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Combined neprilysin and renin–angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis

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Aims The combined neprilysin/renin–angiotensin system (RAS) inhibitor sacubitril/valsartan reduced cardiovascular death or heart failure hospitalization, cardiovascular death, and all-cause mortality in a large outcomes trial. While sacubitril/valsartan is the only currently available drug in its class, there are two prior clinical trials in heart failure with omapatrilat, another combined neprilysin/RAS inhibitor. Using all available evidence can inform clinicians and policy-makers.

Methods and results We performed a meta-analysis using data from three trials in heart failure with reduced EF that compared combined neprilysin/RAS inhibition with RAS inhibition alone and reported clinical outcomes: IMPRESS ($n = 573$), OVERTURE ($n = 5770$), and PARADIGM-HF ($n = 8399$). We assessed the pooled hazard ratio (HR) for all-cause death or heart failure hospitalization, and for all-cause mortality in random-effects models, comparing combined neprilysin/RAS inhibition with ACE inhibition alone. The composite outcome of death or heart failure hospitalization was reduced numerically in patients receiving combined neprilysin/RAS inhibition in all three trials, with a pooled HR of 0.86, 95% confidence interval (CI) 0.76–0.97, $P = 0.013$. For the endpoint of all-cause mortality, the pooled HR was 0.88, 95% CI 0.80–0.98, $P = 0.021$. Combined neprilysin/RAS inhibition compared with ACE inhibition was associated with more hypotension, but less renal dysfunction and hyperkalaemia in all three trials.

Conclusions Pooled estimates from three trials with two separate drugs of combined neprilysin/RAS inhibition support the use of combined neprilysin/RAS inhibition in heart failure with reduced EF.

Keywords Heart failure • Neprilysin • Renin–angiotensin system • Meta-analysis

Introduction

Neprilysin, or neutral endopeptidase, an enzyme responsible for the breakdown of several vasoactive peptides including the biologically active natriuretic peptides, has long been a potential therapeutic target in heart failure. Neprilysin inhibition has been envisaged as a way to counteract abnormal neurohormonal activation by augmentation of endogenous mechanisms.[1,2] Several neprilysin inhibitors, including ecadotril, racecadotril, and candoxatril, have been tested in both heart failure and hypertension, with minimal efficacy.[3–5] That neprilysin also breaks down angiotensin II, with inhibition of neprilysin resulting in increases in angiotensin II levels,[6] is one potential explanation for the limited success of neprilysin inhibitors alone in both of these therapeutic areas, and provides the rationale for combined inhibition of both neprilysin and the renin–angiotensin system (RAS).[7,8]

Several pharmacological compounds that have combined neprilysin and RAS inhibitors have been developed and tested in humans, although only two have been compared with RAS inhibitors in heart failure—omapatrilat and sacubitril/valsartan

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(LCZ696). Omapatrilat, a single molecule that inhibits several proteases including neprilysin, ACE, and aminopeptidase, was originally developed for hypertension, yet showed promising results in a phase II heart failure trial.[9] Nevertheless, an outcomes trial with omapatrilat, the OVERTURE trial,[10] failed to meet its primary endpoint of death or heart failure hospitalization. While a post-hoc analysis using a slightly different and more contemporary definition of heart failure hospitalization was statistically significant, further development of omapatril was discontinued because of an increased incidence of angioedema, primarily observed in hypertension trials.[11]

In the recent PARADIGM-HF trial, sacubitril/valsartan,[12] designed to have less risk of angioedema, and tested in hypertension[13] and heart failure with preserved EF,[14] reduced the combined endpoint of cardiovascular death or heart failure hospitalization by 20%, reduced cardiovascular death by 20%, and reduced all-cause mortality by 16% compared with enalapril in heart failure with reduced ejection fraction.[15,16] While results from individual clinical trials are informative, meta-analyses of all available independent clinical trials of a new therapy may provide estimates of the effect of treatment on outcomes in a broader range of patients and therapies, and play a central role in comprehensive evidence-based decision-making. We therefore performed a meta-analysis of heart failure trials in which combined inhibitors of the RAS and neprilysin were compared with RAS inhibitors alone, and reported clinical outcomes.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] for the conduct and reporting of this meta-analysis. We searched Medline and Embase databases as well as the Cochrane Library of Trials, Clinicaltrials.gov, and Google for 'vasopeptidase,' 'endopeptidase', 'neutral endopeptidase', and 'neprilysin', and crossed this with 'heart failure', for mansucripts published in any language. After initially identifying 12 809 potential manuscripts or trials, standard filters were used to limit the search to include articles only with human participants, revealing 914 potential studies. Of these, reviews and studies that were not clinical trials were initially removed, leaving 110 potential trials. This search was supplemented by knowledge of each of the co-authors of trials in this field. Further culling of studies not involving heart failure patients, but in the disciplines of hypertension, asthma, and renal failure, left 25 potential trials. Each of these were reviewed by two authors who manually determined if the trials met the pre-specified criteria of a randomized controlled trial of a combined inhibitor of neprilysin and the RAS compared with an inhibitor of the RAS (ACE inhibitor or ARB) tested in patients with heart failure with reduced EF, with 50 or more participants that reported clinical outcomes. Trials were excluded if mortality was not a component of the pre-specified primary or secondary endpoint.

The primary outcome of this meta-analysis was the composite endpoint of death or heart failure hospitalization, which was reported in the earlier IMPRESS and OVERTURE trials. The hazard ratios (HRs) for these endpoints were obtained from published articles for IMPRESS and OVERTURE and from patient-level data in PARADIGM-HF. A secondary analysis was performed based on the post-hoc heart failure hospitalization endpoint in OVERTURE in which the use of oral diuretics was sufficient to define heart failure. For the outcome of mortality, HRs were available only for OVERTURE and PARADIGM-HF, and so we pooled the estimates from these two studies. As a sensitivity analysis, we utilized published event counts and calculated treatment effect odds ratios (ORs) for each of the three studies, and performed a meta-analysis of these OR estimates. We abstracted adverse event data from the following adverse events of particular interest: hypotension, renal dysfunction, and hyperkalaemia.

All meta-analyses were performed using random effects models.[18] We assessed for heterogeneity using the I^2 test ($I^2 \geq 25\%$ or corresponding P-value <0.10 was assumed to be a result of significant heterogeneity). Where $I^2 < 25\%$ and $P > 0.10$, we also report results from fixed-effects models as sensitivity analyses. Specific adverse events of interest, including hypotension, renal dysfunction or elevation in serum creatinine, and hyperkalaemia, are also reported for the three trials. The risk of bias for the studies utilized was assessed. All analyses were performed in STATA (College Station, TX, USA). All P-values were two-tailed with statistical significance specified at 0.05 and confidence intervals (CIs) reported at the 95% level.

Results

Three studies were identified that fulfilled the pre-specified criteria: IMPRESS,[9] OVERTURE,[10] and PARADIGM-HF.[16] The details and designs of the three trials have been reported. One additional study comparing the neprilysin inhibitor ecadotril alone with placebo, but on top of standard of care ACE inhibition or an ARB was considered, but was rejected by the authors because the doses of RAS inhibitors utilized were not pre-specified.

Briefly, IMPRESS randomized 573 patients to omapatrilat target dose 40 mg q.d. or lisinopril 20 mg q.d. Patients were followed for up to 24 weeks. The primary endpoint was improvement in maximum exercise treadmill test at week 12. Secondary endpoints included death and co-morbid events indicative of worsening heart failure. The OVERTURE trial was a randomized controlled outcomes trial of 5770 patients with NYHA class II–IV heart failure assigned to double-blind treatment with either the ACE inhibitor enalapril 10 mg b.i.d. or omapatrilat 40 mg q.d. for a mean of 14.5 months. The primary endpoint was the combined risk of death or hospitalization for heart failure requiring intravenous treatment. Hospitalization for heart failure was defined as an admission for or with worsening heart failure that required an intravenous treatment for the first 3 days. A secondary analysis was performed utilizing the SOLVD heart failure definition that did not require treatment with intravenous therapy. The PARADIGM-HF trial randomized 8399 patients to sacubitril/valsartan (LCZ696) 200 mg or enalapril 10 mg b.i.d. PARADIGM-HF employed an active run-in phase in which all patients received enalapril titrated to 10 mg b.i.d. followed by sacubitril/valsartan titrated to 200 mg b.i.d. Patients who tolerated run-in were randomized to enalapril 10 mg b.i.d. or sacubitril/valsartan 200 mg b.i.d. The average duration of follow-up was 27 months. The primary endpoint for PARADIGM-HF was a composite of cardiovascular death or heart failure hospitalization. Heart failure hospitalization was defined as an overnight stay at an acute care facility in which signs and symptoms of heart failure were present, in which patients were treated with heart failure therapy, including intensification of oral diuretics. The risk of bias was assessed in the three studies and generally

Table 1 **Baseline characteristics of the IMPRESS, OVERTURE, and PARADIGM-HF trials**

	IMPRESS		OVERTURE		PARADIGM-HF	
	Omapatrilat ($n = 289$)	Lisinopril ($n = 284$)	Omapatrilat ($n = 2886$)	Enalapril ($n = 2884$)	Sacubitril/valsartan ($n = 4817$)	Enalapril ($n = 4212$)
Age	64.3 ± 10.7	63.6 ± 10.0	63.4 ± 11.6	63.5 ± 11.9	63.8 ± 11.5	63.8 ± 11.3
Female sex	21%	21%	20%	22%	21%	22.6%
White race	82%	85%			66%	66%
NYHA class						
II	64%	62%	48%	48%	71.6%	69.3%
III	34%	38%	48%	48%	23.1%	24.9%
IV	1%	1%	4%	4%	0.8%	0.6%
LVEF (%)	28.4 ± 7.5	27.8 ± 7.5	23.5 ± 5.4	23.5 ± 5.3	29.6 ± 6.1	29.4 ± 6.3
Resting HR	79.6 ± 12.9	79.5 ± 14.8			72 ± 12	72 ± 12
Systolic blood pressure	126.6 ± 19.7	125.7 ± 17.8	123 ± 18	124 ± 18	122 ± 15	121 ± 15
Medications at baseline						
ACE inhibitors	99%	99%	90%	91%	78%	77.5%
ARBs	1%	1%	NR	NR	22.2%	22.9%
Diuretics	80%	81%	99%	99%	80.3%	80.1%
Beta-blockers	29%	31%	52%	51%	93.%	92.9%
Aldosterone antagonists	NR	NR	42%	42%	54.2%	57.0%

HR, heart rate; NR, not reported.

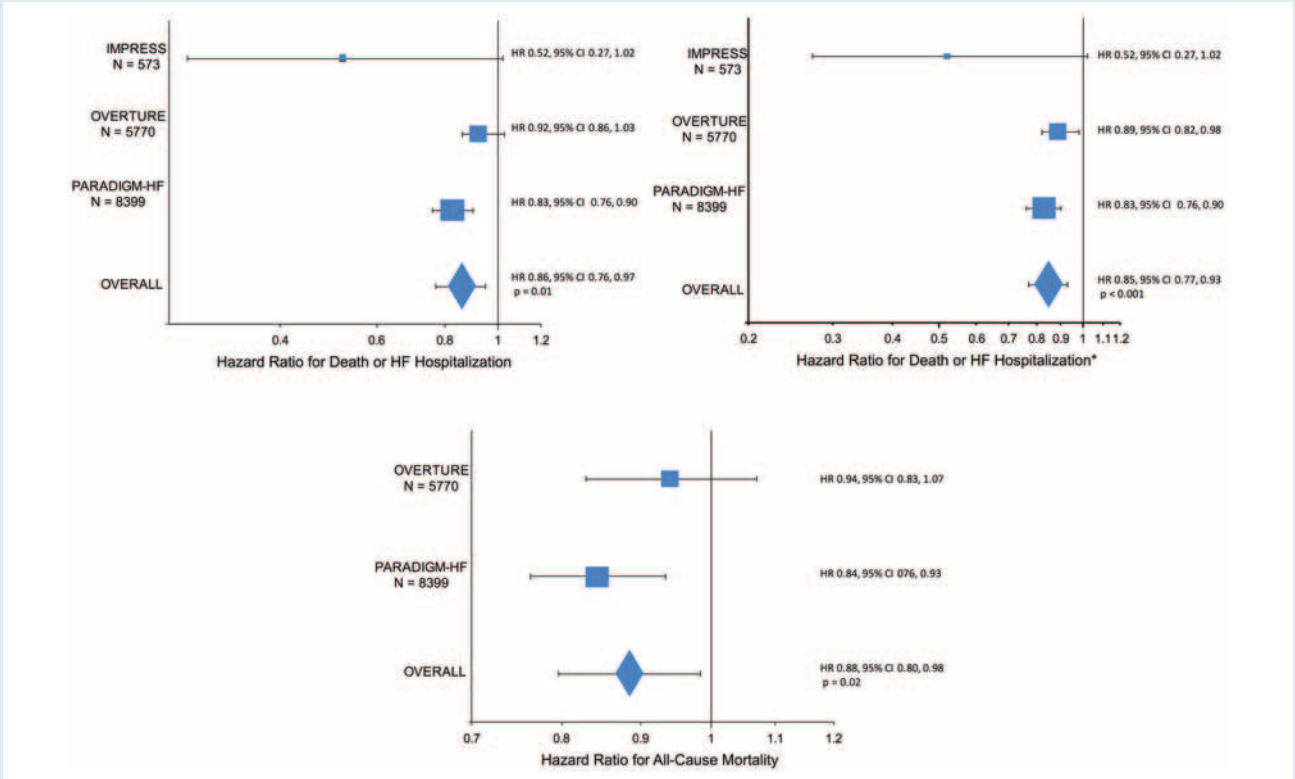

Figure 1 Forest plots showing random-effects meta-analyses from three trials of inhibitors of neprilysin/renin–angiotensin system, IMPRESS, OVERTURE, and PARADIGM-HF, for the following endpoints: all-cause death or heart failure (HF) hospitalization (upper left), all-cause death or HF hospitalization utilizing the revised endpoint in OVERTURE in which oral diuretics, rather than intravenous diuretics, were allowed for adjudication of HF hospitalization (upper right), and all-cause mortality (lower). CI, confidence interval; HR, hazard ratio.

Table 2 Adverse events of interest between trials

	IMPRESS		OVERTURE		PARADIGM-HF	
	Omapatrilat ($n = 289$)	Lisinopril ($n = 284$)	Omapatrilat ($n = 2886$)	Enalapril ($n = 2884$)	Sacubitril/valsartan ($n = 4817$)	Enalapril ($n = 4212$)
Symptomatic hypotension[a]	10%	6%	19.5%	11.5%	14%	9.2%
Creatinine elevation or impaired renal function[b]	1.8%	6.1%	6.8%	10.1%	3.3%	4.5%
Potassium elevation[c]	3.6%	2.1%	NR	NR	4.3%	5.6%

NR, not reported.
[a]Reported in IMPRESS as 'hypotension', in OVERTURE as 'hypotension', and in PARADIGM-HF as 'symptomatic hypotension'.
[b]Reported in IMPRESS as 'significantly elevated creatinine'; reported in OVERTURE as 'impaired renal function' ; reported in PARADIGM-HF as 'elevated serum creatinine >3.0 mg/dL'.
[c]Reported in IMPRESS as 'significantly elevated potassium'; not reported in OVERTURE; reported in PARADIGM-HF as 'elevated potassium >6.0 mg/dL'.

found to be low in each (see Supplementary material online, *Table S1*).

Reported baseline characteristics are shown for the three trials in *Table 1*. All trials were similar with respect to age and gender distribution. NYHA class was higher, and LVED was lower, in OVERTURE than in IMPRESS or PARADIGM-HF, whereas baseline systolic blood pressure was lower in PARADIGM-HF than in the other two trials. Medication use reflects changes in standard of care therapy for heart failure over the decade between the trials. Both beta-blocker use and mineralocorticoid receptor antagonist (MRA) use rose over time, with 92% of patients in PARADIGM-HF taking beta-blockers compared with only 30% in IMPRESS.

The composite outcome of death or heart failure hospitalization was reduced numerically in patients receiving combined neprilysin/RAS inhibition in all three trials (*Figure 1*), with a pooled HR of 0.86, 95% CI 0.76–0.97, $P = 0.013$ ($P = 0.07$ for heterogeneity; $I^2 = 62\%$). Utilizing the more contemporary definition of heart failure hospitalization allowing for hospitalization based on oral diuretics intensification in OVERTURE (as was done in PARADIGM-HF), the pooled HR was 0.85, 95% CI 0.77–0.93, $P = 0.001$ ($P = 0.17$ for heterogeneity; $I^2 = 44\%$). For the endpoint of all-cause mortality, the pooled HR based on two studies was 0.88, 95% CI 0.80–0.98, $P = 0.021$ ($P = 0.19$ for heterogeneity; $I^2 = 41\%$). The OR for mortality based on all three studies was 0.86, 95% CI 0.79–0.94, $P = 0.001$ in both random-effects and fixed-effects analyses $P = 0.42$ for heterogeneity; $I^2 = 0\%$).

Although adverse event reporting differed substantially between trials, all three trials provided data on hypotension, renal dysfunction or elevation in serum creatinine, and elevation in serum potassium. Combined neprilysin/RAS inhibition was associated with an increased risk of hypotension in all three trials, and a reduced incidence of renal dysfunction or elevation in serum creatinine, and less frequent elevation in serum potassium in all three trials (*Table 2*).

Discussion

Evidence-based medicine needs to consider the totality of evidence to understand potential heterogeneity of results and integration of available evidence to inform clinical practice. Sacubitril/valsartan is the first drug proven to be superior to enalapril for mortality reduction since the randomized clinical trials which first established the benefits of ACE inhibitor therapy in heart failure with reduced EF, and therefore appears to have the potential to improve the outcomes of patients with heart failure with reduced EF substantially. However, as PARADIGM-HF represents a single clinical trial which had an active treatment run-in phase and neprilysin inhibition represents a first-in-class novel therapeutic agent being applied to care, some have argued that additional trials data would be required for widespread adoption of this new therapy despite the robustness of the PARADIGM-HF results. Although there is no other combined neprilysin/RAS inhibitor currently available or in later stages of development, prior experience with agents in this class that have been tested in clinical trials may be informative. Combining data from the three trials of neprilysin/RAS inhibitors, the HRs and CIs found in this meta-analysis are comparable with those reported in PARADIGM-HF, with consistency across all three trials analysed. Despite differences in reporting, the major side effects were also similar between trials. These data further suggest, based on the totality of clinical trial evidence, that the addition of a neprilysin inhibitor to a RAS inhibitor is superior to an ACE inhibitor alone for reducing death or heart failure hospitalization as well as all-cause mortality.

Meta-analyses may provide additional evidence beyond that provided by individual studies.[19] The current standards for guideline generation generally reserve level (strength) of evidence A as requiring high-quality evidence from more than one randomized clinical trial, or meta-analyses of high quality randomized clinical trials.[20] Data from a single randomized clinical trial may be considered by some guidelines groups no higher than level of evidence B. Indeed both the recently published ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure and the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure have given sacubitril/valsartan a class IB recommendation,[21,22] and the Canadian guidelines position it similarly.[23] While the PARADIGM-HF data should be sufficient to inform the community about the benefits of combined neprilysin/RAS inhibition with sacubitril/valsartan compared with RAS inhibition alone, there has been intense debate regarding the need for additional trials or the limitations of generalizing the PARADIGM-HF results given the active run-in period.

While omapatrilat was not nearly as effective in OVERTURE as sacubitril/valsartan was in PARADIGM-HF, OVERTURE employed no run-in period, and the point estimates in OVERTURE and the pilot IMPRESS trial were both to the left of unity. While PARADIGM-HF does contribute the majority of data to this meta-analysis, OVERTURE was also large and also contributed substantially. That the net observed point estimate was significantly in favour of combined neprilysin/RAS inhibition despite the fact that the primary endpoint in OVERTURE was negative suggests that indeed this class of drugs as a whole may be effective, and provides further support for use of drugs in this class. While sacubitril/valsartan is currently the only neprilysin inhibitor/RAS inhibitor available, and while PARADIGM-HF provided the majority of data for this meta-analysis, additional agents in this broad class may be introduced in the years to come. As such, the additional information provided in this meta-analysis may be informative.

There are some clear differences between the therapeutic interventions, study designs, patient populations, background therapy, and endpoints in the three trials comprising this meta-analysis that may account for some of the disparities observed in the trials. Both omapatrilat and sacubitril/valsartan inhibit neprilysin, although omapatrilat is a less selective neprilysin inhibitor.[24] Moreover, in both omapatrilat studies, omapatrilat was dosed once daily, in comparison with twice-daily dosed enapapril, whereas in PARADIGM-HF, sacubitril/valsartan was dosed twice daily, which may have increased bioavailability of the drug throughout the day and reduced the likelihood of hypotensive events leading to withdrawal. While the decade between these studies was responsible for differences in background therapy, with substantially higher use of beta-blockers and MRAs in PARADIGM-HF than in the other two trials, these differences should, if anything, have worked against the new agent. PARADIGM-HF employed an active run-in phase, while the other two studies did not. This was designed to maximize the dose of the active comparator enalapril by ensuring tolerability prior to randomization, but has been criticized for potentially excluding patients who would not tolerate the drug and thus limiting the generalizability of the results. The findings of this meta-analysis which combined trials that did not employ this design should assuage these concerns somewhat. Although the OVERTURE trial fell short of its primary endpoint, the addition of heart failure hospitalizations in which oral rather than intravenous diuretics were administered, as was done in PARADIGM-HF and most modern heart failure clinical trials, resulted in a post-hoc statistically significant reduction in primary events. Regardless of which endpoint is used in the meta-analysis, the pooled ORs are significantly in favour of combined neprilysin/RAS inhibition for the composite endpoint and for all-cause mortality.

Omapatrilat was withdrawn from the market by the sponsor not based on the OVERTURE results, but because of the increased risk of serious angioedema observed in hypertension trials. This risk played a large role in the design and development of sacubitril/valsartan which, by not combining three proteases, was expected to have a lower risk for angioedema than omapatrilat. While other neprilysin inhibitors may be in early stage development, sacubitril/valsartan is the only currently available agent, recently approved in the USA, Europe, and many other countries. Thus, these combined results have direct clinical applicability only to the use of this agent.

Some limitations of this analysis should be noted. We acknowledge that this analysis is not a comprehensive systematic review but rather a meta-analysis of trials that met our pre-specified criteria: randomized controlled trials in heart failure comparing a combined neprilysin inhibitor/RAS inhibitor in heart failure with reduced EF, including at least 50 patients and reporting clinical outcomes of death and heart failure hospitalizations. We chose not to include smaller trials and those outside the therapeutic area of heart failure. This meta-analysis was based on published data in the case of both IMPRESS and OVERTURE, where patient-level data are not available, from either the investigators or the sponsor despite attempts to obtain them. Moreover, we acknowledge heterogeneity with respect to the drugs and dosages utilized in these studies, and differences in baseline risk, concurrent therapy, and the definitions of heart failure employed. The primary endpoint reported in both of these, the composite of all-cause death or heart failure hospitalization, was different from the primary endpoint of PARADIGM-HF, which utilized a composite of cardiovascular death or heart failure hospitalization. Nevertheless, the same composite endpoint was available from the data set and used in this meta-analysis for comparability. Finally, adverse event reporting is notoriously different between trials, and comparisons between trials is probably meaningless. Nevertheless, all three trials are directionally consistent with respect to major adverse events of interest. One adverse event that has received recent attention is dementia, since neprilysin may play a role in the breakdown of amyloid-beta protein in the brain, some components of which may contribute to the development of Alzheimer's dementia.[25,26] While cognition, memory, and dementia-related adverse events were not increased in the LCZ696 group in PARADIGM-HF, dementia-related events from OVERTURE have not been formally reported.

In summary, in a meta-analysis of three trials of combined inhibitors of neprilysin and the RAS in heart failure with reduced EF that reported clinical outcomes, we found that pooled estimates were significantly in favour of combined neprilysin/RAS inhibition over ACE inhibitors for the composite endpoints of death or heart failure hospitalization, and for all-cause mortality. These findings are supportive of the use of combined neprilysin/RAS inhibition in heart failure and of the benefit observed in PARADIGM-HF with sacubitril/valsartan, which currently is the only available inhibitor of neprilysin/RAS available for clinical use.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Risk of bias assessment.

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