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Effect of renin-angiotensin system inhibition on cardiac structure and function and exercise capacity in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials

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Abstract

Targeting the renin-angiotensin system (RAS) pathways has been considered a logical intervention for patients with heart failure with preserved ejection fraction (HFpEF), due to its hypothesized link to left ventricular (LV) remodeling. Although the effects of RAS inhibitors including angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and direct renin inhibitors (DRIs) on LV structure and function and exercise capacity in HFpEF patients have been examined in multiple randomized controlled trials (RCTs), results are inconsistent due partly to limited power. We conducted a meta-analysis of RCTs on the effects of RAS inhibitors on LV structure and function as well as exercise capacity in HFpEF patients. The search of electronic databases identified 7 trials including 569 patients; 4 trials were on ACE-Is; 2 on ARBs; and 1 on DRIs. Follow-up duration ranged across trials from 12 to 52 weeks. The pooled analysis showed that RAS inhibitors significantly increased EF compared with control (weighted mean difference [95% CI] = 2.182 [0.462, 3.901] %). In contrast, RAS inhibitors did not significantly change the ratio of peak early to late diastolic mitral inflow velocities (weighted mean difference [95% CI] = 0.046 [− 0.012, 0.105]), early diastolic mitral annular velocity (0.327 [− 0.07, 0.725] cm/s), the ratio of early diastolic mitral inflow to annular velocities (0.291 [− 0.937, 1.518]), LV mass (− 6.254 [− 15.165, 2.656] g), or 6-min walk distance (1.972 [− 14.22, 18.163] m) compared with control. The present meta-analysis suggests that RAS inhibitors may increase LVEF in HFpEF patients.

Keywords Heart failure · Meta-analysis · Randomized controlled trial · Pharmacotherapy · Renin angiotensin system

Introduction

Nearly half of patients with heart failure (HF) in the community have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved (HFpEF) are high [1–3]. However, there is no established therapy to improve survival in these patients [4–8]. Patients with HFpEF are often elderly and their primary chronic symptom is severe exercise intolerance [9, 10]. Improvement of exercise capacity presents another important clinical outcome in HFpEF patients.

Targeting the renin–angiotensin system (RAS) pathways has been considered a logical intervention for HFpEF, due to its hypothesized link to left ventricular (LV) remodeling [11, 12]. The effects of RAS inhibitors including angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and direct renin inhibitors (DRIs) on LV structure and function or exercise capacity in HFpEF patients have been examined in multiple randomized controlled trials (RCTs) [13–18]. However, the results are inconsistent due partly to limited power. Accordingly, we aimed to conduct a meta-analysis of RCTs on the effects of RAS inhibitors on LV structure and function as well as exercise capacity in HFpEF.

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Methods

This meta-analysis was performed and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [19]. Studies on the effect of RAS inhibitors on LV structure and function in patients with HFpEF published until November 30, 2019, were identified using PubMed and EMBASE databases. For the search of the eligible studies, the following keywords and medical subject heading were used: *diastolic heart failure*, *heart failure with normal (preserved) ejection fraction*, and *randomized controlled trial*. Our literature search was limited to studies involving human subjects and those published in English. Additionally, we manually searched the references that were cited in other relevant publications. Studies were considered eligible if they (1) included HFpEF; (2) were RCT; (3) used RAS inhibitors (ACE-Is, ARBs, or DRIs); (4) compared with standard medical care or placebo control group; and (5) assessed at least one of the following outcome measures: LV systolic or diastolic function, LV mass, and exercise capacity.

Primary outcomes of interest were LV structure and function. In the measure of LV structure, LV mass was extracted. In the measure of LV systolic function, LVEF was extracted. In the measures of LV diastolic function, the ratio of peak early to late diastolic mitral inflow velocities (E/A), early diastolic mitral annular velocity (e'), and the ratio of early diastolic mitral inflow to annular velocities (E/e') were extracted. Secondary outcome of interest was exercise capacity. In the measure of exercise capacity, 6-min walk distance (6MWD) was extracted. Other outcomes of interest were systolic and diastolic blood pressure.

Information on the study and patient characteristics, methodological quality, intervention strategies, and clinical outcomes was systematically extracted separately by 2 reviewers (TG and KW). Disagreements were resolved by consensus.

For each outcome, the effect size for the intervention was calculated by the difference between the means of the intervention and control groups at the end of the intervention. If the outcome was measured on the same scale, the weighted mean difference (WMD) and 95% confidence interval (CI) were calculated. For each outcome, heterogeneity was assessed using Cochran's Q and I^2 statistic; for Cochran's Q and I^2 statistic, a p value of < 0.1 and $I^2 > 50\%$ were considered significant, respectively [20]. When there was significant heterogeneity, the data were pooled using a random-effects model; otherwise, a fixed-effects model was used. All analyses were based on intension-to-treat data. All the included studies did not report the standard deviation of the change or the correlation of the pre and post measurements and did only the pre and post measurements. Accordingly, the correlation was conservatively set at 0.5 as previously reported [21]. Meta-regression was used to determine the factors that impact on the effect size. A one-study-removed analysis was performed to assess the influence of any one particular study on the overall meta-analysis result. Publication bias was assessed graphically using a funnel plot and mathematically using the Egger test. For all analyses, Comprehensive Meta-Analysis Software version 2 (Biostat, Englewood, NJ, USA) was used.

Results

The study identification and selection process is summarized in Fig. 1. A total of 7 trials including 569 patients were included in the present meta-analysis. The Hong Kong diastolic heart failure study was split into two sub-trials because the included patients were randomized to two different drug interventions (irbesartan and ramipril), both compared with usual medication [15].

The characteristics of the included trials are summarized in Table 1. Of the included trials, 4 trials were on ACE-Is; 2 on ARBs; and 1 on DRIs. Follow-up duration ranged across trials from 12 to 52 weeks. As to the primary outcomes of interest in the present meta-analysis, 6 trials reported the effect of RAS inhibitors on LV mass, EF, and E/A and 4 trials on E/e' and e'. As to the secondary outcomes of interest, 5 trials reported the effect of RAS inhibitors on 6MWD.

Baseline patient characteristics of the included trials are summarized in Table 2. Many patients were taking HF standard medications such as diuretics from 54 to 100%. Baseline measures of the primary and secondary outcomes of interest in the present meta-analysis are shown in supplement Tables 1 and 2.

The effects of RAS inhibitors on LV structure and function are shown in Fig. 2. RAS inhibitors significantly increased EF compared with control (WMD [95% CI] = 2.182 [0.462, 3.901] %; $p_{fix} < 0.05$). In contrast, RAS inhibitors did not significantly change LV mass (WMD [95% CI] = − 6.254 [− 15.165, 2.656] g; $p_{fix} > 0.10$), E/A (0.046 [− 0.012, 0.105]; $p_{fix} > 0.10$), e' (0.327 [− 0.07, 0.725] cm/s; $p_{fix} > 0.10$), or E/e' (0.291 [− 0.937, 1.518]; $p_{fix} > 0.10$) compared with control. In meta-regression, no variables listed in Table 2 were significantly associated with the increase in EF (all $p > 0.1$).

The effects of RAS inhibitors on exercise capacity and blood pressure are shown in Fig. 3. RAS inhibitors did not significantly change 6MWD (WMD [95% CI] = 1.972 [− 14.22, 18.163] m; $p_{fix} > 0.10$) compared with control. RAS inhibitors significantly decreased systolic blood pressure (WMD [95% CI] = − 5.686 [− 10.84, − 0.532] mmHg; $p_{random} < 0.05$) and diastolic blood pressure (− 4.343 [− 6.750, − 1.936] mmHg; $p_{random} < 0.001$) compared with control.

No evidence of publication bias was found for each outcome either at visual inspection of funnel plots or the Egger test (all $p > 0.1$). A one-study-removed analysis showed that none of the individual study substantially influenced the pooled estimate for the differences in outcomes of interest between RAS inhibitors and control groups.

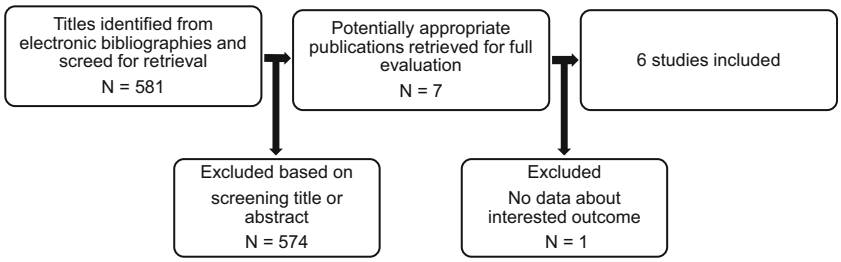


Fig. 1 Selection process for studies included in meta-analysis

Among the included trials, 6 trials reported adverse outcomes during drug intervention. Although minor or moderate events including cough [14, 15, 17] and hypotension [14, 16, 17] were reported to be possibly related to RAS inhibitors, there were no serious adverse events judged related to RAS inhibitors.

Discussion

In the present study, we conducted a meta-analysis of RCTs examining the effects of RAS inhibitors on LV structure and function as well as exercise capacity in HFpEF patients. We observed that RAS inhibitors increased EF compared with control. However, there was no significant difference in changes in LV mass, LV diastolic function measures, or 6MWD between RAS inhibitors and control groups. Thus, our meta-analysis suggests that RAS inhibitors may improve LV systolic function in HFpEF patients.

Several previous meta-analyses of RCTs have reported that RAS inhibitors do not improve clinical outcomes, including cardiovascular mortality, heart failure hospitalization, all-cause mortality, or health-related quality of life in HFpEF patients [22–24]. To the best of our knowledge, the present

Table 1 Study characteristics

Study, year	Country	Entry *N*, intervention/control	Entry EF (%)	Drug	Control	Duration (weeks)	Outcome measures
Aronow 1993 [13]	USA	10/11	> 50	Enalapril + diuretic	Diuretic only	12	LV mass, EF, E/A Systolic and diastolic BP
Zi 2003 [14]	UK	36/38	≥ 40	Quinapril	Placebo	24	6MWD
Hong Kong DHF (ARB) 2008 [15]	Hong Kong	56/50	> 45	Irbesartan + diuretic	Diuretic only	52	LV mass, EF, E/A, e', E/e' 6MWD Systolic and diastolic BP
Hong Kong DHF (ACE-I) 2008 [15]	Hong Kong	45/50	> 45	Ramipril + diuretic	Diuretic only	52	LV mass, EF, E/A, e', E/e' 6MWD Systolic and diastolic BP
Parthasarathy 2009 [16]	UK	68/82	≥ 40	Valsartan	Placebo	14	LV mass, EF, E/A 6MWD Systolic BP
Kitzman 2010 [17]	USA	35/36	≥ 50	Enalapril	Placebo	48	LV mass, EF, E/A, e', E/e' 6MWD Systolic and diastolic BP
Upadhya 2018 [18]	USA	25/27	≥ 50	Aliskiren	Placebo	24	LV mass, EF, E/A, e', E/e' 6MWD Systolic and diastolic BP

6MWD, 6-min walk distance; *ACE-I*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BP*, blood pressure; *DHF*, diastolic heart failure; *E/A*, the ratio of peak early to late diastolic mitral inflow velocities; *E/e'*, the ratio of early diastolic mitral inflow to annular velocities; *e'*, early diastolic mitral annular velocity; *EF*, ejection fraction; *LV*, left ventricular; *NR*, not reported

Table 2 Patient characteristics

Author, year	Mean age, year	Men, %	NYHA functional class >II, %	Mean BMI, kg/m^2	CAD, %	AF, %	Valvular disease, %	Hypertension, %	Diabetes, %	COPD, %	BBs, %	Diuretics, %
Aronow 1993 [13]	80	15	100	NR	100	0	0	NR	NR	0	0	100
Zi 2003 [14]	78	35	22	28	57	35	15	30	15	0	14	96
Hong Kong DHF (ARB) 2008 [15]	75	38	29	27	9	16	0	74	19	NR	0	100
Hong Kong DHF (ACE-I) 2008 [15]	74	41	31	27	14	13	0	75	21	NR	0	100
Parthasarathy 2009 [16]	62	50	NR	30	0	13	0	90	18	0	34	NR
Kitzman 2010 [17]	70	15	21	30	0	9	0	73	13	0	34	54
Upadhya 2018 [18]	70	20	29	33	0	6	0	96	40	0	46	71

ACE-I, angiotensin-converting enzyme inhibitor; *AF*, atrial fibrillation; *ARB*, angiotensin receptor blocker; *BBs*, beta-blockers; *BMI*, body mass index; *NR*, not reported; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *DHF*, diastolic heart failure; *NYHA*, New York Heart Association

meta-analysis is the first to examine the effects of RAS inhibitors on LV structure and function and exercise capacity in HFpEF patients and to show that RAS inhibitors improved LV systolic function in these patients.

Although the present meta-analysis does not provide the mechanisms for the observed potentially beneficial effect of RAS inhibitors on LV systolic function in HFpEF patients, there are several possible explanations. First, the observed increased EF may be due to the protective effect of RAS inhibitors on LV remodeling. In an animal model of hypertensive heart disease, treatment with RAS inhibitors prevented LV dilatation and retained LV contractility normal [25, 26]. Similarly, animal and human studies reported that RAS inhibitors prevented LV dilatation after myocardial infarction [25, 27]. Furthermore, hypertensive heart disease and coronary artery disease are the two most common underlying cardiac diseases in HFpEF patients [28, 29]. Second, the observed increased EF may be due to the vasodilating effect of RAS inhibitors. In the present meta-analysis, we observed that RAS inhibitors reduced blood pressure. Given the afterload dependence of EF [30], the observed increased EF may partly result from the vasodilating effect of RAS inhibitors.

In the present-meta-analysis, despite the increased EF, RAS inhibitors did not improve exercise capacity in HFpEF patients. There appear to be several possible explanations for the observations. First, LV diastolic abnormalities were reported to contribute to limited exercise capacity greater than LV systolic performance in HFpEF patients [31]. Furthermore, emerging data suggest that a limited increase in heart rate (chronotropic incompetence) as well as impaired oxygen utilization by active muscles during exercise may also play an important role in limiting exercise performance in HFpEF patients [32]. Consistent with this explanation, one meta-analysis reported that aerobic exercise training improved exercise capacity without significant change in LV function in HFpEF patients [33].

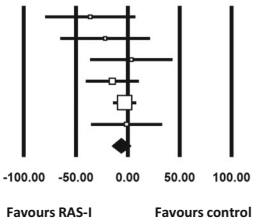
Our observed potentially beneficial effect of RAS inhibitors on LV systolic function in HFpEF patients may have an important clinical implication. There is accumulating evidence that a substantial proportion of HFpEF patients develop reduced EF over time and that these patients have a worse prognosis [34–36]. Although several RCTs have reported that RAS inhibitors did not improve survival in HFpEF patients [22–24], our meta-analysis suggests the potential prognostic benefit of RAS inhibitors for HFpEF patients with declining EF. Further studies are warranted to examine whether RAS inhibitors may improve survival in HFpEF patients with declining EF.

There are several limitations to our study. First, our meta-analysis included trials that were conducted before the definition of HFpEF was developed. Several of these trials defined preserved EF as greater than or equal to 40% or 45% [14–16], which is not consistent with a definition of HFpEF in recent guidelines [28, 29]. However, the mean values of baseline EF in these trials were generally higher than those in the trials which used 50% as a cutoff point of EF (Supplement Table 1). Thus, there appeared to be only a very few patients with EF < 50% included in the present meta-analysis. Second, the effects of the doses of RAS inhibitors on outcomes were not assessed. Further studies are warranted to examine whether different doses of RAS inhibitors differently impact on LV function and structure as well as exercise capacity in HFpEF

Fig. 2 Forest plots showing the effects of renin–angiotensin system inhibitors (RAS-I) on left ventricular (LV) mass (g; **a**), ejection fraction (EF; %, **b**), the ratio of peak early to late diastolic mitral inflow velocities (E/A; **c**), early diastolic mitral annular velocity (e'; cm/s, **d**), and the ratio of early diastolic mitral inflow to annular velocities (E/e'; **e**) ▶

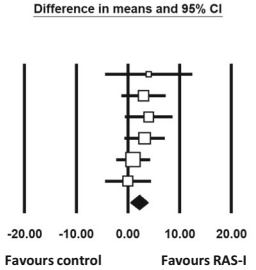
(a) LV mass

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aronow (enalapril)	-36.000	21.927	480.800	-78.976	6.976	-1.642	0.101
Hong Kong DHF (irbesartan)	-21.690	21.915	480.248	-64.642	21.262	-0.990	0.322
Hong Kong DHF (ramipril)	3.580	20.084	403.368	-35.784	42.944	0.178	0.859
Parthasarathy (valsartan)	-14.880	12.761	162.833	-39.890	10.130	-1.166	0.244
Kitzman (enalapril)	-3.000	5.570	31.030	-13.918	7.918	-0.539	0.590
Upadhya (aliskiren)	-1.000	17.218	296.460	-34.747	32.747	-0.058	0.954
	-6.254	4.546	20.668	-15.165	2.656	-1.376	0.169



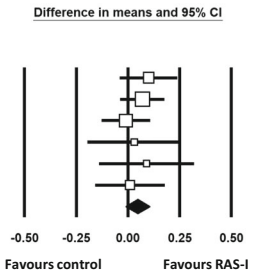
(b) EF

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aronow (enalapril)	4.000	4.275	18.277	-4.379	12.379	0.936	0.349
Hong Kong DHF (irbesartan)	3.000	2.155	4.642	-1.223	7.223	1.392	0.164
Hong Kong DHF (ramipril)	4.000	2.306	5.319	-0.520	8.520	1.734	0.083
Parthasarathy (valsartan)	3.220	1.962	3.851	-0.626	7.066	1.641	0.101
Kitzman (enalapril)	1.000	1.621	2.629	-2.178	4.178	0.617	0.537
Upadhya (aliskiren)	0.000	2.232	4.983	-4.375	4.375	0.000	1.000
	2.182	0.877	0.770	0.462	3.901	2.486	0.013



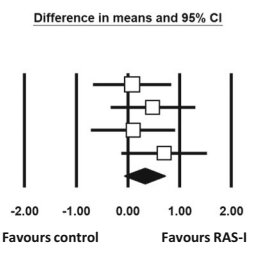
(c) E/A

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aronow (enalapril)	0.100	0.070	0.005	-0.038	0.238	1.425	0.154
Hong Kong DHF (irbesartan)	0.070	0.054	0.003	-0.035	0.175	1.304	0.192
Hong Kong DHF (ramipril)	-0.010	0.059	0.004	-0.126	0.106	-0.169	0.866
Parthasarathy (valsartan)	0.030	0.115	0.013	-0.195	0.255	0.262	0.794
Kitzman (enalapril)	0.090	0.116	0.013	-0.137	0.317	0.777	0.437
Upadhya 2018 (aliskiren)	0.010	0.085	0.007	-0.157	0.177	0.118	0.906
	0.046	0.030	0.001	-0.012	0.105	1.555	0.120



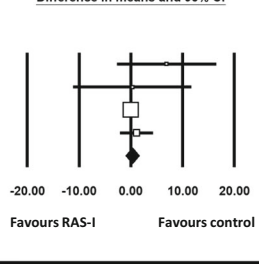
(d) e'

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hong Kong DHF (irbesartan)	0.080	0.382	0.146	-0.669	0.829	0.209	0.834
Hong Kong DHF (ramipril)	0.480	0.414	0.171	-0.331	1.291	1.160	0.246
Kitzman (enalapril)	0.100	0.411	0.169	-0.706	0.906	0.243	0.808
Upadhya (aliskiren)	0.700	0.417	0.174	-0.117	1.517	1.679	0.093
	0.327	0.203	0.041	-0.070	0.725	1.615	0.106



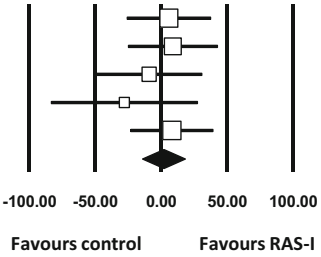
(e) E/e'

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hong Kong DHF (irbesartan)	6.920	4.876	23.778	-2.637	16.477	1.419	0.156
Hong Kong DHF (ramipril)	0.280	5.788	33.504	-11.065	11.625	0.048	0.961
Kitzman (enalapril)	0.000	0.694	0.482	-1.360	1.360	0.000	1.000
Upadhya (aliskiren)	1.100	1.578	2.491	-1.993	4.193	0.697	0.486
	0.291	0.626	0.392	-0.937	1.518	0.464	0.643



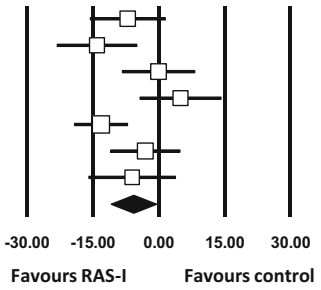
(a) 6MWD

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hong Kong DHF (irbesartan)	6.000	16.237	263.647	-25.824	37.824	0.370	0.712
Hong Kong DHF (ramipril)	9.000	17.320	299.995	-24.947	42.947	0.520	0.603
Kitzman (enalapril)	-9.000	20.492	419.931	-49.164	31.164	-0.439	0.661
Zi (quinapril)	-27.800	28.366	804.658	-83.397	27.797	-0.980	0.327
Upadhya (aliskiren)	8.230	16.009	256.291	-23.148	39.607	0.514	0.607
	1.972	8.261	68.249	-14.220	18.163	0.239	0.811



(b) Systolic blood pressure

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aronow (enalapril)	-7.000	4.376	19.151	-15.577	1.577	-1.600	0.110
Zi (quinapril)	-14.000	4.652	21.637	-23.117	-4.883	-3.010	0.003
Hong King DHF (irbesartan)	0.000	4.235	17.932	-8.300	8.300	0.000	1.000
Hong King DHF (ramipril)	5.000	4.736	22.430	-4.282	14.282	1.056	0.291
Parthasarathy (valsartan)	-13.100	3.112	9.686	-19.200	-7.000	-4.209	0.000
Kitzman (enalapril)	-3.000	4.049	16.397	-10.936	4.936	-0.741	0.459
Upadhya (aliskiren)	-6.000	5.053	25.536	-15.904	3.904	-1.187	0.235
	-5.686	2.630	6.915	-10.840	-0.532	-2.162	0.031



(c) Diastolic blood pressure

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aronow (enalapril)	-6.000	2.374	5.637	-10.653	-1.347	-2.527	0.011
Hong King DHF (irbesartan)	-7.000	2.053	4.214	-11.023	-2.977	-3.410	0.001
Hong King DHF (ramipril)	-4.000	2.353	5.535	-8.611	0.611	-1.700	0.089
Kitzman (enalapril)	-4.000	2.627	6.902	-9.149	1.149	-1.523	0.128
Upadhya (aliskiren)	0.000	2.399	5.753	-4.701	4.701	0.000	1.000
	-4.343	1.228	1.508	-6.750	-1.936	-3.536	0.000

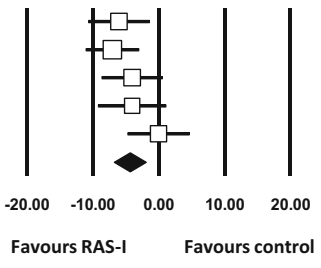


Fig. 3 Forest plots showing the effects of renin–angiotensin system inhibitors (RAS-I) on 6-min walk distance (6MWD; m, **a**) and systolic and diastolic blood pressure (mmHg; **b** and **c**)

patients. Third, the limited number of studies in our meta-analysis did not allow us to perform pooled analysis by drug class. Studies have reported that ARBs favorably impact exercise capacity in various populations, while the results of the impact of ACE-Is are mixed [37]. Further studies are warranted to examine the comparative effects of ARBs and ACE-Is on exercise capacity in HFpEF patients. Fourth, the number of patients included in our meta-analysis was relatively small and measures of LV diastolic function or structure were not consistently reported in the included trials. In experimental animal models of HFpEF, RAS inhibitors have been reported to exert beneficial effects on LV hypertrophy and fibrosis [38, 39].

Our observed neutral effects of RAS inhibitors on LV diastolic function and structure may be due in part to limited power. Furthermore, there is substantial variation in baseline clinical characteristics including gender, comorbidities such as atrial fibrillation and coronary artery disease, exercise capacity, echocardiographic variables, and drug treatment across the included trials. Further trials with larger sample size as well as more homogeneous baseline clinical characteristics are necessary. Finally, RCTs have strict enrollment criteria and patients with HFpEF are often elderly with many comorbidities [40]. Thus, the patients who participated in the RCTs in our meta-analysis might represent a selected group of patients that was poorly representative of patients treated in routine clinical practice. Consistent with this, the prevalence of comorbidities such as atrial fibrillation and coronary artery disease in our meta-analysis is lower than that in observational studies [40]. Further studies are necessary to examine whether our observed potential benefit of RAS inhibitors could be extended to real-world patients.

In conclusion, our meta-analysis suggests that RAS inhibitors may improve LV systolic function in HFpEF patients. Given the limited number of patients and the substantial variation in baseline clinical characteristics in the included trials, further large trials for HFpEF patients with homogeneous clinical characteristics are necessary not only to confirm our observed potential benefit of RAS inhibitors on LV systolic function but also to determine the effects on LV structure and diastolic function in HFpEF patients.

Compliance with ethical standards

Conflict of interest Dr. Ohte has received lecture fees from Daiichi Sankyo Co. and grant support from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., and Otsuka Pharmaceutical Co., Ltd. Dr. Kamiya has received lecture fees from Astellas Pharma Inc. and Mochida Pharmaceutical Co., Ltd.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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