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Effect of Mineralocorticoid Receptor Antagonists on Cardiac Structure and Function in Patients With Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: A Meta-Analysis and Systematic Review

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Background—There has been an increasing interest in use of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure with preserved ejection fraction (HFPEF). However, a comprehensive evaluation of MRA effects on left ventricular (LV) structure and function in these patients is lacking. In this meta-analysis, we evaluated the effects of MRAs on LV structure and function among patients with diastolic dysfunction or HFPEF.

Methods & Results—Randomized, controlled clinical trials evaluating the efficacy of MRAs in patients with diastolic dysfunction or HFPEF were included. The primary outcome was change in E/e' , a specific measure of diastolic function. Secondary outcomes included changes in other measures of diastolic function, LV structure, surrogate markers for myocardial fibrosis (carboxy-terminal peptide of procollagen type I [PICP] and amino-terminal peptide of pro-collagen type-II [PIIINP]), blood pressure, and exercise tolerance. In the pooled analysis, MRA use was associated with significant reduction in E/e' (weighted mean difference [WMD] [95% confidence interval {CI}]: -1.68 [-2.03 to -1.33]; $P < 0.0001$) and deceleration time (WMD [95% CI]: -12.0 ms [-23.3 to -0.7]; $P = 0.04$) as compared with control, suggesting and improvement in diastolic function. Furthermore, blood pressure and levels of PIIINP and PICP were also significantly reduced with MRA therapy with no significant change in LV mass or dimensions.

Conclusion—MRA therapy in patients with asymptomatic diastolic dysfunction or HFPEF is associated with significant improvement in diastolic function and markers of cardiac fibrosis without a significant change in LV mass or dimensions. (*J Am Heart Assoc.* 2015;4:e002137 doi: 10.1161/JAHA.115.002137)

Key Words: diastolic dysfunction • heart failure with preserved ejection fraction • mineralocorticoid receptor antagonist

Heat failure (HF) with preserved ejection fraction (HFPEF) is a significant public health problem with increasing prevalence, high morbidity and mortality, and lack of effective proven therapies.^{1,2} Although substantial progress has been made in the management and outcomes of heart

failure with reduced ejection fraction (HFREF), outcomes associated with HFPEF remain unchanged.^{1,2} Well-established pharmacological therapies for HFREF have failed to improve prognosis in HFPEF.^{3–6} This has largely been attributed to the phenotypic variability and the complex pathophysiological mechanisms underlying the development of HFPEF.⁷

Left ventricular (LV) diastolic dysfunction (LVDD) and LV hypertrophy (LVH) are frequently implicated in the pathogenesis of HFPEF⁸ and are independently associated with heightened risk for HF hospitalization and cardiovascular (CV) mortality in HFPEF.^{9,10} Progression of LVDD has been shown to play an important role in development of symptomatic HF in patients with hypertensive heart disease.^{11,12} As a result, there has been a significant interest in therapies that could ameliorate LVDD and adverse LV remodeling in order to potentially prevent or treat HFPEF. Mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, are one such class of drugs that have been shown to reduce LVDD, LVH, and myocardial fibrosis in animal models.^{13,14} Furthermore, MRAs

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have been shown to improve CV outcomes in subjects with HFREF.^{15–19} Several studies have evaluated the efficacy and safety of MRAs in patients with asymptomatic LVDD^{20–24} as well as established HFPEF.^{25–30}

Recently, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial showed that use of spironolactone did not significantly reduce the overall incidence of adverse CV outcomes among HFPEF patients. However, there was a beneficial effect of spironolactone observed in patients with higher baseline N-terminal pro-B-type natriuretic peptide (NT-ProBNP) levels and in patients enrolled in the Americas.^{31,32} A better understanding of the effects of MRA therapy on LV structure and function is imperative to delineate the potential mechanisms underlying these favorable effects of MRAs. Against this background, the present meta-analysis was done to assess the impact of MRA therapy on echocardiographic parameters, surrogate measures for myocardial fibrosis (markers of collagen turnover such as carboxy-terminal peptide of procollagen type I [PICP] and amino-terminal peptide of pro-collagen type II [PIIINP]), and surrogate clinical outcomes (exercise capacity and serum potassium levels) in patients with HFPEF or asymptomatic LVDD.

Methods

Search Strategy

A search of PubMed, EMBASE, the Cochrane Controlled Trial registry, and US Clinical Trials databases was performed using these key terms: *diastolic dysfunction; heart failure; diastolic heart failure; heart failure with normal ejection fraction; heart failure with preserved ejection fraction; aldosterone receptor antagonist, blocker, blockade, blocking agent; canrenoate; potassium canrenoate; canrenoic acid; spironolactone; aldosterone; Inspra; eplerenone; human*. No language limitations were imposed in the search strategy. From these lists, published clinical trials investigating the effects of MRAs on LV structure and function among patients with HFPEF or hypertension (HTN) without clinical HF were identified. The references cited in the included articles were also examined for additional studies. The search strategy, study selection, and analysis were carried out in accord with the PRISMA statement for systematic reviews.³³

Study Selection

All selected abstracts and titles were scanned independently by 2 reviewers (A.P. and S.G.) to identify articles for potential inclusion. Studies included in this analysis were required to have: (1) randomized, controlled trial (RCT) design; (2) a study population with either symptomatic HFPEF or HTN without

clinical HF; (3) described method of HF or LVDD diagnosis with reported ejection fraction >45%; (4) data on baseline symptom status of study participants (HF symptoms versus asymptomatic with diastolic dysfunction); (5) clearly defined intervention and control groups; and (6) echocardiographic outcome data available, such as measures of LVDD and LV dimension. Studies involving subjects with recent myocardial infarction or known valvular heart disease were excluded.

Data Extraction and Risk of Bias Assessment

Clinical, echocardiographic, and outcome data were extracted from individual studies and entered into a data extraction form. This included information about study design, patient characteristics (age, sex, ejection fraction, and functional status), intervention strategy (drug used and dose), length of follow-up, and measures of individual outcome results at baseline and follow-up. For multiple studies published from a single data set, the largest study with primary findings was included in the analysis. Risk of bias was assessed using the Cochrane risk of bias assessment tool.³⁴ Discrepancies between reviewers were resolved through discussion and consensus.

Outcome Variables

Changes in E/e', a specific measure of diastolic function, was assessed as the primary outcome in this study. Secondary outcomes analyzed in this study include changes in other measures of diastolic function (E/A and deceleration time [DT]), indexed LV mass, LV end diastolic diameter, serum biomarkers of collagen turnover (PICP and PIIINP), 6-minute walk distance (6-MWD) test, and serum potassium.

Statistical Analysis

Statistical analysis was conducted using Revman software (version 5.2; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2008). Quantitative outcomes changing from baseline to follow-up were summarized and compared by weighted mean difference (WMD) with 95% confidence interval (CI) between treatment group and control group using fixed and random-effects models. Heterogeneity between studies was assessed using I² statistic and publication bias with Begg's funnel plot method.³⁵ For outcomes with significant heterogeneity (I²>50%), the random-effects model is reported in the text and figures; for all others, the fixed-effects models are reported. Predefined subgroup analyses were conducted a priori for studies with HFPEF versus asymptomatic LVDD patients for all outcomes. All P values were 2-tailed with statistical significance specified at 0.05 and CI computed at 95% level.

Results

Eleven RCTs that enrolled 942 participants were included in the present meta-analysis, with a weighted mean duration of follow-up of 9.1 ± 3.0 months (Figure 1). Six trials included patients with symptomatic HFPEF, whereas the other 5 included patients with asymptomatic LVDD and/or LVH. The characteristics of the included studies are summarized in Table. Spironolactone was used in 8 of the included trials, whereas eplerenone was used in 2 studies and canrenone was used in 1 trial. Seven studies were conducted in a double-blind fashion comparing MRA against placebo. Four studies compared MRAs against usual care without placebo administration in the control group. All 11 studies included baseline and follow-up echocardiographic examination of study participants. In all studies, the timing of outcome follow-up coincided with the completion of drug intervention.

Quality Assessment

Cochrane risk of bias assessment tool was used to perform quality assessment. During quality assessment, random sequence generation was observed in all studies. Double-blind design was used in 7 studies. Incomplete outcome data or selective reporting of results were not observed in any of the selected studies. Details of risk of bias assessment are given in Figure 2. We did not observe a significant risk of publication bias for the primary outcome in the included studies (Begg's test correlation coefficient: 0.19; $P=0.85$).

Effect of MRAs on Diastolic Function

Overall pooled estimates and subgroup (HFPEF and asymptomatic LVDD) effect estimates for measures of diastolic function are shown in Figure 3. E/e' , the primary outcome,

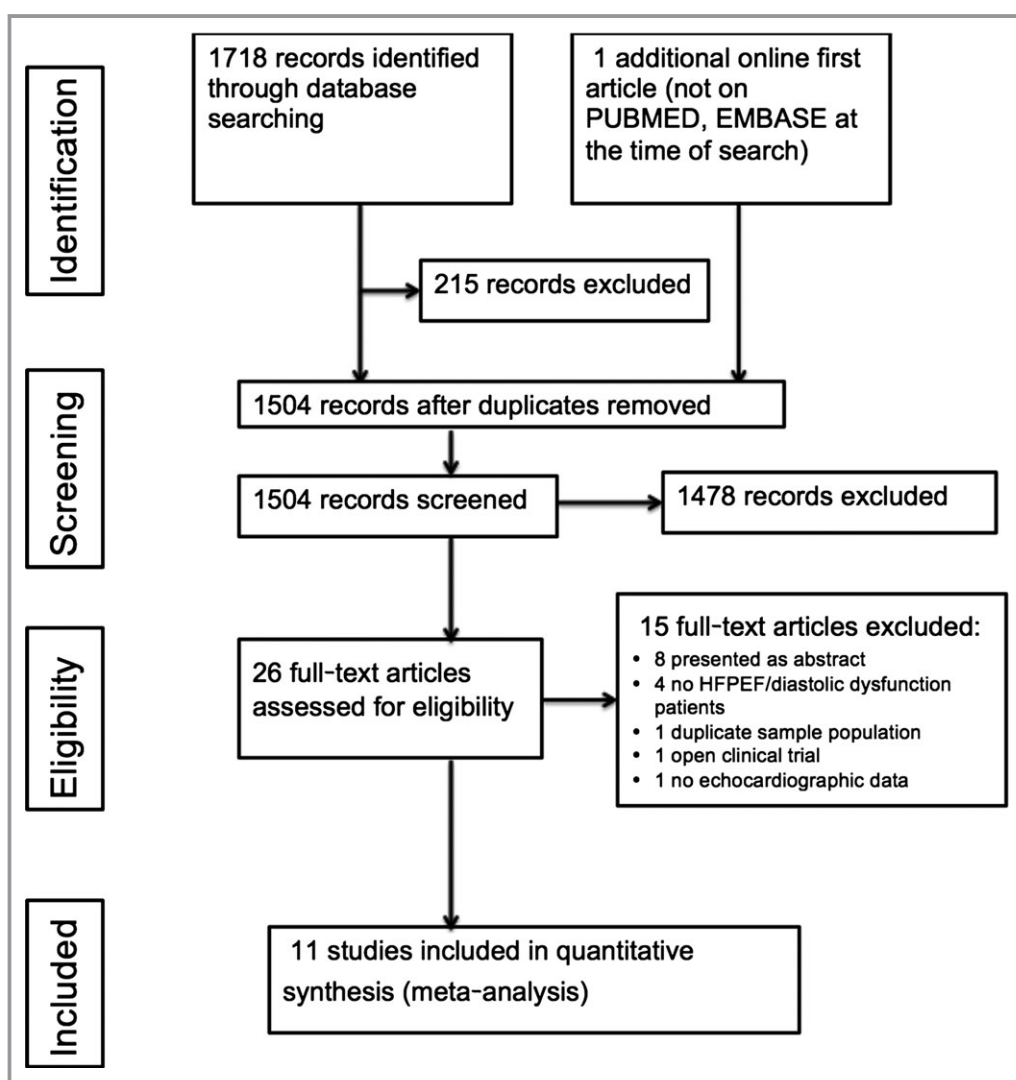


Figure 1. Summary of study identification and selection. HFPEF indicates heart failure with preserved ejection fraction.

Table. Characteristics of Trials Included in the Meta-Analysis

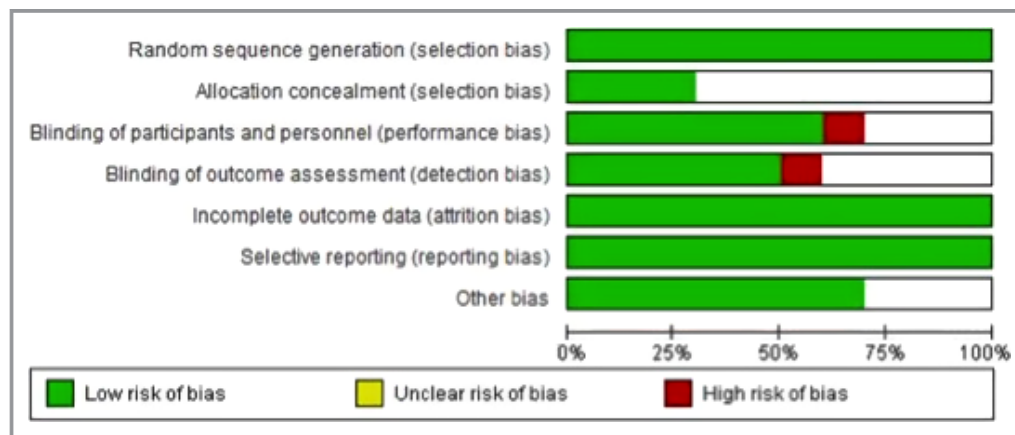
Author, Year	Follow-up (Months)	Intervention Group	Control Group	Clinical Characteristics	Ejection Fraction	Patients Treatment/Control (% Women)	Mean Age, Years (SD)
Sato 2002 ²⁰	15 months	Spironolactone 25 mg/day+ACE inhibitor	ACE inhibitor only	Essential Hypertension, LVH	>50%	10/10 (45%)	53
Grandi 2002 ²⁴	6 months	Canerenone 50 mg/day+ACE inhibitor	ACE inhibitor only	Essential HTN, LVH and LVDD	Normal	17/17 (38%)	56
Roonsitrong 2005 ²¹	4 months	Spironolactone 25 mg/day	Placebo	Mild diastolic dysfunction	>50%	15/15 (78%)	71
Kosmala 2011 ²²	6 months	Spironolactone 25 mg/day	Placebo	Metabolic syndrome	>50%	40/39 (54%)	59
Kosmala 2013 ²³	6 months	Spironolactone 25 mg/day	Placebo	BMI >30+diastolic dysfunction	>50%	58/55 (62%)	58
Mottram 2004 ²⁶	6 months	Spironolactone 25 mg/day	Placebo	Hypertension, diastolic heart failure (NYHA class II)	>50%	15/15 (63%)	62
Liu 2006 ²⁹	6 months	Spironolactone Mean dose: 47 mg/day	Usual care	Diastolic heart failure (NYHA class II/III)	>50%	40/38 (80%)	NA
Mak 2009 ²⁷	12 months	Eplerenone 25 to 50 mg/daily	Usual care	HFPEF+evidence of diastolic dysfunction	>45%	24/20 (54%)	80
Deswal 2011 ²⁵	6 months	Eplerenone 25 to 50 mg/daily	Placebo	HFPEF (NYHA class II/III)	>50%	21/23 (7%)	70
Edlemann 2013 ²⁸	12 months	Spironolactone 25 mg/day	Placebo	HFPEF (NYHA class II/III)	>50%	213/209 (52%)	67
Kurrelmeyer 2014 ³⁰	6 months	Spironolactone 25 mg/day	Placebo	HFPEF (NYHA class II/III)	>50%	24/24 (100%)	71

ACE indicates angiotensin-converting enzyme; BMI, body mass index; HFPEF, heart failure with preserved ejection fraction; HTN, hypertension; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; NA, not available; NYHA, New York Heart Association.

was reported at baseline and follow-up in 6 studies. In the pooled analysis of all available studies, MRA use was associated with a significant reduction in E/e' compared with control (WMD [95% CI]: -1.68 [-2.03 to -1.33]; $P<0.00001$), suggesting improvement in diastolic function. This beneficial effect of MRA on E/e' was also evident across

HFPEF (n=4 studies; WMD [95% CI]: -1.85 [-2.24 to -1.46]; $P<0.00001$) and asymptomatic LVDD subgroups (n=2 studies; WMD [95% CI]: -0.96 [-1.77 to -0.15]; $P=0.02$; Figure 3A).

Among other measures of diastolic function, 10 studies reported DT. In the pooled analysis of all available studies, there was a significant, but modest, reduction in DT with MRA

**Figure 2.** Risk of bias assessment for studies included in the meta-analysis.

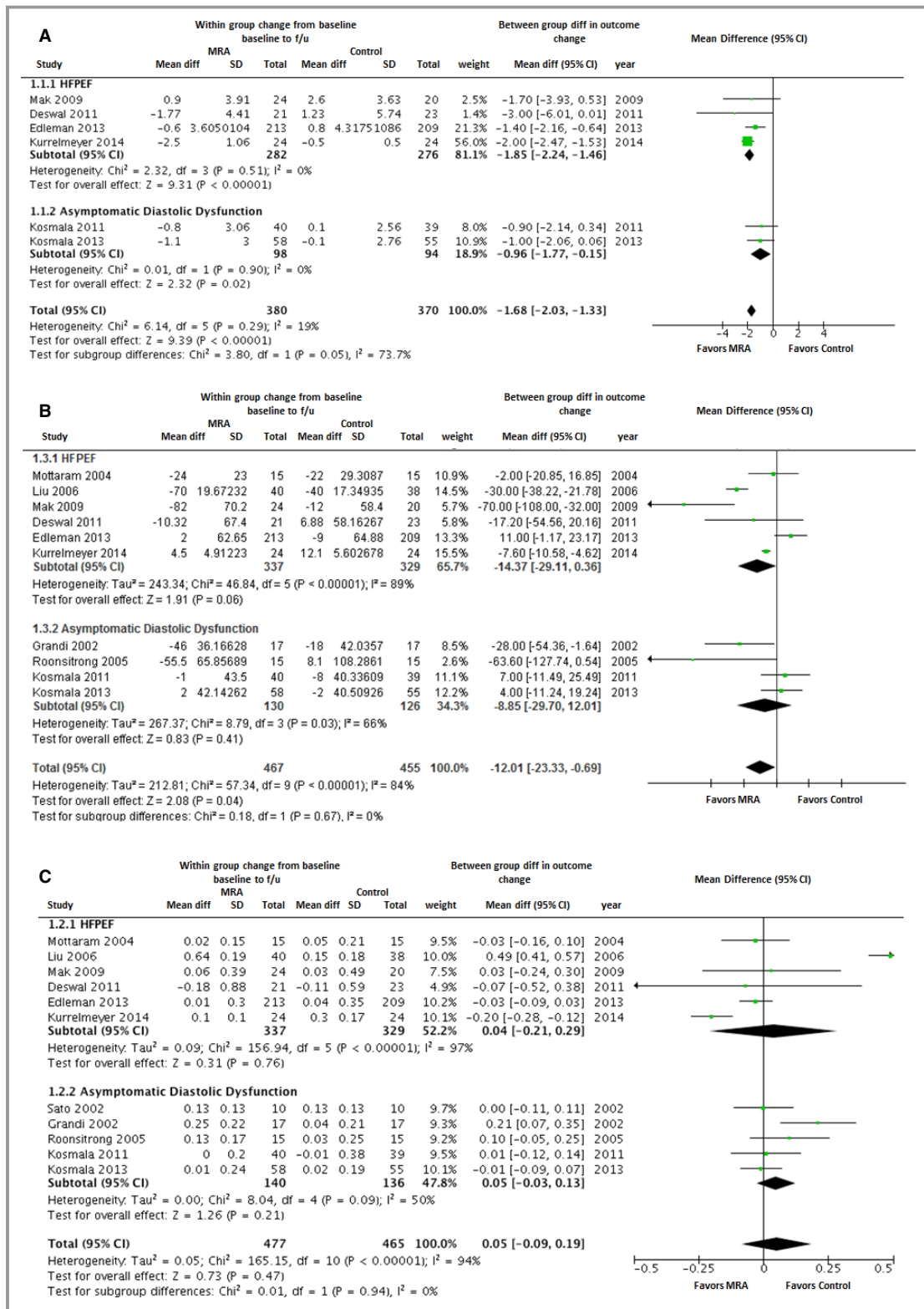


Figure 3. Forest plot showing the pooled difference between the mineralocorticoid receptor antagonist therapy group and the control group for changes in measures of left ventricular diastolic function from baseline to follow-up. Results are presented for the pooled analyses of all available studies as well as subgroups of studies with HFPEF and asymptomatic diastolic dysfunction. A, E/E'; (B) deceleration time; (C) E/A. Results are presented for the pooled analyses of all available studies as well as the subgroups of studies with HFPEF and asymptomatic diastolic dysfunction. CI, indicates confidence interval; HFPEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist.

use (WMD [95% CI]: -12.0 ms [-23.3 to -0.7]; $P=0.04$). In subgroup analyses, MRA use was associated with a modest reduction in DT with a trend toward significance in the HFPEF group (WMD [95% CI]: -14.4 ms [-29.1 to 0.4]; $P=0.06$), but not in asymptomatic LVDD subgroup (Figure 3B). E/A at baseline and follow-up was also reported in 11 studies. There was no significant change in E/A with use of MRA compared to control group in the overall pooled analysis (WMD [95% CI]: 0.05 [-0.09 to 0.19]; $P=0.47$) as well as the HFPEF and asymptomatic LVDD subgroups (Figure 3C).

Effect of MRAs on LV Size and Mass

Overall pooled estimates and subgroup (HFPEF and asymptomatic LVDD) effect estimates for LV end-diastolic diam-

eter and indexed LV mass are shown in Figure 4. LV end-diastolic diameter was reported at baseline and follow-up in 6 studies. In the pooled analysis of all available studies, MRA use was not associated with any significant change in LV end-diastolic diameter (WMD [95% CI]: -0.51 mm [-1.3 to 0.28]; $P=0.21$). Among HFPEF patients ($n=3$), there was a modest reduction in LV end-diastolic diameter with a trend toward significance with MRA use (WMD [95% CI]: -1.04 mm [-2.11 to 0.04]; $P=0.06$; Figure 4A). Four studies (3 HFPEF and 1 asymptomatic LVDD) reported indexed LV mass at baseline and follow-up. In the pooled analysis, indexed LV mass did not change significantly with use of MRA compared to the control group (WMD [95% CI]: 0.60 g/m² [-7.75 to 8.95]; $P=0.90$; Figure 4B).

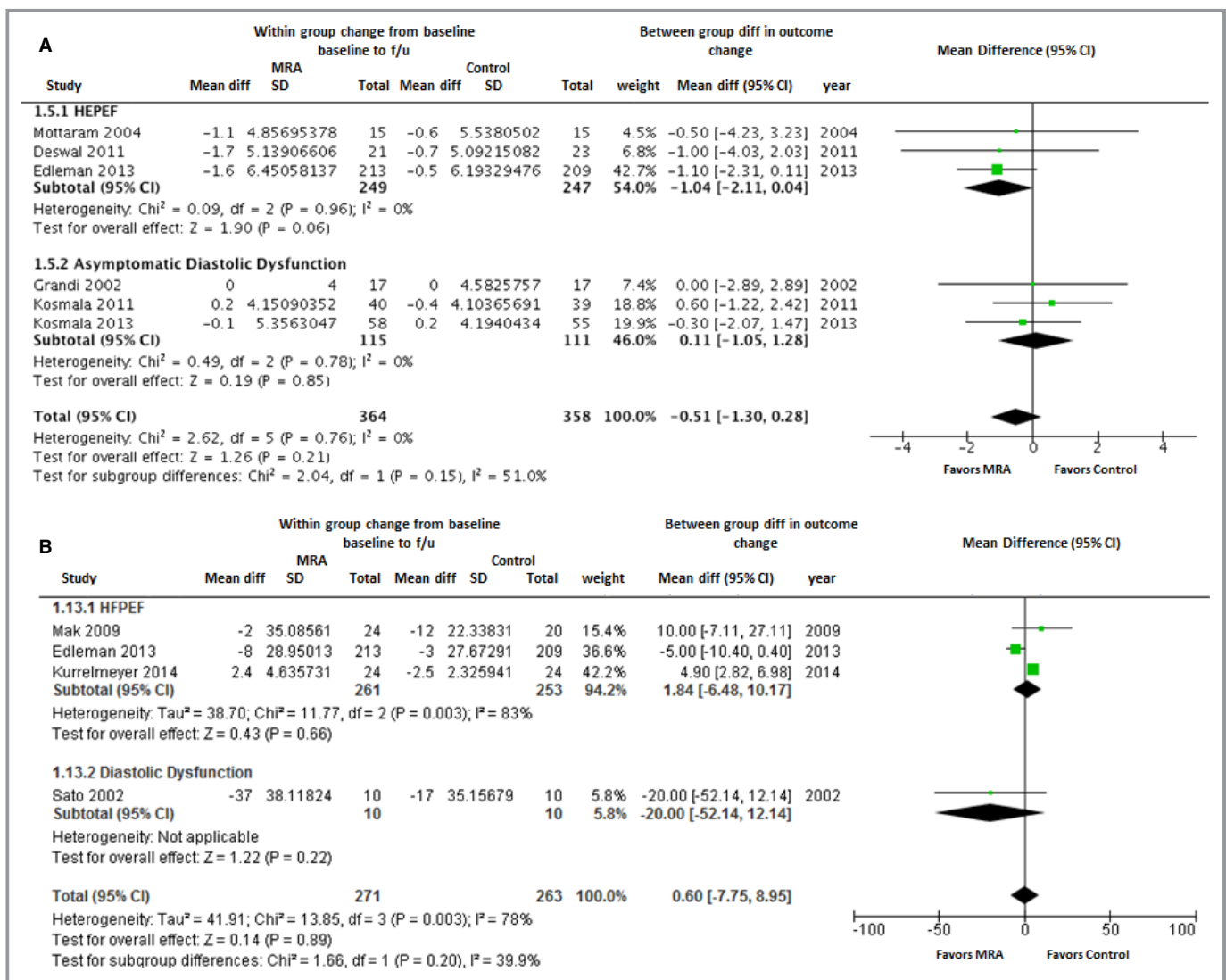


Figure 4. Forest plot showing the pooled difference between the mineralocorticoid receptor antagonist therapy group and the control group for changes in left ventricular end diastolic diameter (A) and left ventricular mass index (B) from baseline to follow-up. Results are presented for the pooled analyses of all available studies as well as the subgroups of studies with HFPEF and asymptomatic diastolic dysfunction. CI, indicates confidence interval; HFPEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist.

Effect of MRAs on Markers of Myocardial Fibrosis

Five studies provided information of surrogate markers of cardiac fibrosis, such as PIIINP and PICP. In the pooled analysis, there was a significant reduction in PIIINP with use of MRAs in the overall cohort (WMD [95% CI]: -0.90 µg/L [-1.38 to -0.43]; *P*=0.0002) as well as in the HFPEF and asymptomatic LVDD subgroups (Figure 5A). Similar reduction in PICP levels was also observed with MRA use in the overall pooled analysis (WMD [95% CI]: -17.6 ng/mL [-31.2 to -4.0]; *P*=0.01; Figure 5B).

Effect of MRAs on Blood Pressure

In the pooled analysis of all available studies with BP measurements, MRA use was associated with significant reduction in systolic blood pressure (SBP; WMD [95% CI]: -3.0 mm Hg [-5.5 to -0.6]; *P*=0.02) as well as diastolic blood pressures (DBP; WMD [95% CI]: -1.7 mm Hg [-2.7 to -0.6]; *P*=0.002). In subgroup analyses, the reduction in SBP and DBP with MRA use was significant in asymptomatic LVDD patients, but not the HFPEF patients (Figure 6).

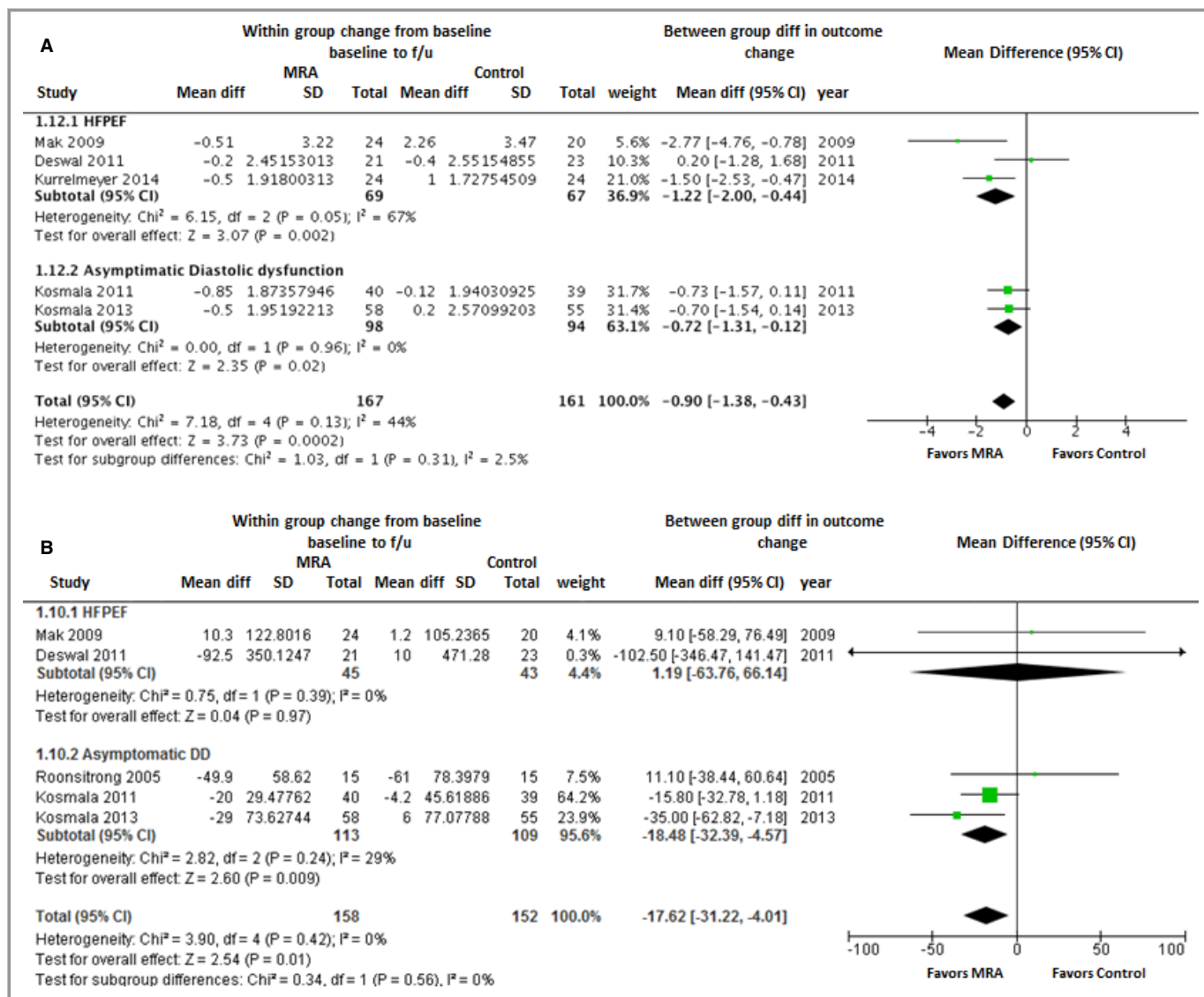


Figure 5. Forest plot showing the pooled difference between the mineralocorticoid receptor antagonist therapy group and the control group for changes in measures of collagen turnover (surrogate for myocardial fibrosis) from baseline to follow-up. A, PIIINP; (B) PICP. Results are presented for the pooled analyses of all available studies as well as the subgroups of studies with HFPEF and asymptomatic diastolic dysfunction. CI, indicates confidence interval; HFPEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; PICP, carboxy-terminal peptide of procollagen type I; PIIINP, amino-terminal peptide of procollagen type II.

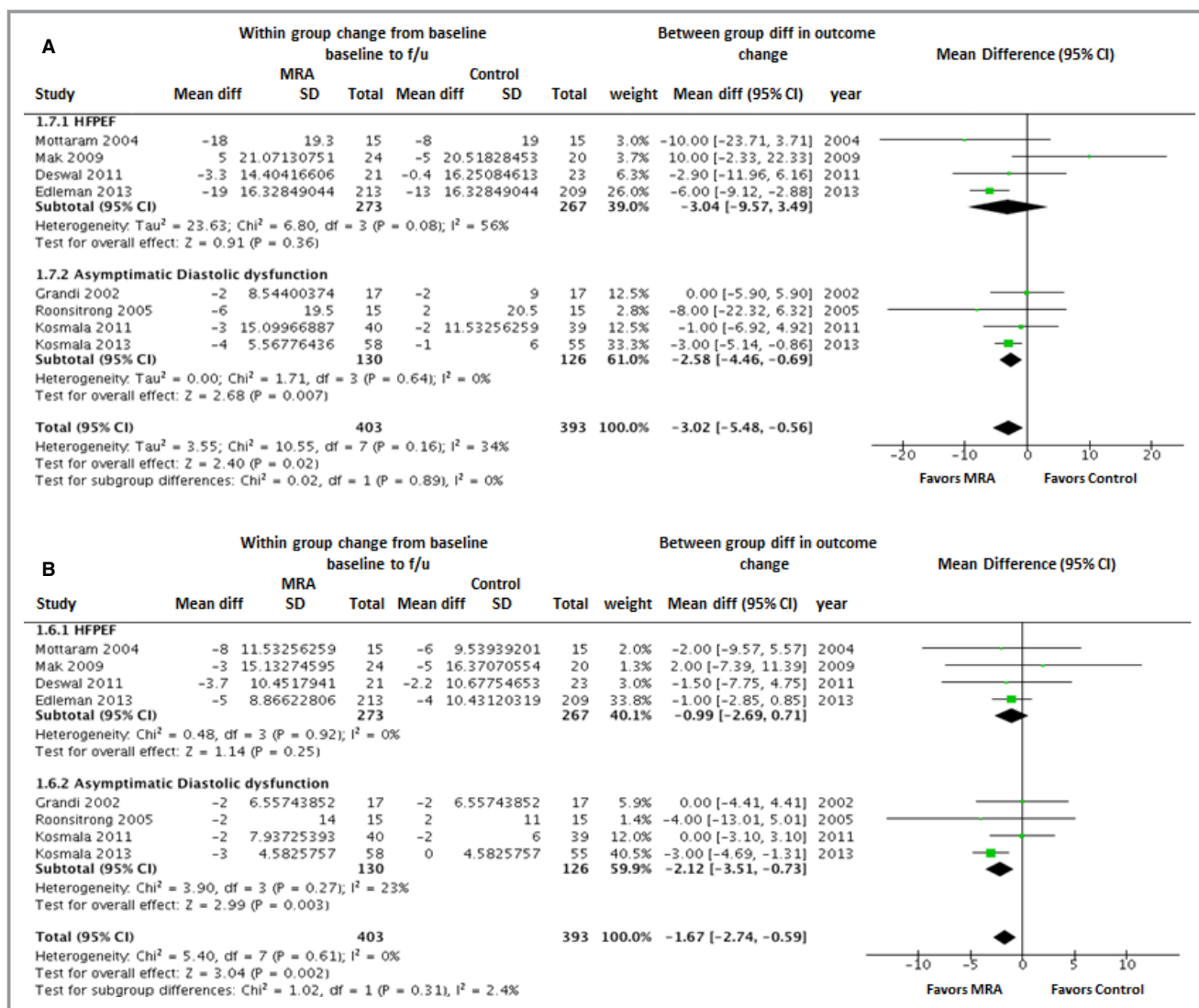


Figure 6. Forest plot showing the pooled difference between the mineralocorticoid receptor antagonist therapy group and the control group for changes in systolic blood pressure (A) and diastolic blood pressure (B). Results are presented for the pooled analyses of all available studies as well as the subgroups of studies with HFPEF and asymptomatic diastolic dysfunction. CI, indicates confidence interval; HFPEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist.

Clinical Safety and Efficacy of MRA Therapy

Exercise capacity (performance on 6-MWD test) was assessed in 3 HFPEF studies. There was no significant change in 6-MWD with use of MRA as compared to the control group (WMD [95% CI]: -8.2 m [-16.7 to 0.2]; $P=0.51$; Figure 7A). Serum potassium levels increased significantly with MRA use as compared to the control group in the overall cohort (WMD [95% CI]: 0.22 mmol/L [0.17 to 0.27]; $P<0.00001$) as well as HFPEF and asymptomatic LVDD subgroups (Figure 7B).

Discussion

The principal findings of this meta-analysis indicate that MRA therapy is associated with an improvement in diastolic

function, blood pressure, and markers of myocardial fibrosis without any significant changes in indexed LV mass or LV cavity size. To our knowledge, this is the largest, most comprehensive evaluation of the impact of MRA therapy on cardiac structure and function in patients with or at risk for HFPEF.

Mineralocorticoids have been associated with cardiac fibrosis and LVH resulting in myocardial stiffness and diastolic dysfunction.^{36,37} A recent meta-analysis of trials on use of MRA in HFREF showed favorable reverse LV remodeling along with improvements in systolic and diastolic function.³⁸ We observe a similar effect of MRA on biomarkers of collagen turnover and cardiac fibrosis in the current study. We also observed that MRA use was associated with a significant improvement in E/e' , a specific measure of LV diastolic

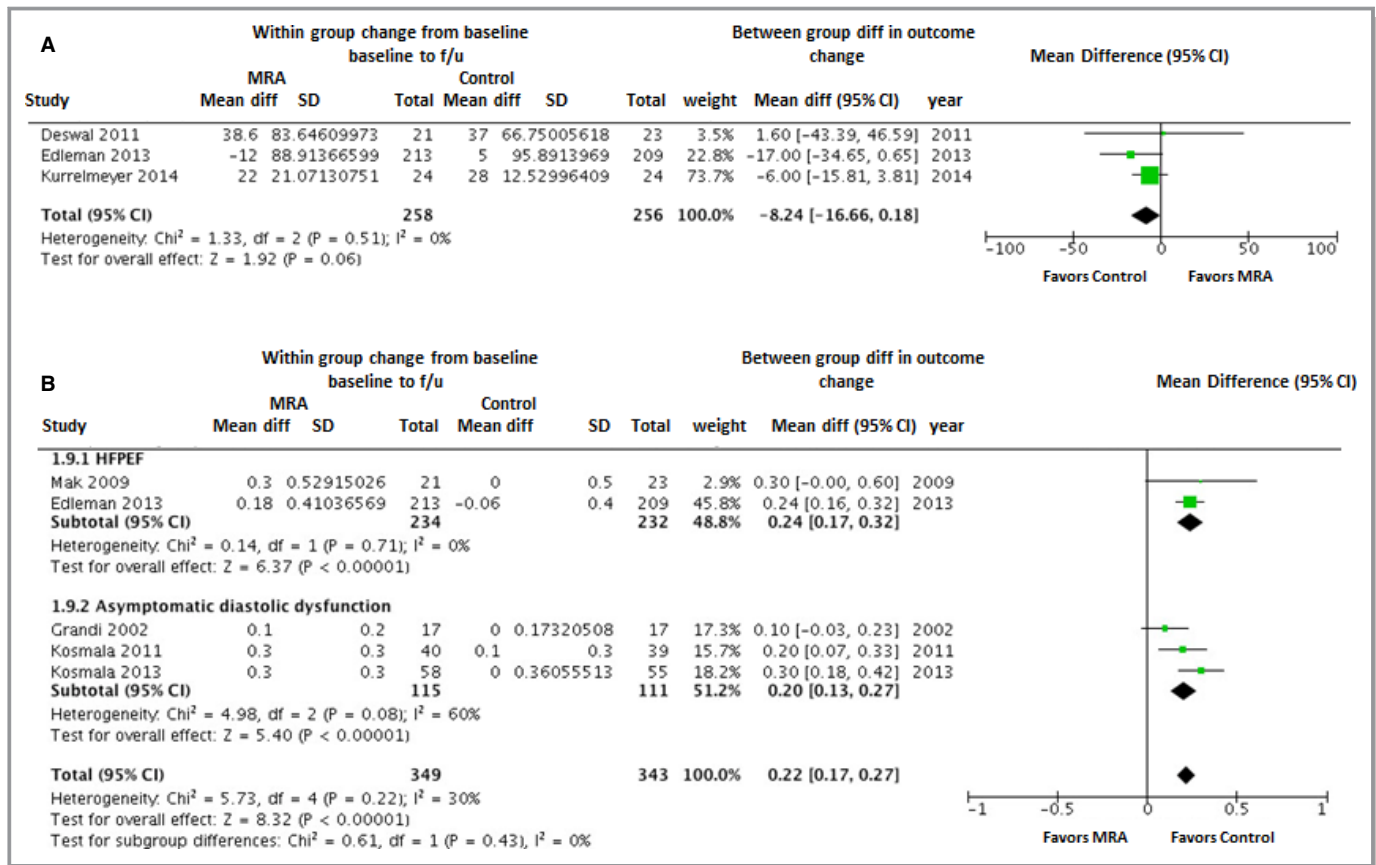


Figure 7. Forest plot showing the pooled difference between the mineralocorticoid receptor antagonist therapy group and the control group for changes in 6-minute walk test (A) and serum potassium levels (B). Serum potassium levels results are presented for the pooled analyses of all available studies as well as the subgroups of studies with HFPEF and asymptomatic diastolic dysfunction. CI, indicates confidence interval; HFPEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist.

function,³⁹ modest improvement in DT, and no change in E/A. Assessment of diastolic dysfunction is frequently challenging, and typically several indices are necessary for optimal identification.^{39,40} The observed heterogeneity in the effect of MRA on different measures of diastolic function could be related to the differences in the outcome definitions. The E/A is most commonly reported in most studies, but is unreliable as a single measure of diastolic dysfunction owing to the nonlinear relationship with dysfunction. Furthermore, both E/A and DT are load dependent and may be influenced by the volume status of the patient on the day of examination. From a physiological standpoint, as myocardial relaxation becomes abnormal, the rate of decrease in the LV pressure is slower and DT becomes longer, but LV filling pressure is not necessarily elevated. E/e' ratio remains normal as long as left atrial pressure remains normal.⁴¹ A reduction in blood pressure with MRA use, as observed in our analysis, would also be expected to lower LV filling pressures and improve the E/e' ratio.⁴²

We did not observe any significant changes in LV mass or LV end diastolic dimension with use of MRA in the overall

study population. Increased LV mass and LV hypertrophy have been identified as significant predictors of adverse clinical outcomes among HFPEF patients.⁹ Lack of significant effect on LV mass or size in the present study could be related to type II error owing to small sample size or relatively short follow-up duration. Future large studies with longer follow-up duration are needed to better understand the biological effect of MRA on LV mass and size.

Despite favorable effects of MRA therapy on diastolic function and myocardial fibrosis, no significant change in 6-MWD was observed on pooled analysis. This could also be owing to a type II error given that 6-MWD was only reported in 3 studies. Furthermore, changes in exercise capacity may lag behind improvements in surrogate serological measures of myocardial fibrosis and diastolic function. It is plausible that the lack improvement in these symptoms despite significant reductions in markers of myocardial fibrosis could be a function of the relatively short duration of follow-up among the included studies.

The recently published TOPCAT trial evaluated the clinical safety and efficacy of MRA in HFPEF.³¹ Although the trial

did not reach statistical significance for the primary endpoint, there were several interesting findings that point toward efficacy of MRA in HFPEF. First, there was a significant reduction in the secondary outcome of HF hospitalization among patients treated with MRAs. Second, participants enrolled in the trial based on elevated NT-ProBNP levels seemed to benefit significantly with use of MRAs.³¹ Finally, the recently published regional post-hoc analyses demonstrated significant clinical improvements among patients from the Americas.³² A beneficial effect on diastolic function observed in our study could potentially explain some of the clinical benefits of MRA among HFPEF patients that were observed by TOPCAT investigators and others.⁴³

There are several limitations of this study. First, because it is a meta-analysis, the validity of our results is dependent on the validity of the studies included. We did not include patient-level data. Second, the overall sample size of the study population is relatively small. Thus, it is possible that type II error may be responsible for some of the negative findings. Third, all measures of diastolic function and LV geometry were not consistently reported in all the included clinical trials. Similarly, the measures of exercise capacity (6-MWD test) were reported in only 3 trials, whereas peak oxygen consumption, a gold standard for measuring exercise capacity, was reported in only 1 study. Fourth, significant heterogeneity was observed on pooled analysis of included studies for most outcomes. This could be related to the differences in the study design with respect to the choice of MRA (spironolactone in 8 studies versus eplerenone/canrenone in 3 studies), lack of consistent use of placebo with usual therapy in the comparator arm (usual therapy+placebo in 7 studies, usual therapy only in 4 studies), and duration of treatment. Also, the mean follow-up duration in these clinical trials was relatively short (<1 year). Finally, none of the included trials reported clinical outcomes, such as HF hospitalizations and mortality.

In conclusion, our meta-analysis indicates that MRA therapy in patients with HFPEF and impaired diastolic function may exert a beneficial effect on diastolic dysfunction and myocardial fibrosis. Further studies with long-term follow-up are needed to determine whether these favorable changes in diastolic function can translate into significant clinical improvement in these patients.

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Disclosures

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