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RESEARCH ARTICLE

Angiotensin receptor neprilysin inhibitors and renal outcomes in patients with heart failure: a systematic review and meta-analysis

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Abstract

Introduction Angiotensin receptor neprilysin inhibitors (ARNi) significantly improve cardiovascular outcomes in patients with heart failure (HF). Their effects on kidney function in this population remain incompletely characterized. A systematic review and meta-analysis were performed to explore the impact of ARNi on renal outcomes.

Methods MEDLINE, Embase, and PubMed databases were searched for randomized trials comparing ARNi with renin–angiotensin–aldosterone system inhibitors (RAASi) alone. Outcomes included the incidence of worsening renal function, hyperkalaemia, hypotension, >50% decrease in eGFR, end-stage renal disease, rise in serum creatinine >2.5 mg/dl, and acute kidney injury. Risk of bias was assessed using the ROB 2.0 tool.

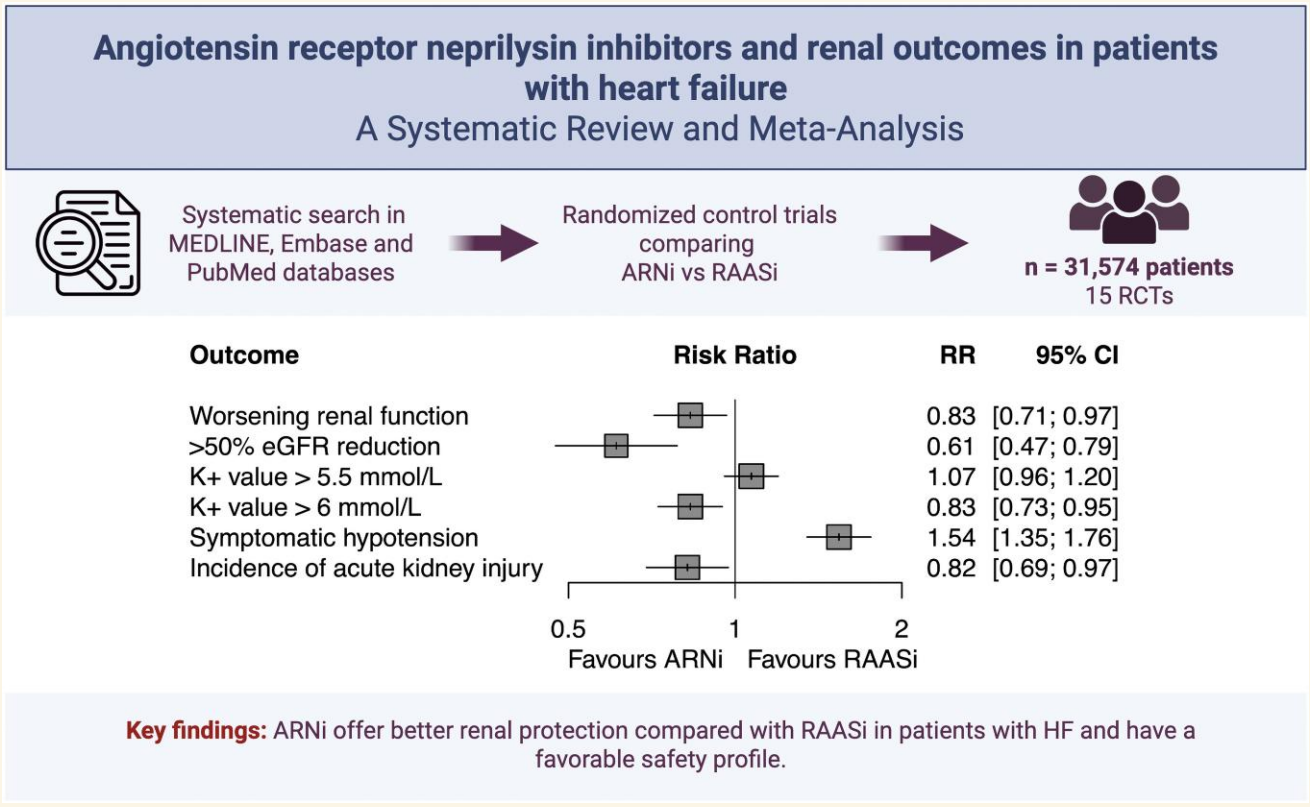
Results Fifteen studies with 31 574 individuals were included. Mean age was 67 years and 33% were female. ARNi significantly reduced the incidence of worsening renal function events [relative risk (RR): 0.83, 95% confidence interval (CI): 0.71–0.96; $P = .01$], corresponding to 13 fewer events per 1000 patients. ARNi were also associated with a lower risk of >50% decline in eGFR (RR: 0.61, 95% CI: 0.47–0.78; $P < .001$) and acute kidney injury events (RR: 0.82, 95% CI: 0.69–0.97; $P = .024$) compared with RAASi alone. There was no significant difference in the incidence of hyperkalaemia >5.5 mmol/L between groups, while ARNi were associated with a higher incidence of symptomatic hypotension (RR: 1.54, CI 95%: 1.35–1.76; $I^2 = 69\%$; $P < .001$).

Conclusions ARNi are associated with a lower risk of adverse renal outcomes compared with RAASi in patients with heart failure. However, this benefit should be interpreted alongside an increased risk of symptomatic hypotension.

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Graphical Abstract



In 15 RCTs (n = 31,574), ARNi compared with RAASi alone reduced the risk of worsening renal function, >50% eGFR decline, severe hyperkalemia and acute kidney injury in patients with heart failure, but increased the risk of symptomatic hypotension.

Keywords ARNi • Renal outcomes • Heart failure • Systematic review

Introduction

Heart failure (HF) affects more than 40 million people worldwide and constitutes one of the leading causes of hospitalization.[1,2] Almost half of patients with HF have concomitant chronic kidney disease (CKD), as the two conditions share many common risk factors, such as age, hypertension, diabetes, and coronary artery disease.[3] The presence of worsening renal function (WRF) among patients with HF is associated with worse patient outcomes and increased mortality.[4]

The disruption of the neurohormonal axis through activation of the sympathetic nervous system and/or the renin–angiotensin–aldosterone system (RAAS), is one of the mechanisms that contribute to the progression of HF and CKD.[5] Counter-regulatory hormones, the natriuretic peptides, are secreted in response to increased myocardial pressure and volume overload to counterbalance those systems. They promote natriuresis, diuresis, have vasodilatory effects, and inhibit aldosterone and renin secretion thereby counteracting the sodium-retaining properties of aldosterone.[6] However, in most stages of heart failure, there is renal resistance to these natriuretic effects, which appears to be caused partially by increased renal endopeptidase activity.[7]

Neprilysin [also known as neutral endopeptidase (NEP)] is the key enzyme responsible for degradation of natriuretic peptides.[8] Neprilysin inhibition results in potent natriuresis and diuresis.[9,10] In the kidney, its vasodilatory effect reduces intraglomerular pressure and proteinuria.[7] NEP inhibitors (NEPi) combined with RAAS inhibitors (RAASi) address the two pathophysiological mechanisms underlying heart failure: activation of RAAS and decreased sensitivity to natriuretic peptides.

Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNi), is the only neprilysin-inhibiting therapy currently used in clinical practice for patients with HF. Omapatrilat, a medication combining neprilysin inhibition with angiotensin-converting enzyme inhibition (ACEi), was also previously evaluated in patients with HF but is no longer clinically available (for that reason, we will refer to both medications as 'ARNi' throughout the text, for simplicity). Together, these agents provide evidence on the renal effects of neprilysin inhibition combined with RAAS modulation, although omapatrilat represents pharmacologically and clinically indirect evidence compared with sacubitril/valsartan. Sacubitril/valsartan is currently recommended by both the European and the American guidelines for the treatment of patients with HF with reduced ejection fraction (HFrEF).[11,12] In a pre-specified pooled analysis of the two landmark trials, PARADIGM-HF [ejection fraction (EF) eligibility ≤ 40%] and PARAGON-HF (EF eligibility ≥ 45%), sacubitril/valsartan significantly reduced hospitalizations and cardiovascular death.[13] However, the impact of ARNi regarding kidney outcomes and kidney-related adverse events is not clear. The secondary renal outcomes reported in HF trials are conflicting.[14–16] Previous meta-analyses investigating the effect of ARNi in the kidneys are either outdated[17] or have combined studies with heterogeneous populations (HF, hypertension, CKD) and thus their results are not directly applicable to patients with HF.

Our aim was to perform a contemporary systematic review and meta-analysis to examine the current evidence from randomized control trials (RCTs) with ARNi (sacubitril/valsartan or omapatrilat) on renal outcomes in patients with heart failure with reduced or preserved ejection fraction.

Methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Material).[18] This study was registered in the Prospective International Register of Systematic Reviews (PROSPERO, 2020 CRD42020197341). All data used and analyses performed were based on previously published studies, thus ethical approval was not required.

Search strategy

The research question was structured using the PICOT (Population, Intervention, Comparison, Outcomes, Type of studies) question frame. The search strategies were developed by a medical librarian to identify RCTs comparing sacubitril/valsartan or omapatrilat with RAASi, and were peer reviewed by a second librarian. Although omapatrilat differs pharmacologically from sacubitril/valsartan and is no longer used clinically, these trials were included because they evaluate the broader therapeutic strategy of neprilysin inhibition combined with RAAS inhibition compared with RAAS inhibition alone. Given the mechanistic focus of this review on renal outcomes associated with neprilysin inhibition added to RAAS modulation, omapatrilat studies were considered relevant. We searched MEDLINE, Embase (via Ovid), and PubMed (limited to the last week of records, to ensure completeness of coverage). The full search strategy is provided in the Supplementary Material. Forward and backward citation searching for included studies and previous systematic reviews was performed. Endnote's duplicate detection function was used to detect duplicates.

Study selection

Clinical studies were eligible if they met the following inclusion criteria: (i) RCTs that compared sacubitril/valsartan or omapatrilat with a RAASi; (ii) the study population should be patients with heart failure with reduced, mid-range, or preserved ejection fraction; (iii) renal outcomes and/or adverse events should be provided; and (iv) articles should be published in peer-reviewed journals with full text available.

We excluded animal studies, review articles, case reports, letters, editorials, congress abstracts, studies in individuals aged <18 years, or studies done in non-heart failure populations.

Records were uploaded to a systematic review web application (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Three independent investigators (C.K.T., R.N.A., and S.J.) screened the titles and abstracts of all identified articles and when required, reviewed full-text manuscripts to identify relevant studies for inclusion. Disagreements were resolved by discussion and if consensus could not be reached a third senior investigator (A.A. or T.A.M.) was consulted.

Outcomes

The primary outcome was the incidence of worsening renal function, as it was defined in each study. Secondary outcomes were (i) hyperkalaemia, (ii) hypotension, (iii) distinct renal outcomes [>50% decrease in eGFR, end-stage renal disease (ESRD)], (iv) rise in serum creatinine value >2.5 mg/dl, and (v) acute kidney injury.

Data collection and extraction

The full text and supplement of included studies was reviewed by three independent investigators (R.N.A., S.J., or C.K.T.) who extracted data in an excel spreadsheet using the same protocol. Discrepancies were resolved by discussion and by consulting a third investigator (A.A. or T.A.M.). For one study in which numerical data were not reported in the text, values were extracted from graphical information using appropriate image analysis software. (Webplotdigitizer: Version 4.6. Pacifica, California, USA). The use of this software results in a small absolute difference from the true values and has excellent consistency. According to Burda *et al.*[19] it can be used in systematic reviews as it has a small margin of error. Data concerning number of patients, baseline characteristics and the definition of the primary outcome (WRF) used in each study, are presented in *Table 1*. The number of events for each outcome of interest was extracted.

Quality assessment

The quality of the included studies was assessed by R.N.A., S.J., and A.A. using Cochrane Risk of Bias 2 assessment tool (ROB 2.0) for RCTs.[20] The GRADE approach was used to rate confidence in effect estimates.[21] The initial rating for RCTs was high and decreased in presence of serious risk of bias, inconsistency, indirectness, imprecision, or when publication bias was likely.

Statistical analysis

The principal summary measure was the relative risk (RR) with associated 95% confidence intervals. A random-effects model with the standard Der Simonian & Laird approach was used to estimate the pooled RR for each outcome.[22] Results were presented in a forest plot. Treatment effect modification was explored for the primary outcome and for the secondary renal outcomes by CKD status, using interaction terms. The between-study heterogeneity was assessed using Cochran's Q test and Higgins I^2 statistic with 0%, <25%, 25%49%, and > 50% denoting no, low, moderate, and high heterogeneity, respectively. In cases of high statistical heterogeneity, sensitivity analyses were performed by removing one study each time to explore the consistency of the results ('leave-one-out sensitivity analysis', Supplementary Material). We also conducted subgroup analysis and meta-regression to explore the impact of different possible moderators on the primary outcome. In the subgroup analyses, the Breslow-Day-Cochran test was used to test for consistency of the treatment effect across the subgroups. Meta-regression was performed using a mixed-effects method that accounts for both within-study and between-study variability. We used the risk in the placebo group, along with the pooled relative risk for overall patients at long-term follow-up from the systematic review, to calculate the absolute effect estimates in our evidence summaries (*Table 2*). Statistical analyses were performed using Stata (version 18 SE; College Station, TX) and meta, metafor packages in R Studio (R Foundation for Statistical Computing).

Results

Study selection

A total of 10 042 studies were retrieved (1621 from MEDLINE, 8 418 from EMBASE and 3 from PubMed; database search up to 30 September 2025). After duplicates removal, 9 736 studies remained for screening and 28 studies were included for full text review. Another study was identified through citation search. Finally, 15 RCTs (20 publications) were included in the systematic review and meta-analysis.[14–16,23–34] Full study selection process is shown in Supplementary Figure S1. A list of excluded studies that met a number, but not all, of the inclusion criteria is available in the Supplementary Material.

Characteristics of included studies

A total of 31 574 individuals were enrolled in 15 trials. The characteristics of the included studies are presented in *Table 1*. For this table, information from the main publication for each trial was used. For some of the outcomes mentioned below, data from subsequent publications were used and this explains minor differences in the denominator for these outcomes. Nine trials included patients with HFrEF (EF ≤ 40%),[14,15,23–25,29–31,33] four with HFmrEF and HFpEF (EF ≥ 40%),[16,26,27,32] one with EF = 25%–49%,[28] and one trial included patients irrespective of EF value.[34] Thirteen trials used sacubitril/valsartan

Table 1 **Characteristics of the included studies**

Study	Number of participants (*n*)	Drug in experimental arm	Drug in control arm	Follow-up duration (months)	Baseline EF	Mean age (years)	Male (%)	Baseline eGFR (ml/min/1.73 m^2)	Definition of worsening renal function
IMPRESS	573	Omapatrilat	Lisinopril	6	'Decreased'	64	79	N/A	Raised concentrations of serum creatinine (>1.5 times baseline and >0.8 times limit of normal)
PARADIGM-HF	8399	S/V	Enalapril	27	≤35%	64	78	N/A	Time to the first occurrence of a decline in renal function (which was defined as end-stage renal disease or as a decrease in the eGFR of at least 50% or a decrease of more than 30 ml/min/per 1.73 m^2 from randomization to less than 60 ml per minute per 1.73 m^2)
OUTSTEP-HF	621	S/V	Enalapril	3	≤40%	67	79	N/A	Serum creatinine increase 25%–49% compared to baseline
OVERTURE	5770	Omapatrilat	Enalapril	15	≤30%	63	79	N/A	Impaired renal function reported as adverse event
PIONEER-HF	881	S/V	Valsartan	2	≤40%	62	72	59.0	Worsening renal function (increase in the serum creatinine concentration of 0.5 mg per decilitre or more (≥44 µmol per litre) and a decrease in the eGFR of 25% or more
PARAGON-HF	4796	S/V	Valsartan	35	≥45%	73	48	63.0	Renal composite outcome was defined (death from renal failure, end-stage renal disease, or a decrease in the estimated glomerular filtration rate of 50% or more from baseline)
PARAMOUNT	301	S/V	Valsartan	9	≥45%	71	44	65.5	WRF was determined by change in serum creatinine and was defined as >0.3 mg/dl increase in creatinine in combination with an increase of more than 25% in serum creatinine between two time points.
PRIME	118	S/V	Valsartan	12	25%–<50%	63	61	N/A	Serum creatinine >2.5 mg/dl
EVALUATE-HF	464	S/V	Enalapril	3	≤40%	67	77	70.0	Worsening renal function defined as decrease in eGFR of ≥35% or increase in serum creatinine of ≥ 0.5 mg/dl from baseline AND decrease in eGFR of ≥25% from baseline
PARALLEL-HF	223	S/V	Enalapril	6	≤35%	68	86	58.0	Renal impairment (not defined more specifically)
LIFE	335	S/V	Valsartan	6	≤35%	59	73	64.7	Worsening kidney function defined as estimated glomerular filtration rate less than 20 ml/min/1.73 m^2 between randomization and week 24
PARALLAX	2566	S/V	Valsartan or enalapril	6	≥40%	72	38	62.6	Glomerular filtration rate decreased

Continued

Table 1 *Continued*

Study	Number of participants (*n*)	Drug in experimental arm	Drug in control arm	Follow-up duration (months)	Baseline EF	Mean age (years)	Male (%)	Baseline eGFR (ml/min/1.73 m^2)	Definition of worsening renal function
PARAGLIDE-HF	466	S/V	Valsartan	8	≥40%	72	48	49.3	Composite endpoint of worsening renal function, defined as renal death, reaching end-stage renal disease or >50% decline in eGFR relative to baseline.
PARADISE-MI	5661	S/V	Ramipril	22	≤40%	64	76	72.0	Renal impairment (broad standardized Medical Dictionary for Regulatory Activities queries)
PREMIER	400	S/V	ACEi or ARB	2	Any EF	76	68	51.7	At least a 50% increase in serum creatinine level or a 30% decline in eGFR

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; EF, ejection fraction; eGFR, estimated glomerular filtration rate; N/A, not available; S/V, sacubitril/valsartan; WRF, worsening renal function.

in the experimental group while two trials used omapatrilat. In the control group an ACEi was used in seven trials, an angiotensin II receptor blocker (ARB) in six, while in two trials either an ARB or an ACEi was used. Three trials reported the primary outcome stratified by eGFR status (eGFR ≥ 60 ml/min/1.73 m^2; eGFR < 60 ml/min/1.73 m^2). The definition of worsening renal function, our primary outcome, in each study can be found in *Table 1*.

Quality assessment for included studies

The overall risk of bias in the included RCTs was low indicating good methodological quality. An overview of the ROB 2.0 tool for the assessment of the RCTs can be found in Supplementary Figure S2.

Pairwise meta-analysis

Primary outcome

The primary outcome of worsening renal function was assessed in all the included studies. ARNi were associated with lower incidence of WRF events (RR: 0.83, CI 95%: 0.71–0.96; $I^2 = 53.3\%$; $P = .013$; *Figure 1*). In absolute terms, this corresponded to 13 fewer WRF events per 1000 patients treated (95% CI: 3 fewer to 21 fewer).

Secondary outcomes

Hyperkalaemia

There was no significant difference in the incidence of hyperkalaemia > 5.5 mmol/L between the two groups (RR: 1.07, CI 95%: 0.96–1.20; $I^2 = 47.5\%$; $P = .228$; *Figure 2*), corresponding to 10 more events per 1000 patients treated (95% CI: 6 fewer to 29 more). However, ARNi were associated with a lower incidence of hyperkalaemia > 6 mmol/L (RR: 0.83, CI 95%: 0.72–0.94; $I^2 = 0.0\%$; $P = .005$; Supplementary Figure S3), corresponding to 7 fewer events per 1000 patients treated (95% CI: 3 fewer to 12 fewer). These results are in accordance with prior meta-analyses.[35]

Hypotension

Angiotensin receptor neprilysin inhibitors were associated with more events of symptomatic hypotension (as defined in each study) (RR: 1.54, CI 95%: 1.35–1.76; $I^2 = 69\%$; $P < .001$; *Figure 3*), corresponding to 64 more events per 1000 patients treated (95% CI: 42 more to 90 more). ARNi were also associated with more events of a systolic blood pressure < 90 mmHg value (RR: 1.85, CI 95%: 1.43–2.38; $I^2 = 0.0\%$; $P < .001$; Supplementary Figure S4), corresponding to 16 more events per 1000 patients treated (95% CI: 8 more to 26 more).

Renal-specific outcomes

A decline > 50% in eGFR occurred less frequently with ARNi (RR: 0.61, CI 95%: 0.47–0.78; $I^2 = 2.3\%$; $P < .001$; *Figure 4*), corresponding to 8 fewer events per 1000 patients treated (95% CI: 4 fewer to 10 fewer). The incidence of progression to ESRD was similar between the two groups (RR: 0.77, CI 95%: 0.40–1.47; $I^2 = 45.6\%$; $P = .426$; Supplementary Figure S5), corresponding to 2 fewer events per 1000 patients treated (95% CI: 4 fewer to 3 more).

ARNi were associated with a lower incidence of a creatinine > 2.5 mg/dl value (RR: 0.84, CI 95%: 0.73–0.97; $I^2 = 0.0\%$; $P = .019$; Supplementary Figure S6), corresponding to 6 fewer events per 1000 patients treated (95% CI: 1 fewer to 10 fewer).

Acute kidney injury events occurred less frequently in the ARNi group than in the RAASi group (RR: 0.82, CI 95%: 0.69–0.97; $I^2 = 0.0\%$; $P = .024$; *Figure 5*).

Sensitivity analyses

Sensitivity analyses using the leave-one-out method, showed that the results of our primary analysis for the vast majority of the outcomes

Table 2 **Clinical outcomes by treatment strategy and certainty of evidence**

Outcome	Study group	ARNi vs RAASi RR (95% CI)	Absolut effect estimate	Quality of evidence
Worsening renal function		0.83 (0.71, 0.96)	13 fewer per 1000 (95% CI 3 fewer, 21 fewer)	MODERATE[a] Serious indirectness
K^+ > 5.5 mmol/L		1.07 (0.96, 1.20)	10 more per 1000 (95% CI 29 more, 6 fewer)	MODERATE[b] Likely reporting bias
K^+ > 6 mmol/L		0.83 (0.72, 0.94)	7 fewer per 1000 (95% CI 3 fewer, 12 fewer)	HIGH
Symptomatic hypotension		1.54 (1.35, 1.76)	64 more per 1000 (95% CI 90 more, 42 more)	HIGH
SBP < 90 mmHg		1.85 (1.43, 2.38)	16 more per 1000 (95% CI 26 more, 8 more)	HIGH
>50% reduction in eGFR		0.61 (0.47, 0.78)	8 fewer per 1000 (95% CI 4 fewer, 10 fewer)	HIGH
ESRD		0.77 (0.40, 1.47)	2 fewer per 1000 (95% CI 3 more, 4 fewer)	HIGH
creatinine > 2.5 mg/dl		0.84 (0.73, 0.97)	6 fewer per 1000 (95% CI 1 fewer, 10 fewer)	HIGH
creatinine > 3 mg/dl		0.80 (0.63, 1.00)	3 fewer per 1000 (95% CI 0 fewer, 6 fewer)	HIGH
Worsening renal function	eGFR < 60 ml/min/1.73 m^2	0.69 (0.52, 0.91)	12 fewer per 1000 (95% CI 4 fewer, 19 fewer)	MODERATE[a] Serious indirectness
	eGFR ≥ 60 ml/min/1.73 m^2	0.86 (0.57, 1.30)	4 fewer per 1000 (95% CI 9 more, 13 fewer)	LOW
>50% reduction in eGFR	eGFR < 60 ml/min/1.73 m^2	0.54 (0.29, 1.00)	8 fewer per 1000 (95% CI 0 fewer, 12 fewer)	MODERATE Serious imprecision
	eGFR ≥ 60 ml/min/1.73 m^2	0.62 (0.39, 0.99)	5 fewer per 1000 (95% CI 0 fewer, 9 fewer)	HIGH
ESRD	eGFR < 60 ml/min/1.73 m^2	0.59 (0.29, 1.20)	3 fewer per 1000 (95% CI 2 more, 6 fewer)	MODERATE Serious imprecision
	eGFR ≥ 60 ml/min/1.73 m^2	0.59 (0.07, 4.99)	1 fewer per 1000 (95% CI 7 more, 2 fewer)	MODERATE Serious imprecision

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RR, relative risk; SBP, systolic blood pressure.
[a]Serious indirectness: The definition of composite renal outcome was highly variable between the studies.
[b]Likely reporting bias: There is asymmetry in the funnel plot. However, Egger's test is not significant.

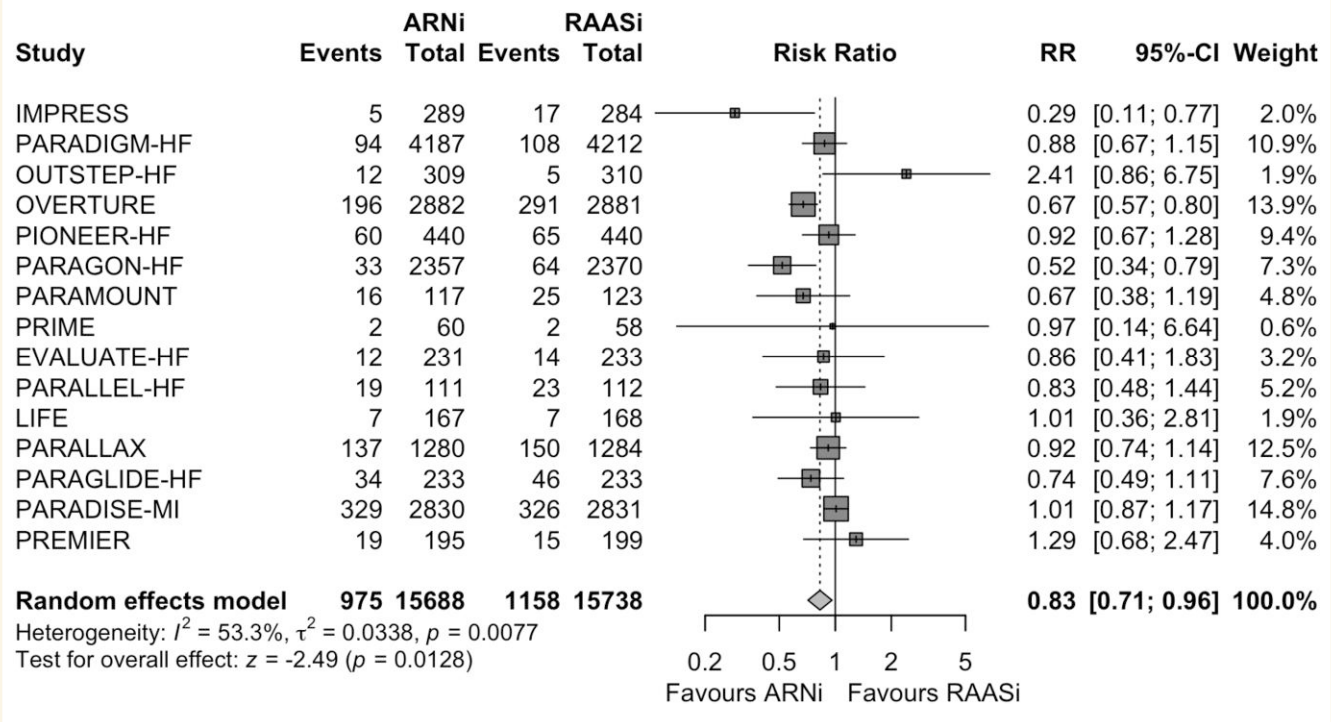


Figure 1 Forest plot of the primary outcome of worsening renal function

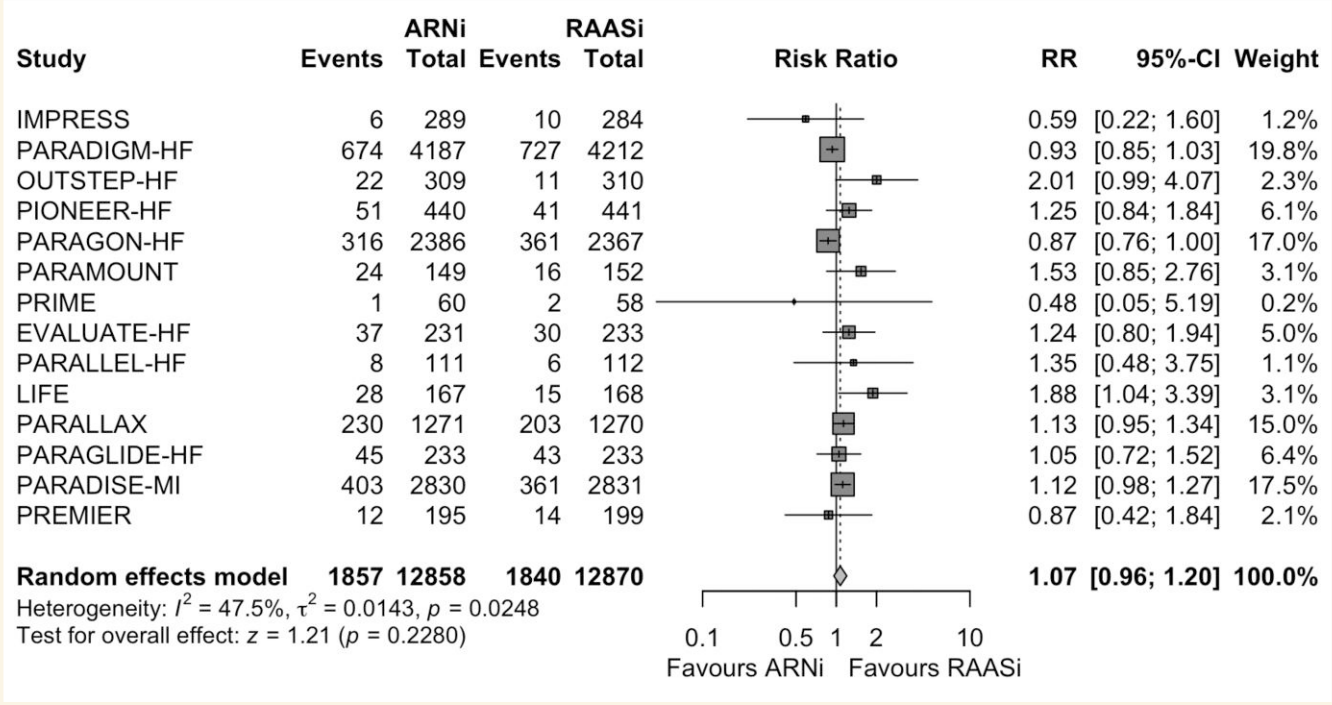


Figure 2 Forest plot of K+ value > 5.5 mmol/L

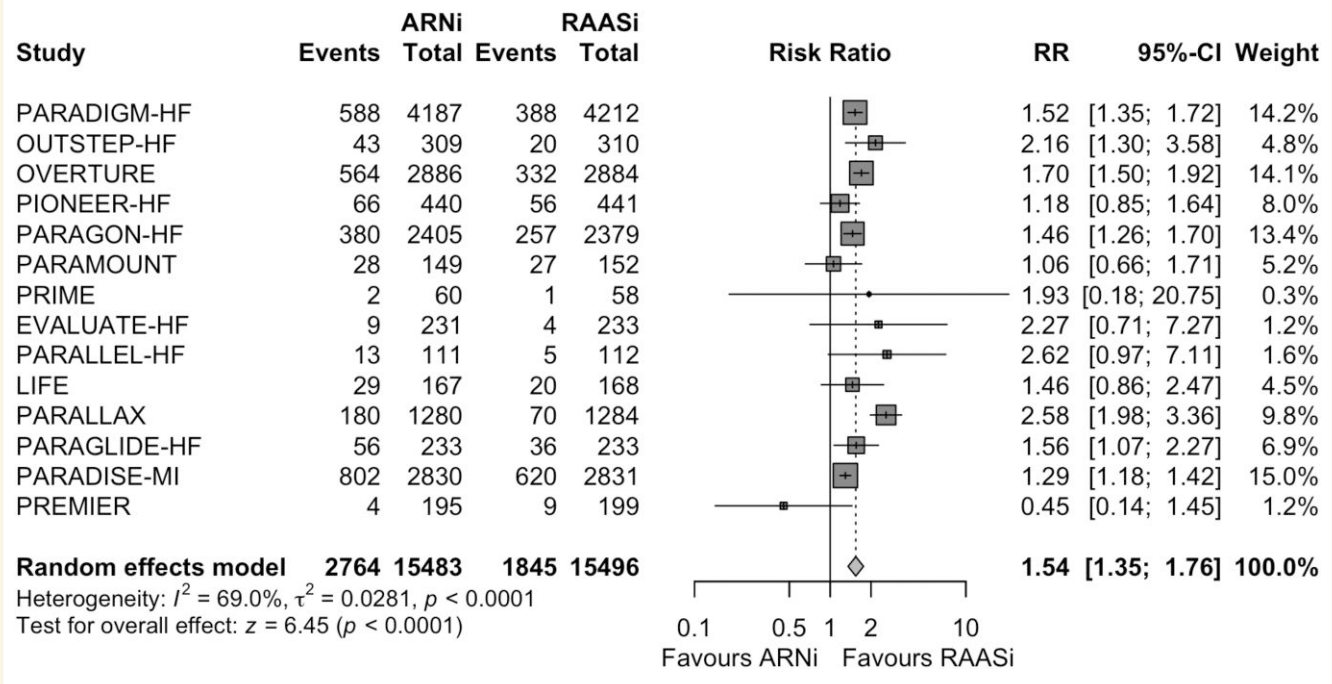


Figure 3 Forest plot of symptomatic hypotension

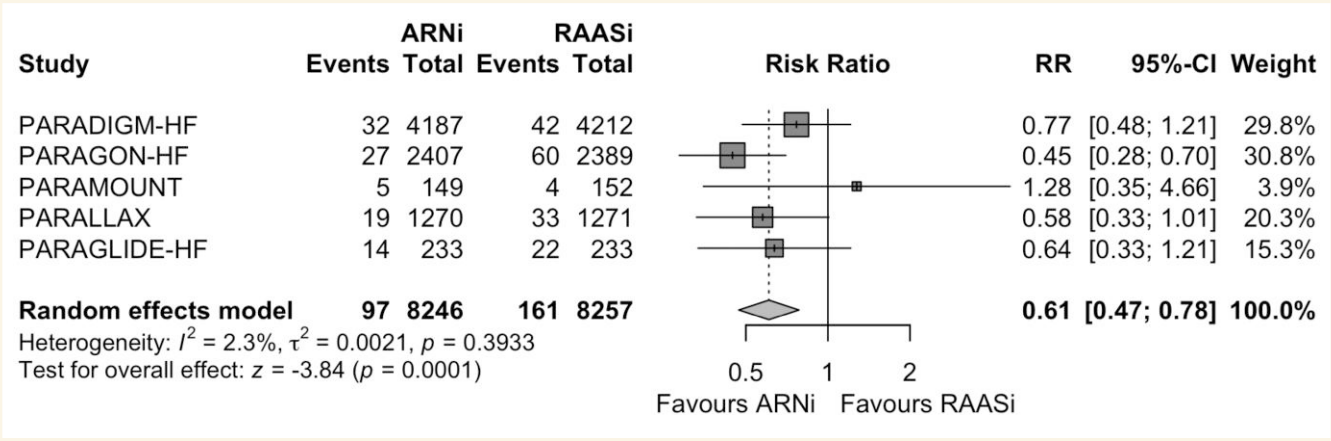


Figure 4 Forest plot of >50% eGFR reduction

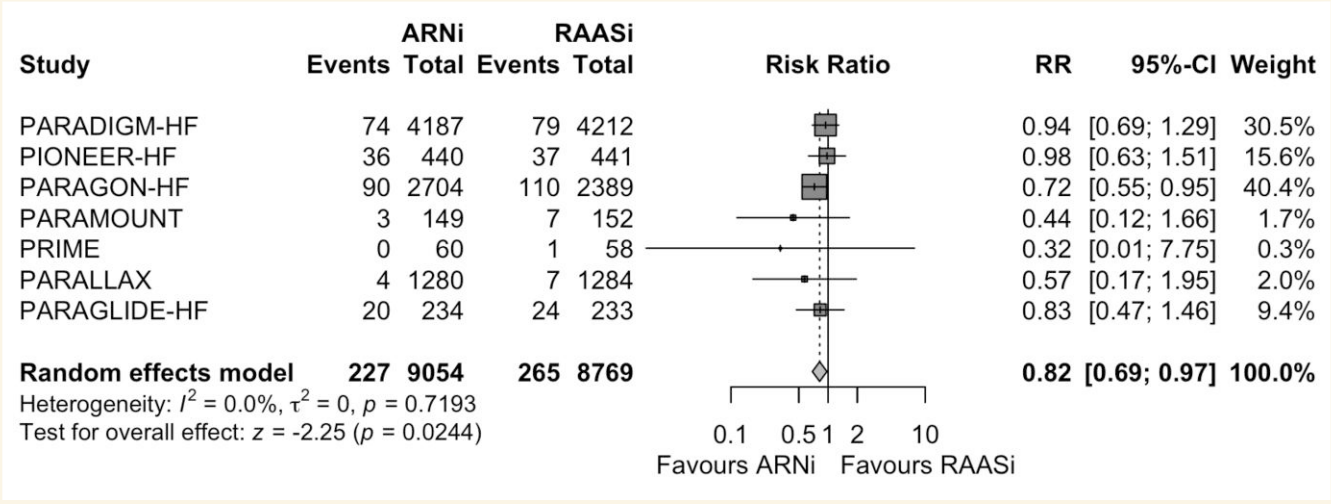


Figure 5 Forest plot of incidence of acute kidney injury

are robust. Only for the outcome of a $K^+ > 6$ mmol/L value the difference between the two groups became not significant by omitting the PARADIGM-HF study (RR: 0.89, CI 95%: 0.74–1.07; $P = .200$). The forest plots of the sensitivity analyses can be found in the supplementary material.

Treatment effect modification by CKD status

Primary outcome by CKD status

Angiotensin receptor neprilysin inhibitors were associated with lower incidence of WRF events in patients with eGFR < 60 ml/min/1.73 m^2 (RR: 0.69, CI 95%: 0.52–0.91; $I^2 = 0.0\%$; $P = .009$; *Figure 6*), while in patients with eGFR ≥ 60 ml/min/1.73 m^2, the difference was not significant (RR: 0.86, CI 95%: 0.57–1.30; $I^2 = 55.9\%$; $P = .486$; *Figure 6*). There was a non-statistically significant interaction between CKD status and the effect of ARNi or RAASi on WRF (P interaction = .361).

Secondary distinct renal outcomes by CKD status

No significant interaction was found between CKD status and the effect of ARNi or RAASi on the reduction of >50% in eGFR (P interaction = .720, Supplementary Figure S10) and on the progression to ESRD (P interaction = .995, Supplementary Figure S11).

Subgroup analyses

Subgroup analyses were conducted to evaluate whether EF or the type of medication used in the control arm modified the treatment effect. Neither variable showed statistically significant treatment-effect modification for the primary outcome. All studies used the same target ARNi dose so we could not examine dose effects. The forest plots of the subgroup analyses performed are available in the Supplementary Material.

Meta-regression

Mixed effects univariate meta-regression was performed with baseline EF, BP, and eGFR being fitted as covariates in the model, one at a time.

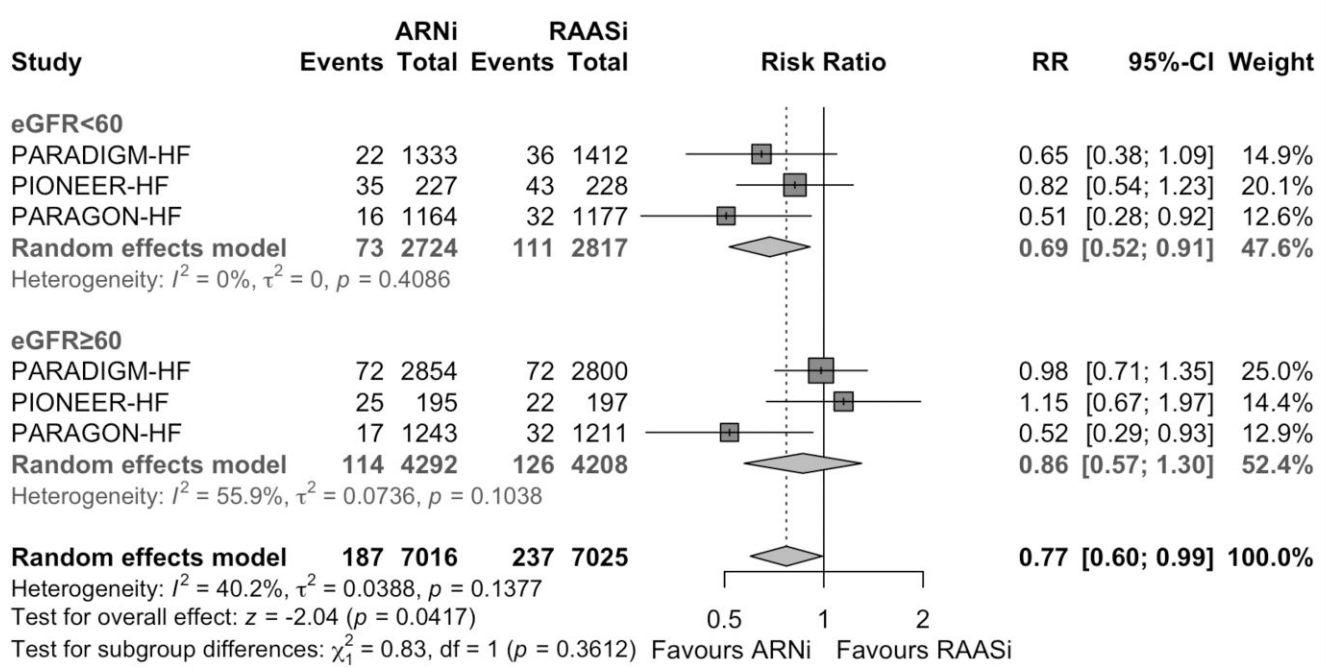


Figure 6 Forest plot of composite renal outcome by CKD status

While baseline EF had no effect on the primary outcome, there is a trend towards a lower incidence of WRF with ARNi for lower values of baseline eGFR and higher values of baseline blood pressure (see bubble plots in Supplementary Material).

Publication bias

Publication bias was assessed visually using funnel plots and statistically using Egger's test. No outcome showed statistically significant evidence of funnel plot asymmetry based on Egger's test (all *P*-values >.05), suggesting no clear evidence of publication bias.

Discussion

This systematic review and meta-analysis summarizes the current evidence regarding the effect of ARNi on renal outcomes in patients with heart failure. We showed that ARNi are associated with lower incidence of WRF events, severe hyperkalaemia ($K^+ > 6$ mmol/L), a >50% decline in eGFR and a creatinine value > 2.5 mg/dl. However, these benefits should be interpreted in the context of modest absolute risk reductions with no significant difference observed in progression to ESRD. ARNi treatment was also associated with a higher incidence of hypotensive episodes.

Renin angiotensin aldosterone system inhibitors have long been used for cardiorenal protection in patients with HF and CKD.[36,37] Their mechanism of ACE inhibition or angiotensin II receptor blockade has been proven to be beneficial on both heart and kidneys not only due to the antihypertensive effect but by also reducing renal remodelling and fibrosis.[38]

In the context of these known effects, several mechanisms may explain our findings. First, by improving heart function in both HFrEF and HFpEF, ARNi lead to better renal perfusion or less renal congestion. Natriuretic peptides have been shown to reduce cardiac hypertrophy and improve myocardial relaxation through cyclic guanosine monophosphate dependent pathways increasing the decreased preload in HFpEF.[27] At the same time, they promote natriuresis, vasodilation, and inhibit the sympathetic nervous system reducing the afterload in HFrEF.[39,40] Second, ARNi have different effects on renal haemodynamics. Both RAASi and ARNi can cause dilatation of the efferent arteriole, decreasing the intraglomerular pressure.[41,42] This reduction in intraglomerular pressure prevents glomerular hyperfiltration, which may explain the long-term beneficial renal effects with these agents. Nevertheless, under conditions of reduced renal blood flow, such as in HF, this could lead to rapid GFR reduction and hyperkalaemia.[43,44] On the other hand, natriuretic peptides lead to increased intraglomerular pressure via predominant dilation of the afferent arteriole, and increased GFR via mesangial cell relaxation and an increased filtration coefficient.[45] This improved renal perfusion in HF caused by ARNi, may be a reason for the lower incidence of selected adverse renal outcomes observed in this analysis. Third, natriuretic peptides promote natriuresis and diuresis by their direct effects on the renal tubules.[46] They inhibit angiotensin II in the proximal tubules,[47] they antagonize the actions of vasopressin in the cortical-collecting ducts,[48] and they block sodium absorption in the medullary-collecting duct.[49] Through these mechanisms, ARNi lower the blood pressure, which may contribute to the observed reduction in WRF, while also increasing the risk of hypotension.

We found that the incidence of WRF events in the subgroup of patients with baseline eGFR <60 ml/min/1.73 m^2 was significantly lower with ARNi, while in patients with eGFR ≥60 ml/min/1.73 m^2 there was no statistical difference between the two groups. This was also demonstrated by our meta-regression analysis that showed a trend of lower WRF events with ARNi for lower values of baseline eGFR.

Hyperkalaemia is a serious concern in HF and strategies to mitigate hyperkalaemia are very important, especially in those with worsening renal function.[50] The use of RAASi is associated with hyperkalaemia ($K^+ > 5$ mmol/L) in around 5% of patients receiving these drugs.[51] In our meta-analysis, patients on RAASi alone or ARNi had a similar

incidence of a serum potassium > 5.5 mmol/L. This threshold is relevant as the discontinuation of RAASi when potassium values are > 5.5 mmol/L has been associated with higher cardiovascular events and mortality.[52] A potassium value > 6 mmol/L, considered a more severe side effect as it increases the risk of cardiac arrhythmia, appears to occur less frequently with ARNi than with RAASi alone.

Symptomatic hypotension is an important concern for patients treated with ARNi. Our meta-analysis confirms that these drugs are associated with higher rates of symptomatic and asymptomatic hypotension, which is clinically relevant because hypotension may limit treatment initiation, dose optimization, and long-term tolerability. This concern is also reflected in clinical trials, where patients generally had to meet blood pressure and tolerability criteria before randomization or treatment initiation.[25] Nevertheless, Matsumoto *et al.*[53] reported that the treatment benefit of sacubitril/valsartan over enalapril was maintained even among patients who experienced asymptomatic or symptomatic hypotension. This effect is well recognized by the ESC HF guidelines that still recommend the use of ARNi as a replacement of RAASi in all HFrEF patients who can tolerate it, supporting careful patient selection and monitoring rather than avoidance of therapy.[11] Despite hypotension, the results from several of the included studies show that the trial completion rate was higher in the ARNi group and the percentage of trial discontinuation due to renal events was higher in the RAASi group.[15,26,33]

In our subgroup analysis, WRF events were found to be significantly less with ARNi in patients with EF > 40%, while there was not significant difference in patients with EF ≤40%. Nevertheless, the test of interaction between the subgroups was not significant ($P_{interaction}$ = .350) and meta-regression did not suggest a significant influence of EF on the treatment effect. These findings suggest that the association between ARNi and lower WRF risk was not clearly modified by EF category in our analysis. However, HF phenotypes differ in their underlying pathophysiology, comorbidity burden, haemodynamic profile, and response to disease-modifying therapies, and therefore subgroup analyses by EF should be interpreted cautiously. In particular, HFpEF and HFmrEF populations are more heterogeneous than HFrEF populations, which may limit the generalizability of pooled estimates across the full HF spectrum. In a previous meta-analysis, Zheng *et al.*[35] reported similar results in their subgroup analysis of WRF events by EF, but no test for interaction or meta-regression was presented, although they discuss EF as a modifier of the treatment effect.

High baseline blood pressure appeared to be associated with lower WRF events in the ARNi group compared with RAASi. A possible explanation could be that in patients with higher baseline blood pressure the potent antihypertensive effect of ARNi did not cause excessive hypotension and the associated harmful effects on the kidneys.

Other meta-analyses have compared ARNi vs RAASi in terms of renal outcomes. However, the majority of these meta-analyses were not specific for HF populations and pooled studies conducted in patients with underlying CKD or hypertension as well.[35,54–57] Two previous meta-analyses of renal outcomes in HF populations comparing ARNi and RAASi have been conducted.[58,59] The study by Shi *et al.*[59] included both RCTs and observational studies so direct comparisons are not appropriate. Chen *et al.*[58] included six studies and looked only at one composite renal outcome which was in accordance with our primary outcome result. We present a larger meta-analysis with more updated studies included (15 RCTs with 31 574 patients vs 18 553 patients in the larger of the prior meta-analyses) and more diverse renal outcomes of interest, showing that ARNi are associated with lower rates of worsening renal function and selected renal outcomes, rather than a uniform benefit across all renal endpoints. In our study, we explored heterogeneity with methods (meta-regression) that have not been previously reported in analyses on this subject. We found the risk of bias of the included studies was low.

We do acknowledge some limitations of our study. The definition of the primary outcome varied across the included RCTs. Although the direction of effect was generally consistent across the definition types in exploratory analyses, this variability remains an important source of clinical heterogeneity and may have introduced outcome misclassification, and the pooled estimate should therefore be interpreted with caution. All the secondary outcomes, though, were very specific and the findings support the result of the composite outcome. Omapatrilat trials provide mechanistically informative but clinically indirect evidence, and the findings should be interpreted primarily in relation to sacubitril/valsartan, the only currently available ARNi. Not all studies included all outcomes and thus caution should be exercised when generalizing some results. High heterogeneity was present in some of the outcomes, so we used random-effects models and performed sensitivity analyses that ensured consistency of our findings and stability of the results. In addition, because this meta-analysis was based on aggregate published data rather than individual patient-level data, we were unable to adjust for patient-level factors that may influence renal outcomes, including baseline kidney function, blood pressure, comorbidities, and background HF therapies. Similar to other meta-analyses, differences in methodological quality of each study, publication bias and the exclusion of studies that lacked reporting of the renal outcomes of interest may have contributed to bias in our results. For outcomes extracted from figures, minor measurement error may also have been introduced despite the use of validated digital extraction software. Most of the HF studies we included pre-dated the use of newer therapeutic agents, such as sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists and even glucagon-like-peptide-1 receptor agonist, so renal outcomes may be different with these contemporary therapies given their benefit on cardiovascular and renal outcomes. In addition, follow-up duration varied substantially across the included trials, and shorter studies may not fully capture long-term renal effects, particularly outcomes such as sustained eGFR decline or progression to ESRD. Finally, pooling studies across different HF phenotypes, including HFrEF, HFmrEF, and HFpEF, may have introduced clinical heterogeneity given differences in pathophysiology, comorbidity burden, and expected treatment response across EF categories. These factors should be considered when interpreting the generalizability of our findings to current HF management.

The association of ARNi with urine albumin-to-creatinine ratio was considered, but only two of the included trials (PARADIGM-HF and PARAMOUNT) reported on this outcome. As a result, we did not formally explore this analysis. The impact of dosing would warrant further investigation given the potential differences between males and females and dose of therapies that modulate the RAAS pathways.

In conclusion, ARNi, in addition to their established cardiovascular benefits, were associated with a lower risk of worsening renal function and selected adverse renal outcomes compared with RAASi alone in patients with HF. However, these renal benefits were modest in absolute terms and should be balanced against the increased risk of symptomatic hypotension. These findings support the use of ARNi as part of standard HF management when tolerated.

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Supplementary data

Supplementary data are available at *ESC Heart Failure* online.

Declarations

Disclosure of Interest

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Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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