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Efficacy and safety of combined neprilysin and RAS inhibition in heart failure: A meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Concerns about safety make physicians reluctant to prescribe neprilysin-renin-angiotensin system (RAS) inhibitors. This meta-analysis was performed to assess the efficacy and safety of combined neprilysin and RAS inhibition in heart failure.
Background: Combined inhibitors of neprilysin and RAS reduced heart failure hospitalization and cardiovascular death. While adverse events of neprilysin-RAS inhibitors in clinical trials are still controversial.
Methods: Medline, the Cochrane Library and Clinicaltrials.gov were searched for randomized controlled trials (RCTs). Twelve studies covering 21,212 patients were eligible for inclusion.
Results: Compared with RAS inhibition, neprilysin-RAS inhibition had a significant decrease in the mortality of heart failure [Odds Ratio (OR) 0.84; 95% Confidence Interval (CI) 0.78–0.91; $P < 0.05$], cardiovascular death (OR 0.78; 95% CI 0.69–0.88; $P < 0.05$), all-cause death (OR 0.86; 95% CI 0.79–0.93; $P < 0.05$) and the occurrence of renal dysfunction (OR 0.78; 95% CI 0.63–0.96; $P < 0.05$). The incidence of hypotension (OR 1.44; 95% CI 1.15–1.80; $P < 0.05$) and dizziness (OR 1.46; 95% CI 1.32–1.62; $P < 0.05$) was obviously increased in neprilysin-RAS inhibition compared with RAS inhibition. There were no significant differences in any adverse events, serious adverse events, myocardial ischemia, angioedema, hyperkalemia, fatigure, cough, gastrointestinal disorders and infections compared neprilysin-RAS inhibition with RAS inhibition alone.
Conclusions: The available evidence are supportive of the use of combined neprilysin and RAS inhibition in heart failure with close observation of blood pressure.

1. Introduction

Neprilysin is one of the key enzymes responsible for the breakdown of natriuretic peptides and angiotensin II [1]. Neprilysin inhibitors can increase the levels of natriuretic peptides and angiotensin II, which provides the rationale for combined inhibition of neprilysin and the renin-angiotensin system(RAS) [1,2]. Therefore, simultaneous inhibition of neprilysin and RAS has beneficial effects in heart failure.

Omapatrilat is a single molecule that inhibits neprilysin and the RAS, which can cause a significant reduction in blood pressure and reduce the risk of death and hospitalization in chronic heart failure. However, omapatrilat was reported to increase the risks of angioedema [3].

LCZ696(sacubitril-valsartan), a first-in-class angiotensin receptor-neprilysin inhibitor(ARNI), has been demonstrated to reduce blood pressure and heart failure hospitalization. However, in the recent PARADIGM-HF trial, LCZ696 has a lower risk of angioedema and a higher proportion of hypotensive patients than omapatrilat [4].

Combined inhibitors of neprilysin and the RAS, LCZ696 and omapatrilat, have been confirmed the potential therapeutic value in hypertension and heart failure, but incidences of adverse events reported in individual clinical trial are still controversial [3–7]. Concerns about efficacy and safety make physicians reluctant to prescribe neprilysin-RAS inhibitors. We therefore performed this meta-analysis to assess the efficacy and safety of combined neprilysin and RAS inhibition in heart failure.

2. Methods

2.1. Search strategy

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines to conduct this meta-analysis. We searched Medline, the Cochrane Library of Trials, and Clinicaltrials.gov to identify the published or unpublished randomized controlled trials (RCTs) in any language from March 1998 to January 2019. The following search terms were used: neprilysin inhibitor, LCZ696, sacubitril-valsartan, entresto, omapatrilat.

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2.2. Selection criteria

The inclusion criteria were as follows: the clinical trial was a randomized controlled trial (RCTs); ARB was used in the control group; trials reported safety outcomes.

The exclusion criteria were: the trial was not RCTs; the trial was without safety assessments; reviews; case reports; abstracts.

2.3. Study selection and quality assessment

Two reviewers (Geng, Li) independently assessed the RCTs that met the inclusion criteria. Discrepancies were resolved by consensus. The risk of bias was estimated by using the Cochrane classification with the following parameters: sequence generation, concealment of group allocation, blinding during outcome assessment, selective reporting and intention-to-treat analysis. A flow diagram is shown in Fig. 1.

For risk of bias assessment, we also used the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) tool to assess the quality of evidence for each outcome [8].

2.4. Data extraction

The following data were extracted: publication year, study design, random sequence generation, blinding method, age, total number, duration of therapy, all-cause death, cardiovascular death, heart failure, myocardial ischemia, renal dysfunction, edema, hypotension, hyperkalemia, discontinuation for any adverse events, dizziness, any adverse events, serious adverse events, fatigure, cough, abdominal pain, diarrhea, nausea, dyspepsia, headache, musculoskeletal and connective tissue disorders, influenza, nasopharyngitis, upper respiratory tract infection.

Six studies [4,5,7,9–11] reported all-cause death. Two studies [4,11] reported cardiovascular death. Five studies [4,5,7,9,10] reported heart failure. Six studies [4,5,9,10,13,14] reported myocardial ischemia. Myocardial ischemia included acute coronary syndrome, angina pectoris, angina unstable. Four studies [4,5,7,10] reported renal dysfunction. Seven studies [4–7,9–11,] reported edema. Six studies [4,5,7,9–11] reported hypotension. Four studies [4,5,7,11] reported hyperkalemia.

Other adverse effects included discontinuation for any adverse events, dizziness, any adverse events, serious adverse events, fatigure, cough, abdominal pain, diarrhea, nausea, dyspepsia, headache, musculoskeletal and connective tissue disorders, influenza, nasopharyngitis, upper respiratory tract [4–7,9–16].

2.5. Statistical analysis

This meta-analysis was performed by using Review Manager software (version 5.3; Cochrane Collaboration, Oxford, UK). Dichotomous variables were calculated by using the odds ratio (OR) based on the Mantel-Haenszel method. The statistics were presented with 95% confidence intervals(CI). The I^2 value were used to test the heterogeneity of the RCTs. Statistically significant heterogeneity was defined as $I^2 > 50\%$ and $P < 0.10$. When $I^2 > 50\%$ and $P < 0.10$, random effects model were used to analyze the data, whereas the fixed effects were used when $I^2 < 50\%$ and $P > 0.10$. Publication bias was assessed by a funnel plot. A two-sided P value <0.05 was considered statistically significant.

3. Results

A total of 2337 studies were initially identified. Twelve studies covering 21,212 patients were selected. Baseline characteristics of patients were summarized in Table 1 and Table S3.

Risk of bias in selected studies was summarized in Table S1. All studies in our meta-analysis were RCTs. All studies adopted random sequence generation, allocation concealment methods and intention-to-treat analysis. All studies reported blinding patients and blinding outcomes assessors. No studies had selective outcome reporting.

GRADE evidence profile was summarized in Fig. S1, Fig. S2 and Fig. S3.

All-cause death were reported in six studies covering 16,378 patients. The rate of all-cause death for neprilysin-RAS inhibition and RAS inhibition was 14.8% and 16.7%, respectively. The OR was statistically significant (OR 0.86; 95% CI 0.79–0.93; $P < 0.05$; Fig. 2 A).

Cardiovascular death were reported in two studies covering 8853 patients. The OR of cardiovascular death was statistically significant (OR 0.78; 95% CI 0.69–0.88; $P < 0.05$; Fig. 2 B).

Heart failure were reported in five studies covering 15,924 patients. The rate of heart failure for neprilysin-RAS inhibition and RAS inhibition was 18.2% and 20.9%, respectively. The OR was statistically significant (OR 0.84; 95% CI 0.78–0.91; $P < 0.05$; Fig. 2 C).

Myocardial ischemia were reported in six studies covering 17,638 patients. The OR of myocardial ischemia did not differ significantly (OR 0.96; 95% CI 0.84–1.10; $P > 0.05$; Fig. 2 D).

Renal dysfunction were reported in four studies covering 15,351 patients. The rate of renal dysfunction for neprilysin-RAS inhibition and RAS inhibition was 8.9% and 11.1%, respectively. The OR was statistically significant (OR 0.78; 95% CI 0.63–0.96; $P < 0.05$; Fig. 3 A).

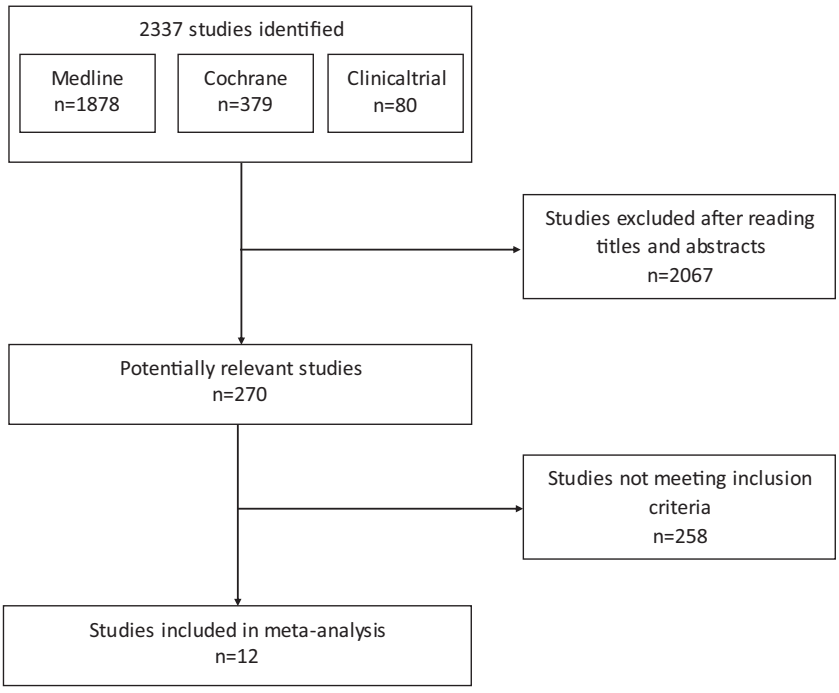


Fig. 1. Study selection flow diagram Initially, a total of 2337 studies were identified; of these, 2325 studies failed to meet the inclusion criteria, 12 studies were included in this meta-analysis.

Table 1
Baseline characteristics of trials included in meta-analysis.

Study	Neprilysin-RAS inhibitor	RAS inhibitor	Mean age(years)		No. of patients		Follow up(months)
			Neprilysin-RAS inhibitor	RAS inhibitor	Neprilysin-RAS inhibitor	RAS inhibitor	
IMPRESS 2000	Omapatrilat 40 mg/d	Lisinopril 20 mg/d	64.3	63.6	289	284	6
OVERTURE 2002	Omapatrilat 40 mg/d	Enalapril 20 mg/d	63.4	63.5	2886	2884	14.5
PARADIGM-HF 2014	LCZ696 400 mg/d	Enalapril 20 mg/d	63.8	63.8	4187	4212	27
PARAMETER 2017	LCZ696 200 mg/d	Olmesartan 20 mg/d	68.2	67.2	229	225	13
PARAMOUNT 2012	LCZ696 400 mg/d	Valsartan 320 mg/d	70.9	71.2	149	152	9
Ruilope LM 2010	LCZ696 100-400 mg/d	Valsartan 80-320 mg/d	53.0	53.0	497	493	2
The RATIO Study 2017	LCZ696 400 mg/d	Valsartan 320 mg/d	61.2	62.0	142	143	2
PIONEER-HF 2018	LCZ696 400 mg/d	Enalapril 20 mg/d	61.0	63.0	440	441	2
NCT01785472	LCZ696 200-400 mg/d	Olmesartan 20 mg/d	57.9	57.0.4	950	484	2
NCT01615198	LCZ696 100-400 mg/d	Olmesartan 10-40 mg/d	70.5	70.9	296	292	2
NCT01599104	LCZ696 200-400 mg/d	Olmesartan 20 mg/d	58.3	59.6	772	389	2
NCT01876368	LCZ696 200 mg/d	Olmesartan 20 mg/d	57.1	58.0	188	188	2

Edema were reported in seven studies covering 16,663 patients. The OR of edema did not differ significantly (OR 1.30; 95% CI 0.97–1.75; $P > 0.05$; Fig. 3 B).

Hypotension were reported in six studies covering 16,378 patients. The rate of hypotension for neprilysin-RAS inhibition and RAS inhibition was 17.6% and 11.8%, respectively. The OR was statistically significant (OR 1.44; 95% CI 1.15–1.80; $P < 0.05$; Fig. 3 C).

Hyperkalemia were reported in four studies covering 10,035 patients. There was no difference in hyperkalemia between neprilysin-RAS inhibition and RAS inhibition group (OR 0.95; 95% CI 0.86–1.06; $P > 0.05$; Fig. 3 D).

Discontinuations for any adverse events were reported in six studies covering 11,598 patients. Neprilysin-RAS inhibition had a significant decrease in discontinuation compared with RAS inhibition group (OR 0.81; 95% CI 0.66–0.99; $P < 0.05$; Table S2).

Dizziness were reported in eleven studies covering 20,051 patients. The OR was statistically significant (OR 1.46; 95% CI 1.32–1.62; $P < 0.05$; Table S2).

There were no significant differences in other adverse effects such as any adverse events, serious adverse events, fatigue, cough, abdominal pain, etc. (Table S2).

4. Discussion

Natriuretic peptides were secreted from heart in response to myocardial wall tension [17] and had natriuretic and diuretic effects. So, neprilysin inhibitors could be beneficial in heart failure by blocking the breakdown of natriuretic peptides. Our results showed that neprilysin-RAS inhibitors were more effective in reducing the risk of death from all causes and cardiovascular causes. In the present study, omapatrilat and sacubitril/valsartan, the inhibitor of neprilysin and RAS, had the potential to reduce the mortality of heart failure and had lower rate of discontinuation. The findings were consistent with PARADIGM-HF, PIONEER-HF and the meta-analysis by Solomon et al. [5] Both ACC/AHA and ESC guidelines for the management of heart failure had given sacubitril/valsartan a class I B recommendation [18,19], but physicians were still worried about the safety. This meta-analysis support the use of combined neprilysin and RAS inhibition in heart failure.

Zhao et al. [20] found that LCZ696 was more effective in reducing blood pressure and had an equal tolerability. As we all known, neprilysin-RAS inhibitors simultaneously blocked RAS activation and natriuretic peptides degradation so that they had a greater antihypertensive efficacy without increasing adverse events [21]. Because of its vasodilator effects, treatment with neprilysin-RAS inhibitors had higher rate of hypotension compared with RAS inhibitors (17.6% VS 11.8%). Therefore, a higher proportion of dizziness in neprilysin-RAS inhibition group may be related to the reduction of blood pressure. As in earlier studies [20], hypotension and dizziness were more frequent in patients with neprilysin-RAS inhibitors, which might need physicians to pay more attention.

In PARADIGM-HF study, ARNI may have beneficial effects on renal function and had lower proportions with renal impairment than enalapril. We also found neprilysin-RAS inhibitors could decrease the occurrence of renal dysfunction. These effects of neprilysin-RAS inhibitors have been confirmed in earlier studies [4,10,21]. Despite greater hypotensive effects, reports of worsening renal function were less frequent in neprilysin-RAS inhibition group. The reason why neprilysin-RAS inhibitors had protection from renal function was that they might increase renal perfusion because of improvement in cardiac function. In contrast, PIONEER-HF and PARAMOUNT trials reported that the rate of worsening renal function did not differ significantly between neprilysin-RAS inhibition and RAS inhibition alone. The conclusion need to be further confirmed by lager RCTs.

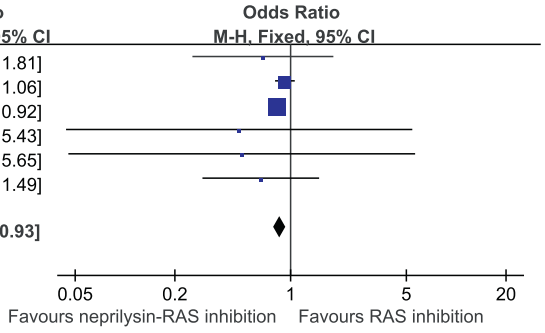
Li's meta-analysis and OCTAVE study found LCZ696 and omapatrilat could significantly increase the risks of angioedema [3,21] by participating in the accumulation of bradykinins. To our surprise, in the present study, neprilysin-RAS inhibitors had no effects on angioedema.

In our meta-analysis, there were no differences in myocardial ischemia, hyperkalemia, any adverse events, serious adverse events, fatigue, cough, gastrointestinal disorders, musculoskeletal and connective tissue disorders, infections between neprilysin-RAS inhibition and RAS inhibition alone. These findings were supportive of the prescription of neprilysin-RAS inhibitors in heart failure.

A all-cause death

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
IMPRESS 2000	7	289	10	284	0.9%	0.68 [0.26, 1.81]
OVERTURE 2002	477	2886	509	2884	37.1%	0.92 [0.81, 1.06]
PARADIGM-HF 2014	711	4187	835	4212	60.4%	0.83 [0.74, 0.92]
PARAMETER 2017	1	229	2	225	0.2%	0.49 [0.04, 5.43]
PARAMOUNT 2012	1	149	2	152	0.2%	0.51 [0.05, 5.65]
PIONEER-HF 2018	10	440	15	441	1.3%	0.66 [0.29, 1.49]
Total (95% CI)		**8180**		**8198**	**100.0%**	**0.86 [0.79, 0.93]**
Total events	1207		1373			

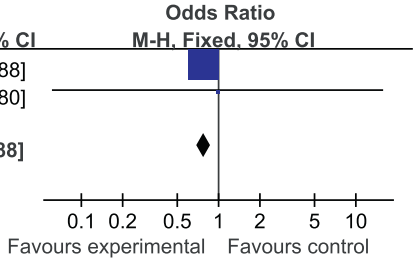
Heterogeneity: Chi² = 2.54, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0005)



B cardiovascular death

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
PARADIGM-HF 2014	558	4187	693	4212	99.8%	0.78 [0.69, 0.88]
PARAMETER 2017	1	229	1	225	0.2%	0.98 [0.06, 15.80]
Total (95% CI)		**4416**		**4437**	**100.0%**	**0.78 [0.69, 0.88]**
Total events	559		694			

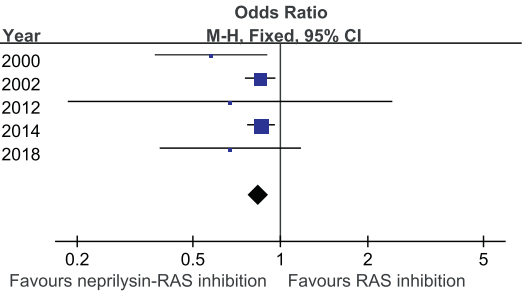
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 4.01 (P < 0.0001)



C heart failure

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
IMPRESS 2000	38	289	59	284	3.8%	0.58 [0.37, 0.90]	2000
OVERTURE 2002	653	2886	737	2884	42.5%	0.85 [0.75, 0.96]	2002
PARAMOUNT 2012	4	149	6	152	0.4%	0.67 [0.19, 2.43]	2012
PARADIGM-HF 2014	730	4187	832	4212	51.0%	0.86 [0.77, 0.96]	2014
PIONEER-HF 2018	22	440	32	441	2.3%	0.67 [0.38, 1.18]	2018
Total (95% CI)		**7951**		**7973**	**100.0%**	**0.84 [0.78, 0.91]**	
Total events	1447		1666				

Heterogeneity: Chi² = 3.63, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 4.34 (P < 0.0001)



D myocardial ischemia

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
IMPRESS 2000	21	289	21	284	4.6%	0.98 [0.52, 1.84]
NCT01599104	1	772	0	389	0.2%	1.51 [0.06, 37.27]
NCT01785472	0	950	1	484	0.5%	0.17 [0.01, 4.17]
OVERTURE 2002	238	2886	256	2884	55.5%	0.92 [0.77, 1.11]
PARADIGM-HF 2014	172	4187	170	4212	38.4%	1.02 [0.82, 1.26]
PARAMOUNT 2012	4	149	4	152	0.9%	1.02 [0.25, 4.16]
Total (95% CI)		**9233**		**8405**	**100.0%**	**0.96 [0.84, 1.10]**
Total events	436		452			

Heterogeneity: Chi² = 1.68, df = 5 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

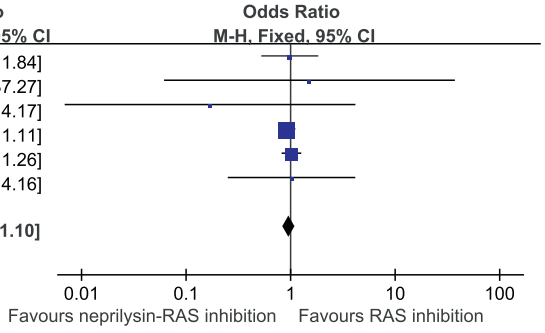
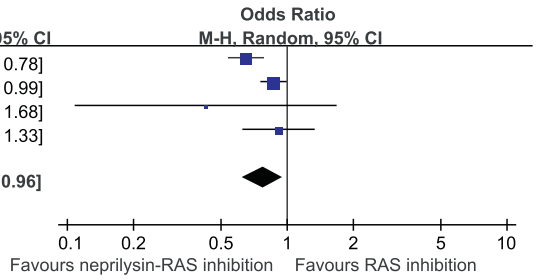


Fig. 2. Forest plots of all-cause death, cardiovascular death, heart failure and myocardial ischemia. **A.** The OR of all-cause death was statistically significant (OR 0.86; 95% CI 0.79–0.93; $P < 0.05$), the rate of death for neprilysin-RAS inhibition and RAS inhibition was 14.8% and 16.7%, respectively; **B.** The OR of cardiovascular death was statistically significant (OR 0.78; 95% CI 0.69–0.88; $P < 0.05$); **C.** The rate of heart failure for neprilysin-RAS inhibition and RAS inhibition was 18.2% and 20.9%, respectively. The OR was statistically significant (OR 0.84; 95% CI 0.78–0.91; $P < 0.05$); **D.** The OR of myocardial ischemia did not differ significantly (OR 0.96; 95% CI 0.84–1.10; $P > 0.05$).

A renal dysfunction

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
OVERTURE 2002	196	2886	291	2884	36.3%	0.65 [0.54, 0.78]
PARADIGM-HF 2014	426	4187	487	4212	41.9%	0.87 [0.75, 0.99]
PARAMOUNT 2012	3	149	7	152	2.3%	0.43 [0.11, 1.68]
PIONEER-HF 2018	60	440	65	441	19.5%	0.91 [0.63, 1.33]
Total (95% CI)		**7662**		**7689**	**100.0%**	**0.78 [0.63, 0.96]**
Total events	685		850			

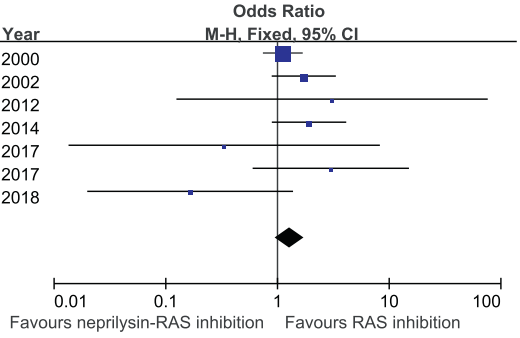
Heterogeneity: Tau² = 0.02; Chi² = 7.21, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 2.34 (P = 0.02)



B edema

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
IMPRESS 2000	60	289	54	284	56.1%	1.12 [0.74, 1.68]	2000
OVERTURE 2002	24	2886	14	2884	18.1%	1.72 [0.89, 3.33]	2002
PARAMOUNT 2012	1	149	0	152	0.6%	3.08 [0.12, 76.23]	2012
PARADIGM-HF 2014	19	4187	10	4212	12.9%	1.92 [0.89, 4.12]	2014
The RATIO Study 2017	0	142	1	143	1.9%	0.33 [0.01, 8.25]	2017
PARAMETER 2017	6	229	2	225	2.6%	3.00 [0.60, 15.02]	2017
PIONEER-HF 2018	1	440	6	441	7.8%	0.17 [0.02, 1.38]	2018
Total (95% CI)		**8322**		**8341**	**100.0%**	**1.30 [0.97, 1.75]**	
Total events	111		87				

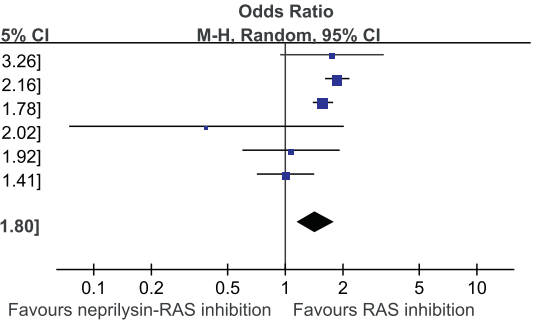
Heterogeneity: Chi² = 7.84, df = 6 (P = 0.25); I² = 23%
Test for overall effect: Z = 1.73 (P = 0.08)



C hypotension

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
IMPRESS 2000	29	289	17	284	9.3%	1.75 [0.94, 3.26]
OVERTURE 2002	564	2886	332	2884	29.4%	1.87 [1.61, 2.16]
PARADIGM-HF 2014	740	4187	506	4212	30.6%	1.57 [1.39, 1.78]
PARAMETER 2017	2	229	5	225	1.7%	0.39 [0.07, 2.02]
PARAMOUNT 2012	28	149	27	152	10.2%	1.07 [0.60, 1.92]
PIONEER-HF 2018	79	440	79	441	18.7%	1.00 [0.71, 1.41]
Total (95% CI)		**8180**		**8198**	**100.0%**	**1.44 [1.15, 1.80]**
Total events	1442		966			

Heterogeneity: Tau² = 0.04; Chi² = 16.12, df = 5 (P = 0.007); I² = 69%
Test for overall effect: Z = 3.21 (P = 0.001)



D hyperkalemia

Study or Subgroup	neprilysin-RAS inhibition Events	Total	RAS inhibition Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
PARADIGM-HF 2014	674	4187	727	4212	91.5%	0.92 [0.82, 1.03]
PARAMETER 2017	18	229	13	225	1.8%	1.39 [0.66, 2.91]
PARAMOUNT 2012	12	149	9	152	1.2%	1.39 [0.57, 3.41]
PIONEER-HF 2018	51	440	41	441	5.4%	1.28 [0.83, 1.97]
Total (95% CI)		**5005**		**5030**	**100.0%**	**0.95 [0.86, 1.06]**
Total events	755		790			

Heterogeneity: Chi² = 3.83, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.85 (P = 0.39)

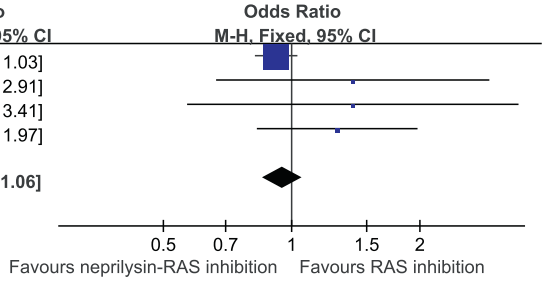


Fig. 3. Forest plots of renal dysfunction, edema, hypotension and hyperkalemia. **A.** The OR was statistically significant (OR 0.78; 95% CI 0.63–0.96; $P < 0.05$), the rate of renal dysfunction for neprilysin-RAS inhibition and RAS inhibition was 8.9% and 11.1%, respectively; **B.** The OR of edema did not differ significantly (OR 1.30; 95% CI 0.97–1.75; $P > 0.05$). **C.** The OR of hypotension was statistically significant (OR 1.44; 95% CI 1.15–1.80; $P < 0.05$), the rate of hypotension for neprilysin-RAS inhibition and RAS inhibition was 17.6% and 11.8%, respectively; **D.** There was no difference in hyperkalemia between neprilysin-RAS inhibition and RAS inhibition group (OR 0.95; 95% CI 0.86–1.06; $P > 0.05$).

There are several limitations in our meta-analysis. First, the follow-up period was different in each trial. The longest follow-up period was 27 months, and the shortest was 2 months. The follow-up is limited and the long-term efficacy and safety of sacubitril-valsartan is unknown. Second, the dosage of LCZ696 and RAS inhibitors was different in included trials. Further large-scale RCTs using the same dosages in

the treatment and control group are required. Third, cognitive impairment is an important side effect. But, the studies included in our meta-analysis did not report this.

In conclusion, our findings were significantly in favor of combined neprilysin and RAS inhibition over RAS inhibition alone. Neprilysin-RAS inhibitors could provide protection from congestive heart failure and renal insufficiency, and also had no risks of hyperkalemia and angioedema. This robust finding provides evidence that combined neprilysin and RAS inhibition is superior to RAS inhibition alone with close observation of blood pressure.

4.1. Clinical perspective

Compared with RAS inhibition, neprilysin-RAS inhibition had a significant decrease in the mortality of heart failure, cardiovascular death and the occurrence of renal dysfunction. However, the incidence of hypotension and dizziness was significantly higher in neprilysin-RAS inhibition group. The available evidence are supportive of the use of neprilysin-RAS inhibition in heart failure with close observation of blood pressure.

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Declaration of Competing Interest

All authors had access to the data and played a role in writing this manuscript. All authors had no financial interests in any commercial companies related to this study.

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