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ORIGINAL ARTICLE

Effects of mineralocorticoid receptor antagonists on left ventricular diastolic function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials

Hidekatsu Fukuta[1] · Toshihiko Goto[2] · Kazuaki Wakami[2] · Takeshi Kamiya[3] · Nobuyuki Ohte[2]

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Abstract

Left ventricular (LV) diastolic dysfunction is associated with the pathophysiology of heart failure with preserved ejection fraction (HFpEF) and contributes importantly to exercise intolerance that results in a reduced quality of life (QOL) in HFpEF patients. Experimental studies have shown that aldosterone plays a role in the genesis of myocardial hypertrophy and fibrosis, thereby enhancing LV diastolic dysfunction, and that aldosterone antagonists (mineralocorticoid receptor antagonists [MRAs]) prevents myocardial hypertrophy and fibrosis. Although the effects of MRAs on LV diastolic function, exercise capacity, and QOL in HFpEF patients have been examined in randomized clinical trials (RCTs), results are inconsistent due partly to limited power with small sample sizes. We aimed to conduct a meta-analysis of RCTs on the effects of MRAs on LV diastolic function, exercise capacity, and QOL in HFpEF patients. The search of electronic databases identified 6 studies including 755 HFpEF patients. In the pooled analysis, MRAs increased early diastolic mitral annular velocity (weighted mean difference [95% CI] = 0.455 [0.232–0.679] cm/s; $P_{fix} < 0.001$) and decreased the ratio of early diastolic mitral inflow to annular velocities (− 1.474 [− 2.073 to − 0.875]; $P_{fix} < 0.001$) compared with control. There was no significant difference in change of peak exercise oxygen uptake, 6-minute walking distance, or QOL questionnaire scores between MRA and control group. In conclusion, our meta-analysis showed that MRAs improved LV diastolic function in HFpEF patients. However, the observed improvement in LV diastolic function with the use of MRAs did not translate into improved exercise capacity or QOL in these patients.

Keywords Mineralocorticoid receptor antagonists · Heart failure with preserved ejection fraction · Diastolic function · Exercise capacity · Quality of life

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 EF (HFpEF) are high [1–3]. However, there is no established therapy to improve survival in HFpEF [4–7]. Patients with HFpEF are often elderly and their primary chronic symptom is severe exercise intolerance that results in a reduced quality of life (QOL) [8, 9]. Thus, improvement of exercise capacity and QOL presents another important clinical outcome in HFpEF patients.

There is much evidence that left ventricular (LV) diastolic dysfunction is associated with the pathophysiology of HFpEF [10–12] and studies have reported that LV diastolic

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✉ Hidekatsu Fukuta
fukuta-h@med.nagoya-cu.ac.jp

[1] Core Laboratory, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

[2] Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[3] Department of Medical Innovation, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

dysfunction contributes importantly to exercise intolerance in HFpEF patients [13–16]. In addition, LV diastolic abnormalities are predictive of worse prognosis in HFpEF patients [17–20].

Experimental studies have reported that aldosterone plays a pivotal role in the genesis of myocardial hypertrophy and fibrosis, thereby enhancing LV diastolic dysfunction [21, 22]. Furthermore, human studies have reported that the renin–angiotensin–aldosterone system is activated in HFpEF patients and that elevated serum aldosterone concentration is associated with concentric LV hypertrophy in these patients [23, 24]. Finally, aldosterone antagonists (mineralocorticoid receptor antagonists [MRAs]) have been reported to prevent or ameliorate myocardial hypertrophy and fibrosis in experimental studies [25, 26]. Thus, MRAs may improve LV diastolic function in HFpEF patients through the favorable effects on cardiac fibrosis and hypertrophy.

Although the effects of MRAs on LV diastolic function, exercise capacity, and QOL in HFpEF patients have been examined in randomized clinical trials (RCTs) [27–33], results are inconsistent due partly to limited power with small sample sizes. Accordingly, we aimed to conduct a meta-analysis of the RCTs on the effects of MRAs on LV diastolic function and exercise capacity as well as QOL in HFpEF patients.

Methods

This meta-analysis was performed and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [34].

Studies on the effect of MRAs on LV diastolic function, exercise capacity, and QOL in patients with HFpEF published until December 31, 2017 were identified using PubMed and EMBASE databases. For search of the eligible studies, the following key words and Medical Subject Heading were used: diastolic heart failure, heart failure with normal (preserved) ejection fraction, spironolactone, eplerenone, and mineralocorticoid receptor antagonists (blockers). Our literature search was limited to studies involving human subjects and those published in English. In addition, we manually searched the references that were cited in other relevant publications. Trials were considered eligible if they: (1) included HF patients with EF $\geq$ 50%; (2) were RCT; (3) compared with standard medical care or placebo control group, with a minimum follow-up of 6 months; and (4) assessed at least one of the following outcome measures: LV diastolic function, exercise capacity, and QOL.

Primary outcomes of interest were LV diastolic function, exercise capacity, and QOL. Secondary outcomes of interest were left-sided cardiac chamber structure. Other outcomes of interest were blood pressure and B-type natriuretic peptide (BNP) levels. The safety outcome of interest was hospitalization for hyperkalemia.

Among various measures of LV diastolic function, early diastolic mitral annular velocity (e'), and the ratio of early diastolic mitral inflow to annular velocities (E/e') were extracted given the linear relationship with LV diastolic dysfunction grade [35]. In the measures of exercise capacity, peak exercise oxygen uptake (VO_2) by expired gas analysis and 6-minute walk distance (6MWD) were extracted. In the measures of QOL, Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score were extracted. In the measures of left-sided cardiac chamber structure, LV mass and left atrial (LA) volume were extracted.

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. The quality of RCTs was assessed by the Jadad quality scale [36].

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% confidential interval (CI) were calculated. Otherwise, the standardized mean difference (SMD) and 95% CI were calculated. For each outcome, heterogeneity was assessed using the Cochran's Q and I^2 statistic; for the Cochran's Q and I^2 statistic, a p value of < 0.1 and $I^2 > 50\%$, were considered significant, respectively [37]. 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 [38]. Publication bias was assessed graphically using a funnel plot and mathematically using 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 6 trials including 755 HFpEF patients were included in the present meta-analysis.

Characteristics of the included trials are summarized in Table 1. Of the included trials, 3 trials were conducted in the USA, 1 in Europe, and 2 in Australia. Of the included

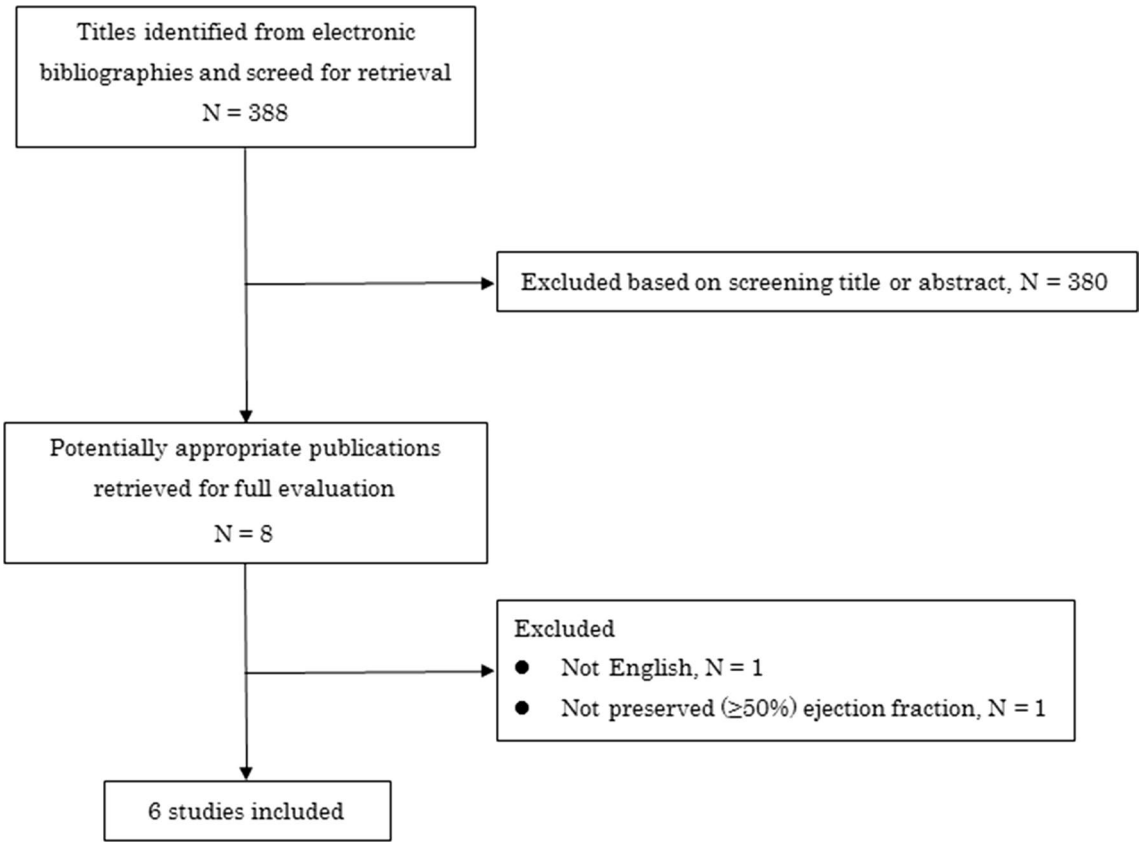

Fig. 1 Selection process for studies included in meta-analysis

Table 1 Study characteristics

References	Country	Follow-up	Intervention/control	Entry EF	*N*, Intervention/control	Primary outcome	Secondary outcome
Mottram [27]	Australia	6 months	Spironolactone/placebo	> 50%	15/15	*e′*	LV mass
Deswal [29]	USA	6 months	Eplerenone/placebo	> 50%	21/23	*e′*, *E*/*e′* 6MWD KCCQ	LV mass LA volume
Edelmann [30]	Germany Austria	12 months	Spironolactone/placebo	> 50%	213/209	*e′*, *E*/*e′* Peak VO_2, 6MWD MLHFQ	LV mass LA volume
Kurrelmeyer [31]	USA	6 months	Spironolactone/placebo	> 50%	24/24	*e′*, *E*/*e′* 6MWD KCCQ	LV mass LA volume
Kosmala [32]	Australia	6 months	Spironolactone/placebo	> 50%	64/67	*e′*, *E*/*e′* Peak VO_2	LV mass LA volume
Upadhya [33]	USA	9 months	Spironolactone/placebo	> 50%	42/38	*e′*, *E*/*e′* Peak VO_2, 6MWD MLHFQ	LV mass

6MWD indicates 6-minute walk distance, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LA* left atrial, *LV* left ventricular, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *Peak* VO_2 peak exercise oxygen uptake

trials, 5 trials reported the effect of spironolactone and 1 trial reported the effect of eplerenone. Follow-up duration ranged across trials from 6 to 12 months. As to the primary outcomes of interest in the present meta-analysis, all trials reported the effect of MRAs on *e′*; 5 trials on *E*/*e′*; 3 trials on peak VO_2; 4 trials on 6MWD; 4 trials on

QOL (2 MLHFQ total score and 2 KCCQ overall summary score). As to the secondary outcomes of interest, all trials reported the effect of MRAs on LV mass and 4 trials reported the effect on LA volume. The Jadad score ranged across trials from 4 to 5 (Supplement Table 1).

Baseline patient characteristics of the included trials are summarized in Table 2. Many patients were taking standard HF and hypertension medications such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers ranging across trials from 0 to 100%, beta-blockers from 30 to 80%, diuretics from 15 to 98%, and calcium channel blockers from 25 to 89%.

Baseline measures of the outcomes of interest in the present meta-analysis are shown in Supplement Tables 2 and 3. Hypertension was generally well-controlled; mean systolic and diastolic blood pressure ranged across trials from 130 to 141 mmHg and from 70 to 81 mmHg, respectively (Supplement Table 3).

The effect of MRAs on LV diastolic function is shown in Fig. 2. MRAs increased e' (WMD [95% CI] = 0.455 [0.232–0.679] cm/s; $P_{fix} < 0.001$) and decreased E/e' (− 1.474 [− 2.073 to − 0.875]; $P_{fix} < 0.001$) significantly compared with control.

The effect of MRAs on exercise capacity is shown in Fig. 3. There was no significant difference in change of peak VO_2 (WMD [95% CI] = 0.866 [− 0.744 to 2.477] ml/min/kg; $P_{random} = 0.29$) or 6MWD (− 11.9 [− 26.2 to 2.26] m; $P_{random} = 0.1$) between MRA and control group.

The effect of MRAs on left-sided cardiac chamber structure is shown in Fig. 4. MRAs significantly decreased LV mass (SMA [95% CI] = − 0.152 [− 0.298 to − 0.007]; $P_{fix} < 0.05$) compared with control. There was no significant difference in change of LA volume (SMA [95% CI] = − 0.079 [− 0.236 to 0.078]; $P_{fix} = 0.34$) between MRA and control group.

The effect of MRAs on QOL is shown in Fig. 5. There was no significant difference in change of QOL questionnaire scores (SMD [95% CI] = − 0.018 [− 0.184 to 0.147]; $P_{fix} = 0.83$) between MRA and control group. Even when the analysis was performed separately for KCCQ overall summary score and MLHFQ total score, there was no significant difference in change of KCCQ overall summary score (WMD [95% CI] = 2.971 [− 7.011 to 12.953] points; $P_{fix} = 0.56$) or MLHFQ total score (− 0.860 [− 4.002 to 2.282] points; $P_{fix} = 0.59$) between MRA and control group.

The effects of MRAs on blood pressure and BNP levels are shown in Supplement Figs. 1 and 2. MRAs decreased systolic blood pressure (WMD [95% CI] = − 8.393 [− 11.376 to − 5.410] mmHg; $P_{fix} < 0.001$) and diastolic blood pressure (− 3.580 [− 5.645 to − 1.516] mmHg; $P_{fix} < 0.01$) significantly compared with control. There was no significant difference in change of BNP levels (WMD

Table 2 Patient characteristics

References	Mean Age, year	Women (%)	NYHA > class II (%)	CAD (%)	Atrial fibrillation	Hypertension (%)	Diabetes (%)	ACE-I/ARB	BBs (%)	Diuretics (%)	CCBs (%)
Mottram [27]	62	63	0	0	NR	100	3	0%	30	33	89
Deswal [29]	70	7	41	57	14%	100	61	98%	80	98	50
Edelmann [30]	67	52	14	40	5%	92	17	77%	72	54	25
Kurrelmeyer [31]	71	100	63	35	25%	83	38	100%	63	79	27
Kosmala [32]	67	84	21	0	0%	92	40	96%	75	15[a]	43
Upadhya [33]	71	80	64	0	NR	88	23	NR	31	83	35

ACE-I indicates angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BBs* beta-blockers, *NR* not reported, *NYHA* New York Heart Association, *CAD* coronary artery disease, *CCBs* calcium channel blockers. Other abbreviations as in Table 1

[a]The value is presented as a proportion of the use of loop diuretics

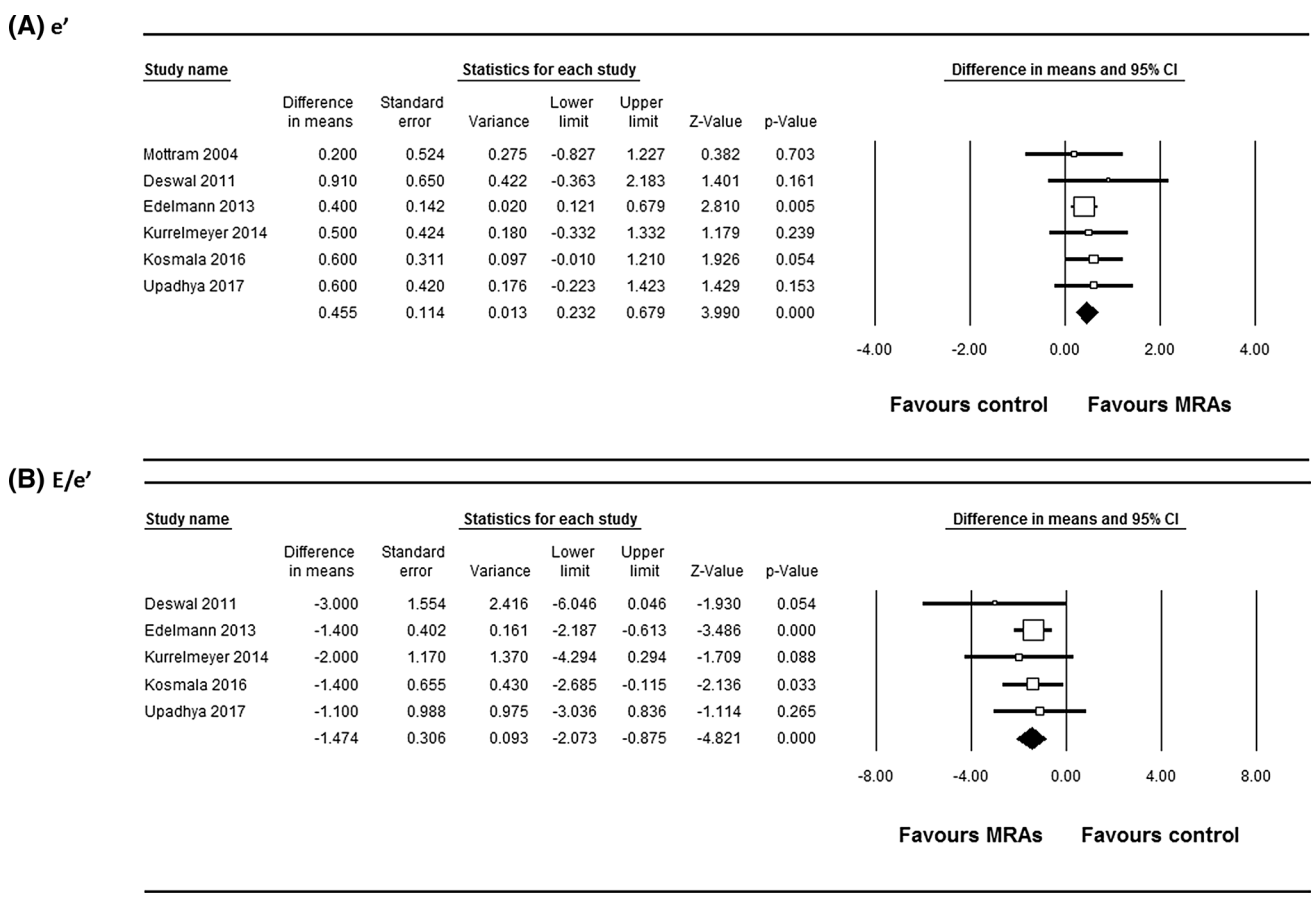

Fig. 2 Forest plots showing the effects of mineralocorticoid receptor antagonists (MRAs) on early diastolic mitral annular velocity (*e'*, cm/s; **a**) and the ratio of early diastolic mitral inflow to annular velocities (*E*/*e'*; **b**)

[95% CI] = 5.226 [− 15.416 to 25.869] pg/ml; $P_{fix} = 0.62$) between MRA and control group.

No evidence of publication bias was found for each outcome either at visual inspection of funnel plots or Egger test (all $p > 0.1$).

As to the safety outcome of interest, hospitalization for hyperkalemia occurred in 3 patients in MRA group (0.79%) and 0 patients in control group (0%). Use of MRAs was not significantly associated with increased risk for hospitalization for hyperkalemia (risk ratio [95% CI] = 7.0 [0.381–129]; $P_{fix} = 0.19$).

Discussion

As to the primary outcomes of interest in the present meta-analysis, MRAs improved LV diastolic function in HFpEF patients. However, MRAs did not improve exercise capacity or QOL. As to the secondary outcomes of interest, MRAs decreased LV mass in HFpEF patients. However, MRAs did not change LA volume.

Our observed improvement in LV diastolic function with the use of MRAs in HFpEF patients is in accordance with a meta-analysis of Pandey et al. including 666 HFpEF patients which reported that MRAs decreased *E*/*e'*, a marker of LV filling pressure [39]. However, we believe that a meta-analysis of Pandey et al. is limited because of the inclusion of the trial that included HF patients with EF ≥ 45% [28] which is not consistent with a definition of HFpEF in recent guidelines [40, 41]. Furthermore, several important RCTs on the effect of MRAs in HFpEF patients have been published, since the meta-analysis was performed [32, 33]. Our meta-analysis is significant in including only RCTs that included HF patients with EF ≥ 50% which is consistent with a recent definition of HFpEF [40, 41] and confirms the reported favorable effect of MRAs on *E*/*e'* with a larger number of patients. Furthermore, our meta-analysis is the first to show the favorable effects of MRAs on *e'*, a measure of LV relaxation, and LV mass in HFpEF patients.

Consistent with a meta-analysis of Pandey et al. [39], treatment with MRAs did not improve 6MWD in HFpEF patients in our meta-analysis. Pandey et al., however, did not perform pooled analysis of the effects of MRAs on peak

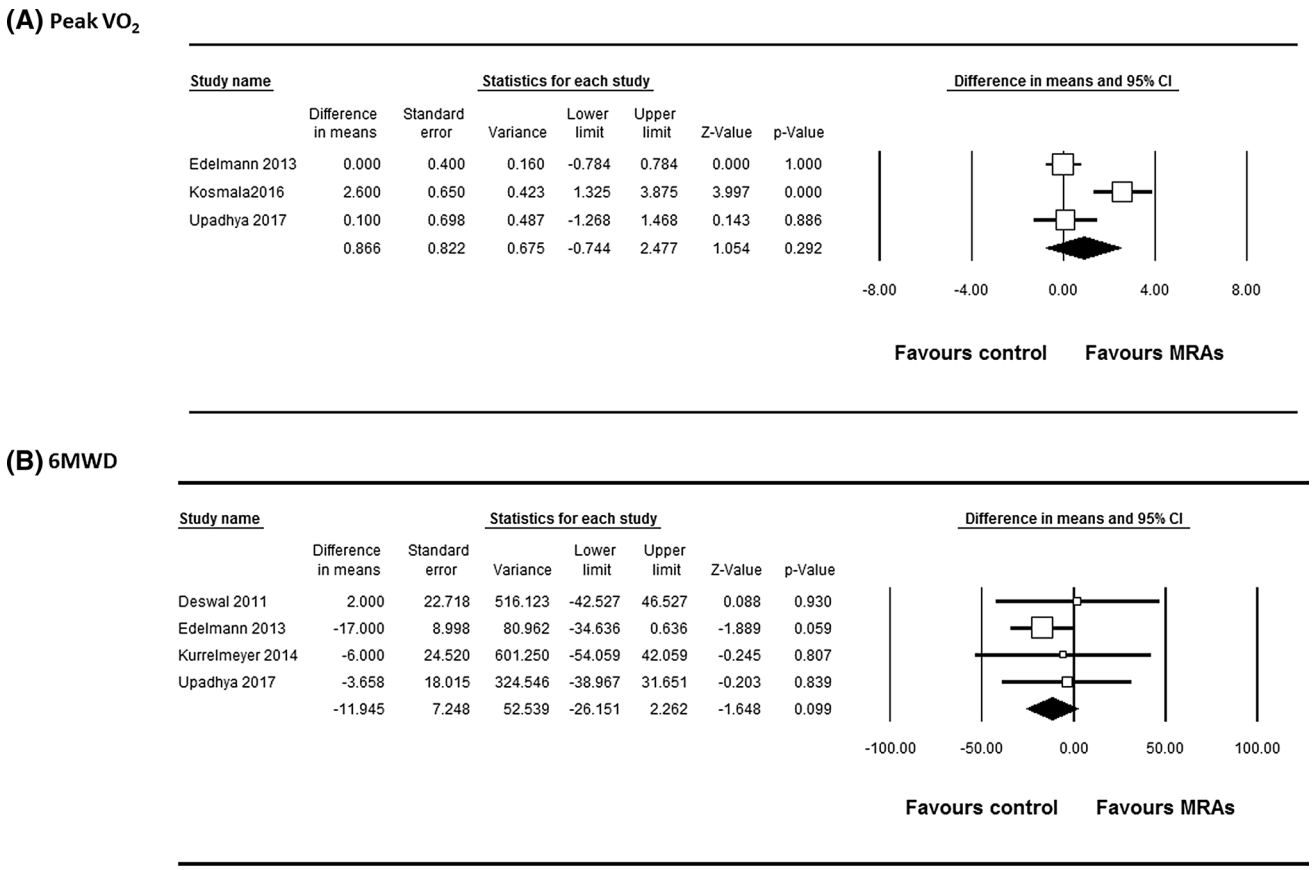

Fig. 3 Forest plots showing the effects of mineralocorticoid receptor antagonists (MRAs) on peak exercise oxygen uptake (VO_2, ml/min/kg; **a**) and 6-minute walking distance (6MWD, m; **b**)

VO_2, an objective measure of exercise capacity, or QOL [39]. Our meta-analysis confirms the reported neutral effect of MRAs on exercise capacity and further extends it to QOL in HFpEF patients. To the best of our knowledge, the present study is the first meta-analysis of the effect of the MRAs on peak VO_2 and QOL in HFpEF patients.

In the present meta-analysis, the observed improvement in LV diastolic function with the use of MRAs did not translate into improved exercise capacity or QOL. To consider the possible explanation, it may be useful to look over the pathophysiological background of exercise intolerance in HFpEF. During exercise, the oxygen consumption in the metabolizing tissues increases dramatically. Normally, this is accomplished by (1) an increase in cardiac output, a product of heart rate and stroke volume, and (2) increased utilization of oxygen by the metabolizing tissues [42]. Earlier studies have reported that, in HFpEF patients, stroke volume during exercise increases or maintains at the expense of increased LV end-diastolic pressure due to diastolic abnormalities, resulting in exertional dyspnea and thereby impaired QOL [13–16]. However, emerging data suggest that a limited increase in heart rate and impaired oxygen utilization by active muscles during exercise may play a relatively greater role in limiting exercise performance in HFpEF patients [42]. Thus, although improved LV diastolic function with the use of MRAs might contribute to a decrease in LV end-diastolic pressure during exercise in HFpEF patients, this potentially beneficial effect might be insufficient to improve exercise capacity or QOL in these patients.

Although MRAs did not improve exercise capacity or QOL in HFpEF patients in our meta-analysis, the observed improvement in LV diastolic function and decrease in LV mass with the use of MRAs may have prognostic implication. Regional post hoc analysis of the TOPCAT trial reported that spironolactone was associated with reduced risk of cardiovascular death and heart failure hospitalization compared with control in HFpEF patients in the Americas [43]. Furthermore, earlier clinical studies have reported that decreased e' and increased E/e' are each predictive of worse survival in cardiac patients including

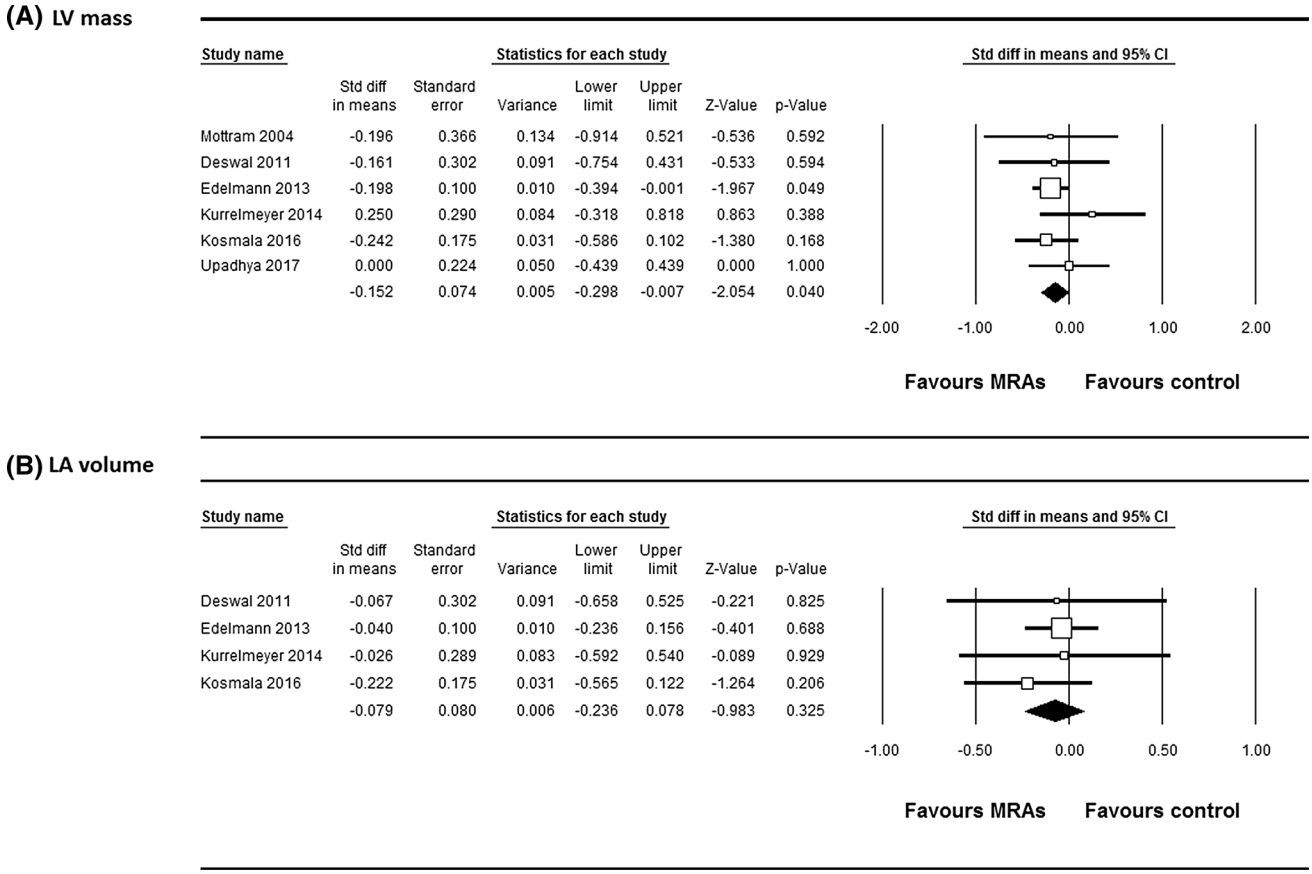

Fig. 4 Forest plots showing the effects of mineralocorticoid receptor antagonists (MRAs) on left ventricular (LV) mass (**a**) and left atrial (LA) volume (**b**)

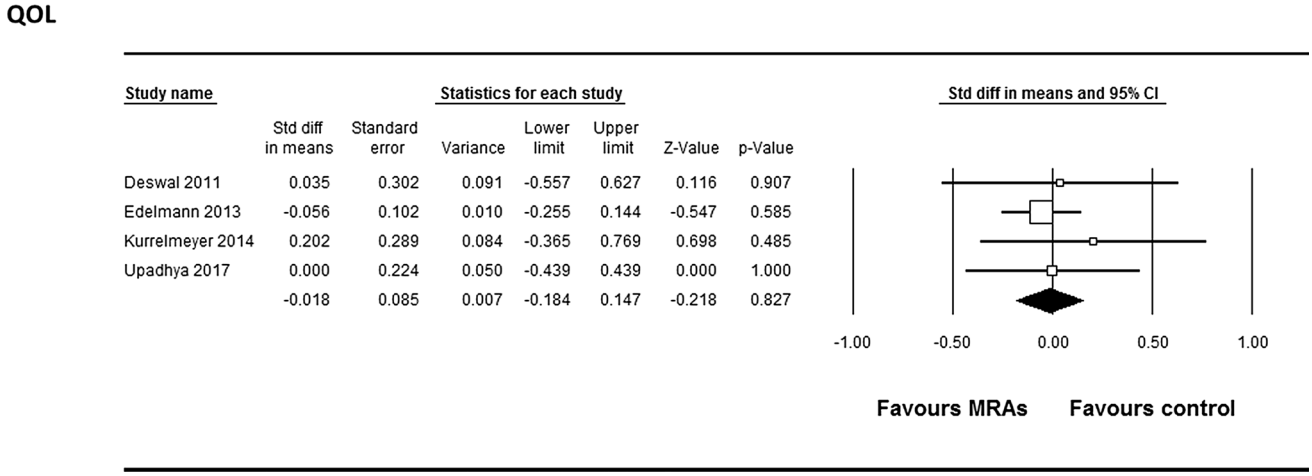

Fig. 5 Forest plots showing the effect of mineralocorticoid receptor antagonists (MRAs) on quality of life (QOL)

HFpEF patients [17–19, 44–47]. Finally, increased LV mass is predictive of future cardiovascular events in hypertensive patients and reduction of LV mass during antihypertensive treatment is associated with improved prognosis in these patients [48, 49]. Thus, our observed improvement in LV diastolic function (increased e' and

decreased *E*/*e*′) and decrease in LV mass with the use of MRAs may explain some of the mortality benefit reported in the post hoc analysis of the TOPCAT trial.

In our meta-analysis, the use of MRAs was not associated with increased risk for hospitalization for hyperkalemia. However, it is important to recognize that serum potassium levels were monitored during the study period and that the study drug was decreased or stopped if necessary.

There are several limitations to our study. First, the number of patients included in our meta-analysis was relatively small and measure of exercise capacity or QOL were not consistently reported in the included trials. Our observed neutral effects of MRAs on exercise capacity or QOL may be due in part to limited power. Second, the effects of the doses of MRAs on clinical outcomes were not determined. Further studies are warranted to examine whether different doses of MRAs differently impact on outcomes in HFpEF patients.

In conclusion, our meta-analysis showed that MRAs improved LV diastolic function in HFpEF patients. However, the observed improvement in LV diastolic function with the use of MRAs did not translate into improved exercise capacity or QOL in these patients. Given that the number of patients included in our meta-analysis was relatively small and that measure of exercise capacity or QOL were not consistently reported in the included trials, further adequately-powered RCTs are warranted to determine the effect of MRAs on exercise capacity and QOL in HFpEF patients.

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Compliance with ethical standards

Conflict of interest Dr. Ohte has received lecture fees from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd, Bayer GA, AstraZeneca plc, and Boehringer Ingelheim and grant support from Takeda Pharmaceutical Co. Ltd., Bayer GA, Daiichi Sankyo Co., Ltd, MSD, Novartis International AG, Boehringer Ingelheim, Astellas Pharma Inc., and Otsuka Pharmaceutical Co., Ltd. No other disclosures were reported.

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

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