypotension history (8,33). The dose is subsequently titrated to a target of 97/103 mg twice daily for 2-4 weeks, as tolerated, to optimize therapeutic benefits and minimize AEs, including hypotension, hyperkalemia or renal dysfunction (8,9). Regular BP, serum electrolyte and renal function monitoring is crucial during titration and throughout therapy, with dose adjustments tailored to patient needs, particularly in the presence of comorbidities (47,48). Park *et al* (49) reported that compared with enalapril and ARBs, sacubitril/valsartan is a cost-effective treatment for HFrEF. This supports its use as a clinically valuable and economically sustainablealternative for cardiologists and decision-makers in selecting therapeutic approaches (49).

Multiple clinical factors predict hypotension risk during ARNI therapy, informing targeted treatment decisions. To minimize this risk, sacubitril/valsartan should be initiated at a low dose (25-50 mg once daily), with close BP monitoring and titrated every 2-4 weeks to a target of 100-150 mg twice daily as tolerated (50). Caution is required in older adult patients, those with arteriosclerosis or those with advanced renal impairment, where reduced renal perfusion increases susceptibility to hypotension and GFR decline (51). To avoid excessively low BP and protect renal function, the use of other antihypertensive drugs, including calcium channel blockers, diuretics and α- and β-blockers, should be decreased. These approaches optimize the renal benefits of ARNI through NP action. Furthermore, multivariate analysis has identified baseline atrial fibrillation, a higher blood urea nitrogen/creatinine (BUN/Cr) ratio and lower SBP as significant independent predictors of hypotension following ARNI administration (52). Recognizing these risk factors allows clinicians to more safely and effectively tailor therapy.

The present study benefits from a large sample size (>20,000 patients), adherence to the PRISMA guidelines and rigorous risk-of-bias assessment, enhancing the reliability and generalizability of the findings. It confirms the efficacy

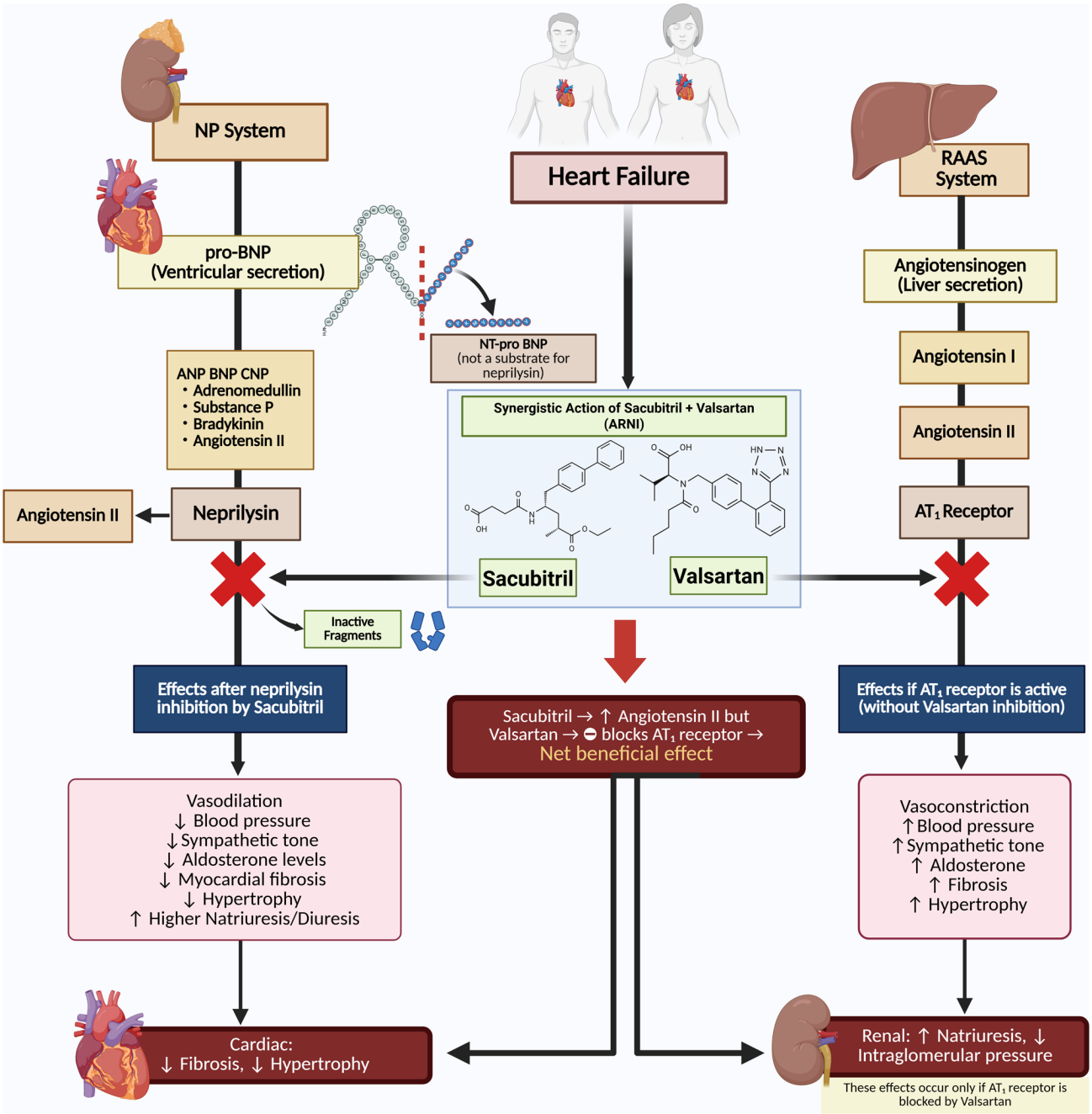


Figure 7. Mechanisms of ARNI in heart failure. ANP, atrial natriuretic peptide; ARNI, angiotensin receptor-neprilysin inhibitor; AT, angiotensin; CNP, C-type natriuretic peptide; NT-proBNP, N-terminal prohormone of brain type natriuretic peptide; RAAS, renin-angiotensin-aldosterone system.

and safety of ARNI in decreasing cardiovascular-associated and all-cause mortality, hospitalization and renal impairment across HF spectrums. Subgroup analyses were conducted to explore potential heterogeneity. Additionally, meta-regression analysis was performed to decrease bias by analyzing the influence of variables, including age, sex, NT-proBNP levels, LVEF, HR, SBP, BMI, eGFR and sCr levels, on outcomes, facilitating more accurate identification of potential confounding factors. However, the present study had limitations. Heterogeneity in the follow-up durations across trials may affect the comparability of the outcomes. The underrepresentation of populations with HFmrEF limits the robustness of the conclusions for this subgroup. The absence of meta-regression accounting for patient comorbidities, including diabetes, chronic kidney disease or atrial fibrillation, prevents a more nuanced interpretation of treatment effects. Fourth, although the overall bias was low, three studies demonstrated some concerns and one exhibited high risk of bias, which may influence the pooled estimates. The predominance of studies conducted in high-income Western countries may limit the generalizability to diverse global populations with differing clinical practices and healthcare infrastructures. A further limitation is the predominant reliance on eGFR to assess renal outcomes. While several studies reported additional parameters, including serum Cr (28,33,34) and urinary albumin-to-creatinine ratio (31), BUN was not consistently included as a diagnostic endpoint across trials. Future research should implement standardized

renal outcome measures that incorporate a broader range of biomarkers to facilitate more comprehensive and clinically relevant assessment of renal function.

ARNIs significantly improve clinical outcomes in patients with HF across the spectrum of EF phenotypes, particularly in reducing all-cause and cardiovascular-associated mortality, HF-associated hospitalization and renal impairment. However, the increased risk of hypotension necessitates close monitoring and targeted dose adjustment. The present findings support the broader adoption of ARNI in HF management, focusing on patient-specific characteristics, including renal function, sex and baseline BP. Future large-scale trials in diverse populations, including underrepresented HF phenotypes and resource-limited settings, are warranted to validate and extend these findings.

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**Availability of data and materials**

The data generated in the present study are included in the figures and/or tables of this article.

**Authors' contribution**

DDCHR, SCS, KCT, INK, BI, AI and MAE designed the study. DDCHR, SCS, KCT, JAJMNL, INK and MAE conceived the study and performed the literature review. DDCHR assessed the risk of bias. JAJMNL and SHR confirm the authenticity of all the raw data.. DDCHR, SCS, JAJMNL, SHR, INK, BI and AI analyzed and interpreted data. DDCHR, SCS, INK, BI, AI, and MAE wrote the manuscript. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Use of artificial intelligence tools**

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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