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Original Article

Impact of Mineralocorticoid Receptor Antagonists on Changes in Cardiac Structure and Function of Left Ventricular Dysfunction

A Meta-analysis of Randomized Controlled Trials

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Background—A comprehensive evaluation of the benefits of mineralocorticoid receptor antagonists on cardiac remodeling is lacking. We aimed to evaluate the impact of mineralocorticoid receptor antagonists on changes in cardiac structure and function of left ventricular dysfunction.

Methods and Results—Articles were identified by online searches in PubMed, EMBASE, Cochrane, and ClinicalTrials.gov databases before June 2012, by hand searches of reviews and relevant journals, and by contact with the authors. Qualified articles were restricted to randomized controlled trials. There were, respectively, 12, 4, and 3 qualified trials that randomized 572, 647, and 407 patients to spironolactone, canrenoate, and eplerenone, and 531, 655, and 395 patients to placebo or active treatment, respectively. Overall, under mineralocorticoid receptor antagonist treatment there was improvement in left ventricular ejection fraction (weighted mean difference, 2.97; 95% confidence interval [95% CI], 2.26–3.67; $P<0.0005$), left ventricular end-systolic and end-diastolic volume index (weighted mean difference, −5.64; 95% CI, −7.94 to −3.34; $P<0.0005$ and weighted mean difference, −7.46; 95% CI, −11.63 to −3.3; $P<0.0005$), serum amino-terminal peptide of procollagen type-III (weighted mean difference, −1.12; 95% CI, −1.49 to −0.74; $P<0.0005$), B-type natriuretic peptide (weighted mean difference, −67.06; 95% CI, −91.24 to −42.88; $P<0.0005$), peak velocities of early mitral inflow (E; weighted mean difference, −9.57; 95% CI, −12.98 to −6.17; $P<0.0005$), and E wave deceleration time (weighted mean difference, 7.08; 95% CI, 4.07–10.09; $P<0.0005$). There was low probability of heterogeneity and publication bias.

Conclusions—Our findings demonstrate that mineralocorticoid receptor antagonist treatment may exert beneficial effects on the reversal of cardiac remodeling and improvement of left ventricular function. **(*Circ Heart Fail*. 2013;6:156-165.)**

Key Words: cardiac remodeling ■ left ventricular dysfunction ■ meta-analysis ■ mineralocorticoid receptor antagonist ■ randomized controlled trial

Aldosterone, a major agonist for mineralocorticoid receptors, is regarded as a potent mediator of cardiac remodeling in left ventricular dysfunction.[1] Increased levels of aldosterone tend to promote the development of fibrosis in hypertrophied cardiac ventricles, reduce myocardial perfusion, and increase the incidence of cardiovascular events.[2] A systematic review of clinical trials by Ezekowitz et al[3] has reported that administration of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure and postmyocardial infarction can account for a 20% reduction in all-cause mortality. However, they did not synthesize data on the corresponding changes in cardiac structure and function. It is universally accepted that cardiac remodeling is a core pathogenetic feature of left ventricular dysfunction. Several clinical trials have been undertaken to explore the potential impact of MRAs on cardiac remodeling in patients with heart failure or myocardial infarction; however, a comprehensive evaluation of this impact is lacking. Given the accumulating

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data on the subject, there is a need to synthesize available randomized controlled trials (RCTs) regarding changes of cardiac structure and function affected by MRAs in patients with left ventricular dysfunction.

Methods

We carried out this meta-analysis of RCTs in accordance with standards set forth by the Quality of Reports of Meta-Analyses (QUOROM) statement.[4]

Search Strategy

A literature search was conducted through PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases covering the period from the earliest possible year to June 25, 2012. MRAs of interest include spironolactone, canrenoate, and eplerenone. The following subject terms were used in the search: aldosterone receptor antagonist, aldosterone antagonist, mineralocorticoid receptor, aldosterone blockade, spironolactone or Aldactone, canrenoate or potassium canrenoate or canrenone or canrenoic acid, eplerenone or Inspra, combined with heart failure, myocardial infarction, cardiac dysfunction, cardiac insufficiency, cardiac inadequacy, or ventricular dysfunction. The search was supplemented by reviews of reference lists, hand-searching of relevant journals, and correspondence with authors. Search results were limited to clinical trials and English language.

Trial Selection

Two investigators (X.L. and W.N.) independently obtained the full texts of articles identified as potentially eligible based on the titles and abstracts. If necessary, we emailed the contributing authors to avoid double counting of participants recruited in >1 trial by the same group. Where more than 1 publication of a trial existed, we abstracted data from the most recent or most complete publication.

Inclusion/Exclusion Criteria

Because relative to heart failure with reduced ejection fraction (HFREF) there are relatively few MRA-therapy trials on heart failure with preserved ejection fraction, and on the premise that HFREF and heart failure with preserved ejection fraction have a different pathophysiology,[5] we, in this meta-analysis, focused only on HFREF in trials involving patients with heart failure. For inclusion, trials had to be conducted in a randomized manner, involve patients with HFREF or myocardial infarction, and examine the usage of MRAs versus placebo or active controls. Trials were excluded if they merely evaluated mortality or hospitalization, MRA treatment was <4 weeks, they were crossover trials, or lacked washout period. Conference abstracts, case reports, editorials, review articles, and non-English articles were also excluded.

Data Extraction

Investigators (X.L. and W.N.) independently extracted data using a standardized Excel template (Microsoft Corp, Redmond, WA). Disagreements were resolved by consensus or by a third investigator (N.J.). Quality assessment was evaluated by a modified Jadad score,[6] with total scores ranging from 0 (worst) to 5 (best).

Data were collected on the first author, year of publication, dosage and treatment duration of MRAs, sample size and withdrawal rate of each arm, cutoffs of creatinine, potassium, New York Heart Association (NYHA) class, and left ventricular ejection fraction (LVEF) at enrollment, and characteristics of trial patients, including age, sex, cause of left ventricular dysfunction, percentages of concurrent diseases (hypertension and diabetes mellitus), usage of calcium channel blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blockers, diuretics, and digitalis.

Table 1. Characteristics of Qualified Trails

						Patients (number)	
Author (y)	Follow-up (mo)	Drug: Dose (mg/d)	Control	Inclusion Criteria	LVEF (mean)	Treatment	Control
Barr CS (1995)[9]	2	SP: 50–100	Placebo	HF with CAD; NYHA: II-III	20	28	14
Zannad F (2000)[27]	6	SP: 12.5–50	Placebo	CHF; NYHA: III-IV; LVEF<35%	26	129	133
Tsutamoto T (2001)[23]	4	SP: 25	Placebo	CHF; II-III; <45	32.2	20	17
Modena MG (2001)[22]	3, 6, 12	CAN: 50	Placebo	MI; Killip I-III	47	24	22
Di Pasquale (2001)[14]	3	CAN: 25	Placebo	MI; Killip I-II	44.3	94	93
Cicoira M (2002)[13]	12	SP: 12.5–50	Placebo	CHF; LVEF<45%	33	54	52
Hayashi MT (2003)[17]	1	SP: 25	Placebo	MI	46	65	69
Di Pasquale (2005)[15]	3, 6	CAN: 25	Placebo	MI; Killip I-II	44.5	341	346
Berry C (2007)[10]	3	SP: 25	Placebo	HF; NYHA: I-III; LVEF<40%	29	20	20
Chan AK (2007)[12]	6, 12	ARB & SP: 25	ARB & Placebo	CHF; NYHA: I-III; LVEF<40%	26	25	26
Gao X (2007)[16]	6	SP: 20	Placebo	CHF; NYHA: II-IV; LVEF<45%	42	58	58
Kasama S (2007)[19]	6	ARB & SP: 25	ARB	CHF; NYHA: II-III; LVEF<45%	32	25	25
Weir RA (2009)[26]	6	EP: 25–50	Placebo	MI; Killip I-II; LVEF<40%	51.5	50	50
Iraqi W (2009)[18]	3, 6, 9	EP: 25–50	Placebo	CHF after AMI; LVEF<40%	34	240	236
Li MJ (2009)[21]	6	SP: 25–50	Placebo	CHF; NYHA: II-IV; LVEF<45%	NA	58	28
Boccanelli A (2009)[11]	12	CAN: 25–50	Placebo	CHF; NYHA: II; LVEF<45%	39.9	188	194
Udelson JE (2010)[24]	9	EP: 50	Placebo	CHF; NYHA: II-III; LVEF<35%	26.2	117	109
Vizzardi E (2010)[25]	6	SP: 25–100	Placebo	HF; NYHA: I-II; LVEF<40%	34.6	79	79
Kimura M (2011)[20]	3, 12	SP: 25	Placebo	CHF; NYHA: II-III; LVEF<40%	34	11	10

ARB indicates angiotensin receptor blocker; CAN, canrenoate; CAD, coronary artery disease; CHF, chronic heart failure; EP, eplerenone; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; NYHA, New York Heart Association; and SP spironolactone.

More importantly, potentially relevant outcomes in cardiac structure and function before and after treatment were extracted: serum indicators—creatinine, potassium, B-type natriuretic peptide (BNP), amino-terminal peptide of procollagen type-III (PIIINP); indexes of left ventricular structure and function—LVEF, left ventricular end-systolic volume index (LVESVI), left ventricular end-diastolic volume index (LVEDVI), left ventricular mass index, peak velocities of early (E) and late (A) mitral inflow, E/A, E wave deceleration time (DT), and isovolumetric relaxation time. Moreover, data on safety and adverse events, including hyperkalemia and gynecomastia, were also drawn. Hyperkalemia is defined as a potassium level >5.0 mmol/L.

Statistical Analysis

For a certain outcome, where data from 3 or more unduplicated trials were available, a meta-analysis was performed. Quantitative outcomes changing from baseline to follow-up were summarized and compared by weighted mean difference (WMD) with 95% confidence interval (95% CI) between treatment group and control group. Pearson correlation analyses were used to test relations between outcomes. The random-effects model using the DerSimonian and Laird method[7] was used irrespective of heterogeneity. Heterogeneity was assessed by χ^2 test and quantified using the inconsistency index (I^2) statistic, which ranges from 0% to 100% and is defined as the percentage of the observed between-trial variability that is due to heterogeneity rather than chance.

Predefined subgroup analyses were conducted a priori according to subtypes of left ventricular dysfunction (HFREF and myocardial infarction), treatment durations (≤3 months, (3, 6) months and >6 months), and MRAs (spironolactone, canrenoate, and eplerenone). If a given trial could be split into 2 or more separate studies due to different time points in treatment, the study with the longest follow-up was used in overall and subgroup analyses, with the exception of the subgroup analysis by treatment durations, where all separate studies were considered.

Sensitivity analyses were performed to assess the contribution of individual trials to pooled effect estimates by sequentially omitting each trial one at a time and computing differential estimates for remaining trials. Meta-regression analyses were carried out to evaluate the extent to which different trial-level variables, including all characteristics of trial patients as mentioned above, explained the heterogeneity of pooled treatment effects of MRAs on serum indicators and indexes of left ventricular structure and function.

Publication bias was assessed by visual inspection of the Begg's and Egger's funnel plots, accompanied by the corresponding Begg's and Egger's tests. The trim and fill method was adopted to estimate the number and outcomes of potentially missing trials resulting from publication bias. $P<0.05$ was considered statistically significant with the exceptions of I^2, Begg's and Egger's statistics, for which a significance level was defined as $P<0.10$.[8] Data management and statistical analyses were conducted using STATA software (StataCorp, College Station, TX, version 11.2 for Windows).

Results

Eligible Trials

Characteristics of the trials included in this meta-analysis are presented in Tables 1 and 2. The primary search for clinical trials on MRAs and left ventricular dysfunction generated 559 potentially relevant articles, of which 19 met the selection criteria and were published between 1995 and 2011.[9–27] A flow diagram schematized the process of selecting and excluding articles with specific reasons (Figure 1). Five of 19 qualified trials recorded outcomes within >1 time point in treatment, yielding a total of 26 studies conducted exclusively in subgroup analyses by treatment durations.

There were, respectively, 12, 4, and 3 qualified trials that randomized 572, 647, and 407 patients to spironolactone,

Table 2. Characteristics of Patient Populations in the Trials

	MRA Treatment Group/Placebo or Active Control Group (%)									
Author (y)	Age (y)	Males	Ischemic*	HT	DM	CCB	ACEI/ARB	β-Blockers	Diuretics	Digoxin
Barr CS (1995)[9]	68/70	78.57/71.43	100/100	0/0	NA	25/28.57	100/100	NA	100/100	NA
Zannad F (2000)[27]	69/69	72/71	51/44	NA	18/28	11/8	93/90	5/5	100/100	57/56
Tsutamoto T (2001)[23]	62.7/65	75/76.47	NA	NA	NA	NA	70/76.47	45/29.41	60/70.59	60/88.24
Modena MG (2001)[22]	59/62	70.83/77.27	100/100	50/51.5	16.6/13.6	20.83/18.18	100/100	41.67/50	8.33/9.09	4.17/4.55
Di Pasquale (2001)[14]	63.6/62.8	65.96/65.59	100/100	44.68/44.09	38.3/39.78	NA	100/100	38.3/36.56	NA	NA
Cicoira M (2002)[13]	62.5/61.7	85.19/88.46	64.81/63.46	NA	NA	NA	100/100	72.22/65.38	NA	NA
Hayashi MT (2003)[17]	64.4/62.9	75.38/73.91	100/100	27.69/30.43	41.54/42.09	30.77/24.64	100/100	29.23/31.88	13.85/14.49	NA
Di Pasquale (2005)[15]	62.6/62.8	71.26/70.52	100/100	35.78/34.97	38.71/40.75	NA	100/100	36.95/36.13	NA	NA
Berry C (2007)[10]	65/59	75/80	90/50	30/30	10/10	NA	100/100	100/100	85/70	5/20
Chan AK (2007)[12]	61.4/65	86.96/80	47.8/64	30.4/40	26.1/32	NA	100/100	69.6/72	47.8/68	NA
Gao X (2007)[16]	55/54	63.79/65.52	50/51.72	60.35/56.9	36.21/34.48	NA	100/98	55.17/56.9	100/100	98.28/96.55
Kasama S (2007)[19]	69/67	64/68	40/52	NA	NA	NA	100/100	68/76	100/100	NA
Weir RA (2009)[26]	61/56.8	74/80	100/100	44/26	0/0	NA	94/94	96/90	18/24	NA
Iraqi W (2009)[18]	62/62	73/75	100/100	59/66	30/29	NA	83/89	77/78	52/51	NA
Li MJ (2009)[21]	59.8/58.2	72.41/71.43	100/100	NA	NA	NA	100/100	100/100	NA	100/100
Boccanelli A (2009)[11]	62.4/62	83.5/85	51.1/49	46.3/43.8	21.4/18.6	6.4/7.7	97.3/96.4	80.9/77.8	68.1/68	23.9/25.7
Udelson JE (2010)[24]	63.3/62	83.8/83.5	60/61	65/56	40.2/36.7	NA	94.9/98.2	96.6/93.6	70.9/69.7	NA
Vizzardi E (2010)[25]	61/58	84.81/82.28	45.57/43.04	27.85/24.05	16.46/24.05	NA	87.34/88.61	88.61/89.87	88.61/89.87	NA
Kimura M (2011)[20]	67/68	72.73/70	63.64/70	NA	NA	NA	55/60	82/80	NA	NA

ACEI/ARB indicates angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; DM, diabetic mellitus; HT, hypertension; MRA, mineralocorticoid receptor antagonists; and NA, not available.

*Ischemic cause of left ventricular dysfunction.

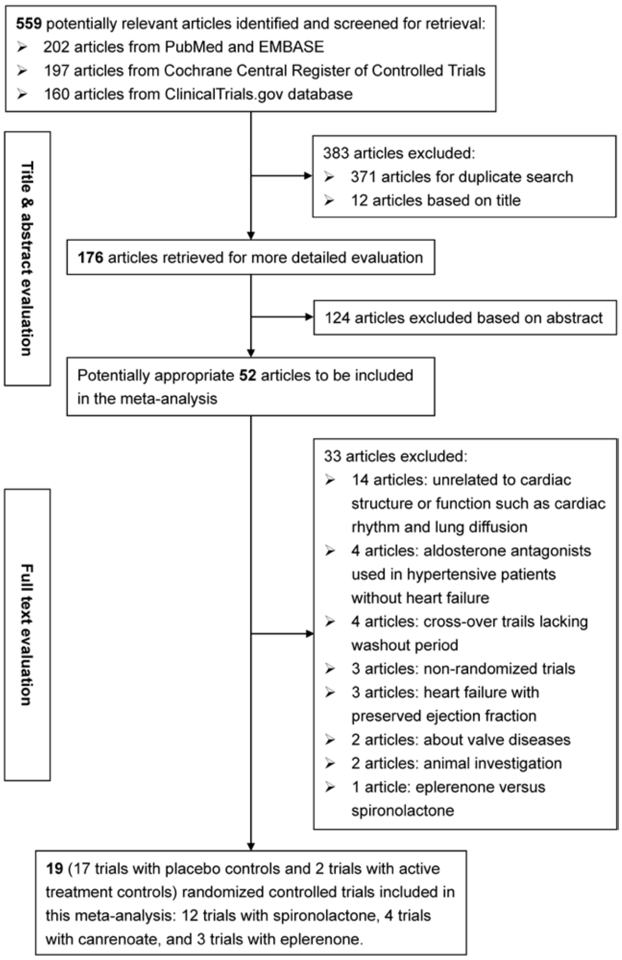

Figure 1. Flow diagram of search strategy and study selection.

canrenoate, and eplerenone, and 531, 655, and 395 patients to placebo or active treatment, respectively. The mean follow-up time of all trials was 7.0 (SD, 3.67; range, 1–12) months. The withdrawal rates were low and comparable between MRA treatment group (mean, 4.21%) and placebo or active control group (mean, 2.97%).

Quality Assessment

Various tools have been designed to perform study quality assessment, and the Jadad score is frequently used to assess the quality of RCTs.[28] In this meta-analysis, we used a modified Jadad scoring system developed by Crowther et al.[6] Quality assessment was performed in duplicate with κ agreement rate of 0.96, and its details are described in Table I in the online-only Data Supplement. The scores of individual trials ranged from 2 to 5 (mean, 3.84; SD, 1.26) of a maximal score of 5.

Indexes of Cardiac Structure and Function

Overall effect estimates and subgroup analyses by subtypes of left ventricular dysfunction are presented in Figure 2, and subgroup analyses by treatment durations and MRAs are presented in Table 3. When all trials were brought to the meta-analysis, improvement was obtained for LVEF (WMD, 2.97; 95% CI, 2.26–3.67; P<0.0005), LVESVI (WMD, −5.64; 95% CI, −7.94 to −3.34; P<0.0005), and LVEDVI (WMD, −7.46; 95% CI, −11.63 to −3.3; P<0.0005; Figure 2). There was no evidence of heterogeneity except for LVEDVI (I^2=53.9%), and low probability of publication bias as reflected by the Begg's (Figure I in the online-only Data Supplement), Egger's (Figure II in the online-only Data Supplement), and Filled (Figure III in the online-only Data Supplement) funnel plots.

Benefit of MRAs on LVEF was particularly evident across subgroups by subtypes of left ventricular dysfunction (Figure 2) and by treatment durations, as well as in subgroups limited to spironolactone or canrenoate (Table 3). As for LVESVI and LVEDVI, significance was attained in patients with myocardial infarction, treated ≤6 months and with spironolactone or canrenoate. Considering the possibility that the more sustained effect of MRAs on chronic heart failure might dilute its robust early effect on postmyocardial infarction, further subgroup analyses were undertaken for LVESVI and LVEDVI by treatment durations in patients with HFREF and myocardial infarction, respectively (Figure IV in the online-only Data Supplement). As expected, in myocardial infarction patients, significance was found in trials with treatment ≤3 and (3, 6) months; as the durations increased, the extent of reduction in LVESVI and LVEDVI was weakened or became nonsignificant. In contrast, there was no clear tendency and statistical significance in trials involving patients with HFREF.

Serum Indicators

Overall effect estimates and subgroup analyses by subtypes of left ventricular dysfunction are presented in Figure 3, and subgroup analyses by treatment durations and MRAs are presented in Table 4. Pooling the results of all qualified trials found a significant reduction in serum PIIINP (WMD, −1.12; 95% CI, −1.49 to −0.74; P<0.0005) and BNP (WMD, −67.06; 95% CI, −91.24 to −42.88; P<0.0005), with no evidence of heterogeneity or publication bias (Figures I–III in the online-only Data Supplement). Of note, a close, positive correlation was identified between changes of PIIINP and LVEF after MRA treatment (R=0.96; P=0.011), but this correlation was somewhat weakened in placebo or active control group (R=0.91; P=0.034). There was no significant correlation between BNP and LVEF (data not shown). As expected, serum creatinine (WMD, 0.05; 95% CI, 0.04–0.07; P<0.0005) and potassium (WMD, 0.22; 95% CI, 0.02–0.42; P=0.034) were higher in MRA treatment group than in placebo or active control group (data not shown).

In subgroup analyses, MRA treatment was observed to reduce serum PIIINP across subgroups by subtypes of left ventricular dysfunction (Figure 3) and by treatment durations, as well as in subgroups limited to spironolactone or canrenoate (Table 4). The longer the duration in treatment, the greater the reduction in PIIINP. Moreover, serum BNP in patients treated (3, 6) and >6 months or with spironolactone or with HFREF was remarkably lower than that of patients receiving placebo or active treatment.

Echo Indexes of Diastolic Function

Overall effect estimates and subgroup analyses by subtypes of left ventricular dysfunction are presented in Figure 4, and

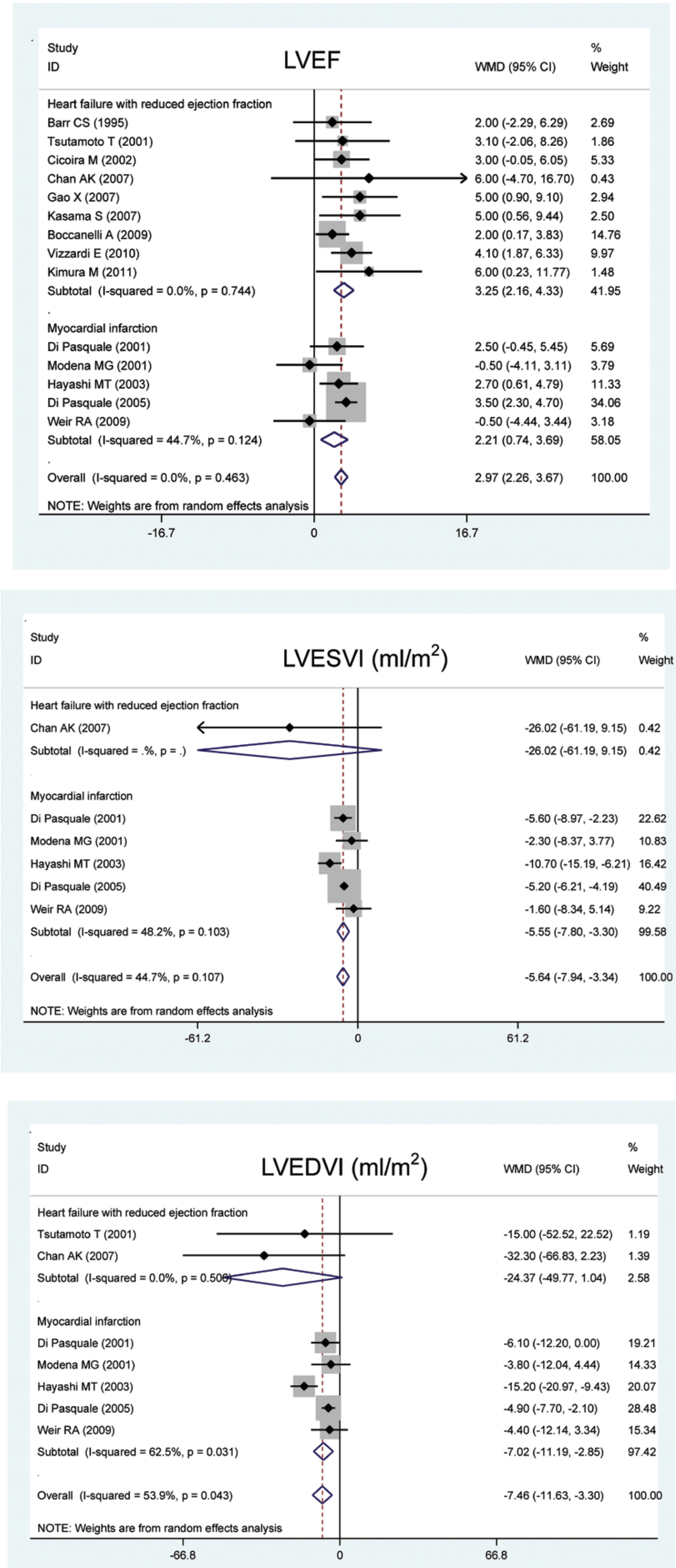

Figure 2. Forest plots for changes of LVEF (left ventricular ejection fraction), LVESVI (left ventricular end-systolic volume index), and LVEDVI (left ventricular end-diastolic volume index) between mineralocorticoid receptor antagonist treatment group and placebo or active control group by subtypes of left ventricular dysfunction. WMD indicates weighted mean difference.

Table 3. Subgroup Analyses of Indexes of Cardiac Structure and Function

Outcomes	Duration	Studies	WMD	95% CI	*P* Value	I^2% (*P* Value)	Drug Type	Trials	WMD	95% CI	*P* Value	I^2% (*P* Value)
LVEF	≤3 m	6	2.33	1.47 to 3.2	0.000	0.0 (0.744)	Spironolactone	9	3.56	2.43 to 4.7	0.000	0.0 (0.914)
	(3, 6) m	8	2.97	1.61 to 4.33	0.000	32.6 (0.168)	Canrenoate	4	2.4	1.0 to 3.81	0.001	43.1 (0.153)
	>6 m	5	2.18	0.57 to 3.8	0.008	13.0 (0.331)	Eplerenone	1	−0.5	−4.44 to 3.44	0.804	NA
LVESVI (mL/m²)	≤3 m	4	−5.45	−8.44 to −2.45	0.000	68.5 (0.023)	Spironolactone	2	−10.95	−15.4 to −6.49	0.000	0.0 (0.397)
	(3, 6) m	4	−5.03	−6.01 to −4.04	0.000	0.0 (0.408)	Canrenoate	3	−5.16	−6.12 to −4.21	0.000	0.0 (0.63)
	>6 m	2	−7.58	−26.91 to 11.76	0.443	41.1 (0.193)	Eplerenone	1	−1.6	−8.34 to 5.14	0.642	NA
LVEDVI (mL/m²)	≤3 m	4	−7.19	−12.19 to −2.2	0.005	73.2 (0.011)	Spironolactone	3	−15.65	−21.28 to −10.02	0.000	0.0 (0.632)
	(3, 6) m	5	−4.75	−7.23 to −2.28	0.000	0.0 (0.728)	Canrenoate	3	−5.0	−7.43 to −2.56	0.000	0.0 (0.9)
	>6 m	2	−12.92	−38.97 to 13.14	0.331	59.6 (0.116)	Eplerenone	1	−4.4	−12.14 to 3.34	0.265	NA
LVMI (g/m²)	≤3 m	0	NA	NA	NA	NA	Spironolactone	3	−12.03	−20.23 to −3.82	0.004	0.0 (1.0)
	(3, 6) m	4	−5.12	−13.47 to 3.23	0.23	48.7 (0.12)	Canrenoate	0	NA	NA	NA	NA
	>6 m	1	−12.1	−28.29 to 4.09	0.143	NA	Eplerenone	1	1.4	−4.22 to 7.02	0.625	NA

CI indicates confidence interval; LVEF, left ventricular ejection fraction; LVESVI/LVEDVI, left ventricular end-systolic/end-diastolic volume index; LVMI, left ventricular mass index; NA, not available; and WMD, weighted mean difference.

subgroup analyses by treatment durations and MRAs are presented in Table 5. Among all independent trials, overall estimates reached significance for E (WMD, −9.57; 95% CI, −12.98 to −6.17; $P<0.0005$) and DT (WMD, 7.08; 95% CI, 4.07–10.09; $P<0.0005$), without heterogeneity or publication bias. Further subgroup analyses revealed improvement on E

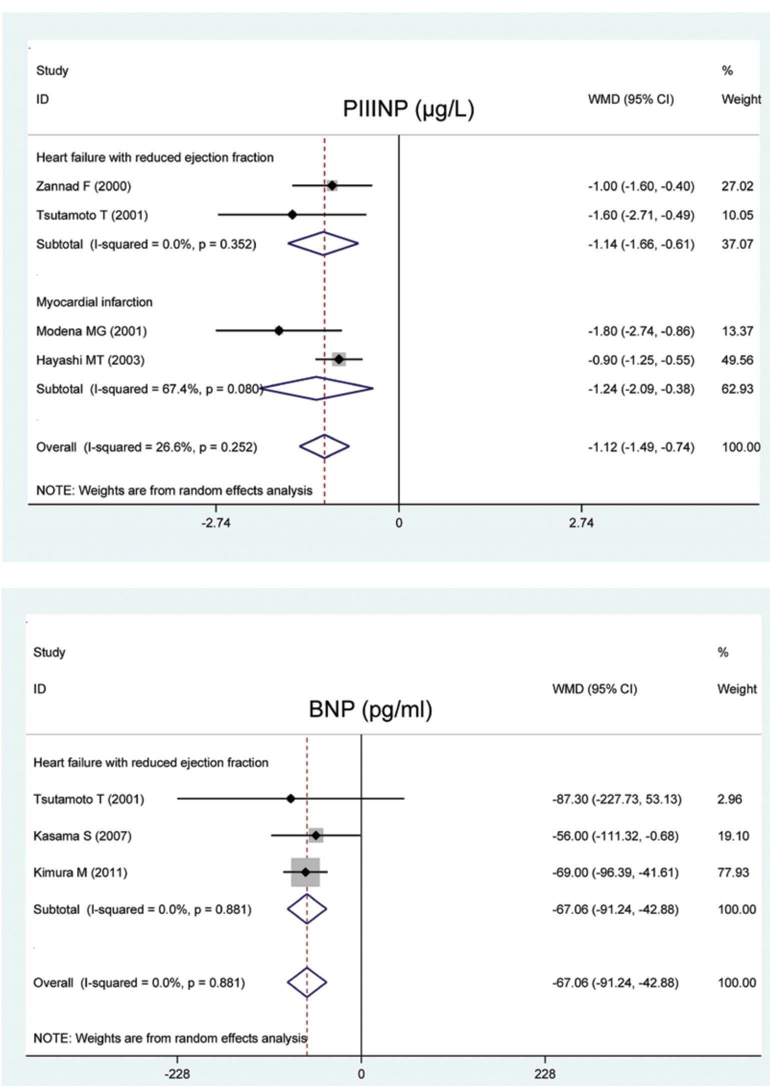

Figure 3. Forest plots for changes of serum amino-terminal peptide of procollagen type-III (PIIINP) and B-type natriuretic peptide (BNP) between mineralocorticoid receptor antagonists treatment group and placebo or active control group by subtypes of left ventricular dysfunction. WMD indicates weighted mean difference.

Table 4. Subgroup Analyses of Serum Indicators

Outcomes	Duration	Studies	WMD	95% CI	*P* Value	I^2% (*P* Value)	Drug Type	Trials	WMD	95% CI	*P* Value	I^2% (*P* Value)
Cr	≤3 m	3	0.03	−0.01 to 0.06	0.102	0.0 (0.704)	Spironolactone	1	0.02	−0.09 to 0.13	0.722	NA
(mg/dL)	(3, 6) m	2	0.04	−0.02 to 0.1	0.187	50.4 (0.156)	Canrenoate	2	0.06	0.04 to 0.07	0.000	0.0 (0.416)
	>6 m	0	NA	NA	NA	NA	Eplerenone	1	−0.01	−0.11 to 0.09	0.836	NA
K	≤3 m	4	0.29	0.08 to 0.5	0.006	95.4 (0.000)	Spironolactone	3	0.16	−0.07 to 0.39	0.173	81.4 (0.002)
(mmol/L)	(3, 6) m	3	0.09	−0.08 to 0.25	0.31	71.9 (0.028)	Canrenoate	2	0.28	−2.56 to 0.82	0.302	98.8 (0.000)
	>6 m	1	0.4	0.23 to 0.57	0.000	NA	Eplerenone	1	0.25	0.08 to 0.42	0.003	NA
PIIINP	≤3 m	2	−0.89	−1.22 to −0.56	0.000	0.0 (0.846)	Spironolactone	3	−0.97	−1.27 to −0.68	0.000	0.0 (0.498)
(μg/L)	(3, 6) m	3	−1.13	−1.6 to −0.66	0.000	0.0 (0.647)	Canrenoate	1	−1.8	−2.74 to −0.86	0.000	NA
	>6 m	1	−1.8	−2.74 to −0.86	0.000	NA	Eplerenone	0	NA	NA	NA	NA
BNP	≤3 m	1	−22.0	−48.38 to 4.38	0.102	NA	Spironolactone	3	−67.06	−91.24 to −42.88	0.000	0.0 (0.881)
(pg/mL)	(3, 6) m	2	−60.2	−111.67 to −8.74	0.022	0.0 (0.684)	Canrenoate	0	NA	NA	NA	NA
	>6 m	1	−69.0	−96.39 to −41.62	0.000	NA	Eplerenone	0	NA	NA	NA	NA

BNP indicates B-type natriuretic peptide; CI, confidence interval; Cr, creatinine; K, potassium; NA, not available; PIIINP, amino-terminal peptide of procollagen type-III; and WMD, weighted mean difference.

and DT in trials with treatment ≤6 months, and effects of spironolactone and canrenoate were more prominent on E and DT, respectively. Significant reduction was also identified for isovolumetric relaxation time in trials with treatment ≤3 months or with canrenoate. There was no detectable heterogeneity across aforementioned subgroups.

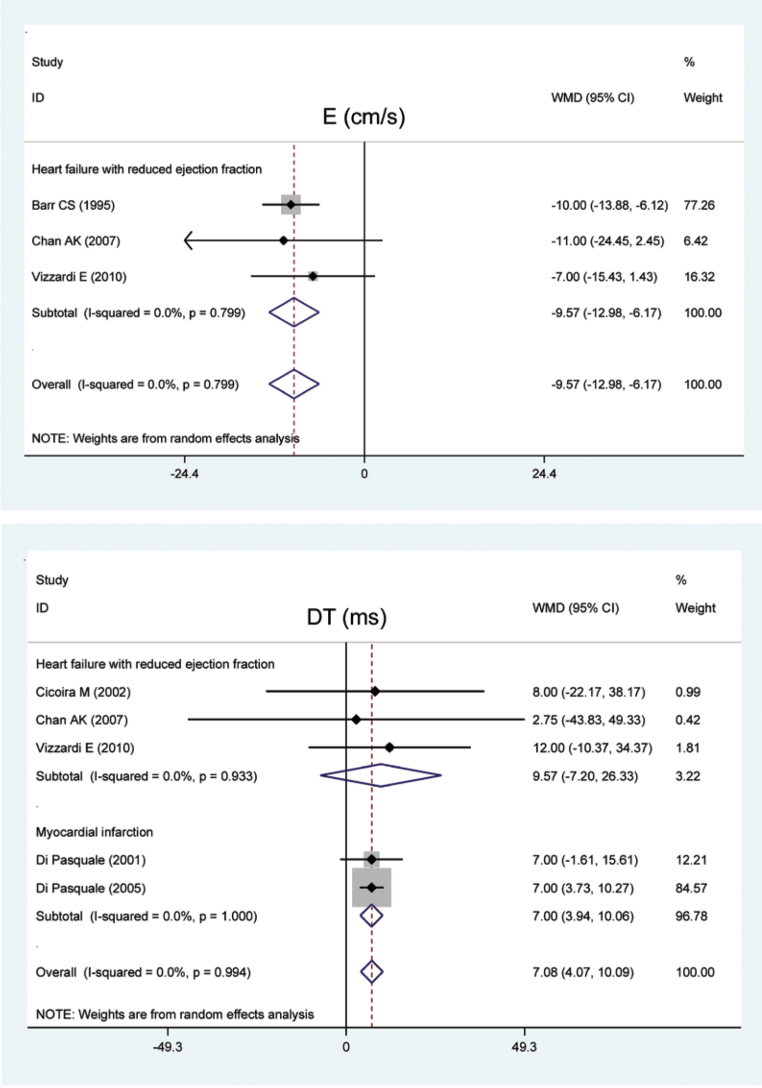

Figure 4. Forest plots for changes of peak velocities of early mitral inflow (E) and E wave deceleration time (DT) between mineralocorticoid receptor antagonists treatment group and placebo or active control group by subtypes of left ventricular dysfunction. WMD indicates weighted mean difference.

Table 5. Subgroup Analyses of the Echo Indexes of Diastolic Function

Outcomes	Duration	Studies	WMD	95% CI	*P* Value	I^2% (*P* Value)	Drug Type	Trials	WMD	95% CI	*P* Value	I^2% (*P* Value)
E	≤3 m	1	−10.0	−13.88 to −6.13	0.000	NA	Spironolactone	3	−9.57	−12.98 to −6.17	0.000	0.0 (0.799)
(cm/s)	(3, 6) m	2	−9.91	−18.17 to −1.66	0.019	19.0 (0.266)	Canrenoate	0	NA	NA	NA	NA
	>6 m	1	−11.0	−24.45 to 2.45	0.109	NA	Eplerenone	0	NA	NA	NA	NA
A	≤3 m	2	−0.45	−11.19 to 10.28	0.934	54.8 (0.137)	Spironolactone	4	−1.1	−6.6 to 4.4	0.695	36.8 (0.191)
(cm/s)	(3, 6) m	2	−0.71	−8.58 to 7.16	0.859	0.0 (0.346)	Canrenoate	0	NA	NA	NA	NA
	>6 m	2	2.23	−12.46 to 16.92	0.766	58.6 (0.12)	Eplerenone	0	NA	NA	NA	NA
E/A	≤3 m	4	0.04	−0.06 to 0.15	0.423	93.5 (0.000)	Spironolactone	4	−0.21	−0.59 to 0.18	0.289	88.2 (0.000)
	(3, 6) m	2	−0.05	−0.43 to 0.32	0.785	83.2 (0.015)	Canrenoate	2	0.14	0.08 to 0.21	0.000	91.8 (0.000)
	>6 m	3	−0.32	−0.74 to 0.09	0.124	81.7 (0.004)	Eplerenone	0	NA	NA	NA	NA
DT	≤3 m	2	5.24	2.27 to 8.21	0.001	0.0 (0.669)	Spironolactone	3	9.57	−7.2 to 26.33	0.263	0.0 (0.933)
(ms)	(3, 6) m	3	7.17	3.94 to 10.4	0.000	0.0 (0.793)	Canrenoate	2	7.0	3.94 to 10.06	0.000	0.0 (1.0)
	>6 m	2	6.45	−18.88 to 31.77	0.618	0.0 (0.853)	Eplerenone	0	NA	NA	NA	NA
IVRT	≤3 m	2	−3.89	−5.92 to −1.86	0.000	0.0 (0.63)	Spironolactone	2	4.68	−1.85 to 11.21	0.16	0.0 (0.817)
(ms)	(3, 6) m	3	−0.54	−7.58 to 6.51	0.881	64.7 (0.059)	Canrenoate	2	−4.17	−6.29 to −2.04	0.000	0.0 (0.702)
	>6 m	1	2.8	−14.42 to 20.02	0.75	NA	Eplerenone	0	NA	NA	NA	NA

CI indicates confidence interval; DT, E wave deceleration time; E and A, peak velocities of early (E) and late (A) mitral inflow; IVRT, isovolumetric relaxation time; NA, not available; and WMD, weighted mean difference.

Sensitivity and Meta-regression Analyses

With regard to serum indicators and indexes of left ventricular structure and function examined, sensitivity analyses confirmed the overall differences in both direction and magnitude.

To explore the extent to which trial-level variables explain heterogeneity among individual WMDs, we performed a set of meta-regression analyses. It is worth noting that differences in angiotensin converting enzyme inhibitor /angiotensin receptor blocker usage explained some part of heterogeneity for serum PIIINP (regression coefficient, −0.012; P=0.015). None of the other confounders contributed to the changes of serum indicators and indexes of left ventricular structure and function under MRA treatment (data not shown).

Safety and Adverse Events

The frequency of hyperkalemia was higher in the MRA treatment group (mean, 6.16%; SD, 1.62%) than in placebo or active control group (mean, 1.68%; SD, 0.94%; P=0.0018). There was no difference in frequencies for gynecomastia between the 2 groups.

Discussion

The principal findings of this meta-analysis are that beneficial effects of MRAs on patients with HFREF or myocardial infarction have been demonstrated by the reduction of LVESVI, LVEDVI, PIIINP, BNP, and E, as well as by the elevation of LVEF and DT. Although potential sources of heterogeneity, albeit disturbing, could not be easily eliminated, this study to date is the first comprehensive evaluation of MRAs on changes of cardiac structure and function in patients with left ventricular dysfunction.

Increased levels of cardiac aldosterone have been detected in animal models, and usage of MRAs resulted in the attenuation of left ventricular dysfunction and the reduction in left ventricular mass and fibrosis.[29] Our findings underlined the risk of developing hyperkalemia and having increased serum creatinine associated with MRA treatment, calling for careful monitoring of serum electrolytes and renal function in clinical practice. Nevertheless, from a pathophysiological point of view, beneficial effects of MRAs are embodied in the improvement of endothelial function and cardiac structure, as well as the reduction of collagen synthesis and thrombosis.[22,30,31] It is therefore of added interest to establish what changes occur in cardiac structure and function during MRA treatment in patients with left ventricular dysfunction.

Serum levels of collagen markers have been proposed as noninvasive indicators of myocardial collagen content, and they are correlated well.[32,33] There is indirect evidence from in vitro experiment that aldosterone can stimulate collagen production.[34] As illustrated in this study, administration of MRAs, especially spironolactone or canrenoate, witnessed a reduction in serum PIIINP for patients with HFREF or myocardial infarction, consistent with the results of most randomized clinical trials.[17,23,27,35] We further observed that treatment with MRAs can significantly reduce serum BNP in patients with HFREF. However, a recent quantitative synthesis of RCTs by Wessler et al[36] documented that the connection between change of BNP and mortality in patients with HFREF is not well established, partly in agreement with the nonsignificant relation between changes of BNP and LVEF. Based on these observations and the close relation between PIIINP and LVEF in this study, it seems plausible that the beneficial effects of MRAs on cardiac function are potentially reflected by serum PIIINP.

It is also of interest to note that as treatment duration increased, the extent of reduction in LVESVI and LVEDVI was alleviated or even became nonsignificant, and this tendency was more prominent in trials involving myocardial infarction patients, suggesting that left ventricular remodeling was stabilized after acute period. Furthermore, MRA treatment brought further benefits on E and DT, which may serve as surrogates for diastolic dysfunction. However, available trials involving patients with heart failure with preserved ejection fraction are sparse in the literature, and fortunately the ongoing Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (TOPCAT) trial[37] is designed to answer whether MRAs are effective in such patients.

The strengths of this meta-analysis include the relatively large sample size, low probability of publication bias, and high quality of most covered trials. However, this study should be interpreted with several technical limitations in mind. First, our focus was limited to RCTs. Although RCTs minimize bias and are the gold standard for determination of experimental effect, they may not be reflective of patients treated in general clinical practice.[38] Second, the included trials of this study span >15 years, and during this period, changes in the management of left ventricular dysfunction may restrict the practical implementation of the integrated data and findings. Third, differences between the included trials in follow-up duration might attribute to heterogeneity, and even though in some subgroups with homogeneous characteristics, heterogeneity still persisted, limiting the interpretation of pooled effect estimates. Last but not least, as with all meta-analyses, although our statistical tests reported low probability of publication bias, selection bias cannot be completely ruled out, because we only retrieved articles from English journals and published trials. Therefore, we cannot reach a definitive conclusion until further verification of our findings in larger, more targeted clinical trials.

Taken together, our findings demonstrate that treatment with MRAs may exert beneficial effects on the reversal of cardiac remodeling and improvement of left ventricular function. In particular, we call for further investigation on serum PIIINP in response to MRAs to prove its predictive value in cardiovascular events. Nevertheless, for practical reasons, we hope that this study will not remain just another end point of research instead a beginning to establish the background data to understand the roles of MRAs in cardiac structure and function.

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Disclosures

None.

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CLINICAL PERSPECTIVE

As a major agonist for mineralocorticoid receptors, aldosterone is regarded as a potent mediator of cardiac remodeling, a core pathogenetic feature of left ventricular dysfunction and heart failure progression. Strong evidence indicates that administration of mineralocorticoid receptor antagonists (MRAs) in patients with left ventricular dysfunction results in a reduction in morbidity and mortality; however, a comprehensive evaluation of MRA-induced changes in cardiac structure and function is lacking. To address this issue, we conducted a meta-analysis of 19 randomized controlled trials that reported effects of MRAs on cardiac structure and function. Most indexes exhibited improvement during treatment with MRAs, especially in patients with heart failure with reduced ejection fraction. Treatment with MRAs also significantly reduced serum aminoterminal peptide of procollagen type-III and B-type natriuretic peptide. MRA treatment was associated with increased risk of developing hyperkalemia and elevated serum creatinine, calling for careful monitoring of serum electrolytes and renal function in clinical practice. These meta-analytic data provide evidence that treatment with MRAs in patients with left ventricular dysfunction results in favorable effects on left ventricular structure and function, which can in part explain the favorable clinical effects seen in randomized trials.

SUPPLEMENTAL MATERIAL

Supplementary Table S1. Quality Assessment of Included RCTs in This Meta-analysis

Author (year)	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Score
Barr CS (1995)	Yes	Yes	No	Yes	Yes	No	Yes	5
Zannad F (2000)	Yes	Yes	No	Yes	Yes	No	Yes	5
Tsutamoto T (2001)	Yes	Yes	No	No	No	No	No	2
Modena MG (2001)	Yes	Yes	No	No	No	No	No	2
Di Pasquale (2001)	Yes	Yes	No	Yes	Yes	No	Yes	5
Cicoira M (2002)	Yes	Yes	No	No	No	No	Yes	3
Hayashi MT (2003)	Yes	Yes	No	No	No	No	Yes	3
Di Pasquale (2005)	Yes	Yes	No	Yes	Yes	No	Yes	5
Berry C (2007)	Yes	Yes	No	Yes	Yes	No	Yes	5
Chan AK (2007)	Yes	Yes	No	Yes	No	No	Yes	4
Gao X (2007)	Yes	No	No	Yes	Yes	No	Yes	4
Kasama S (2007)	Yes	No	No	Yes	Yes	No	No	3
Weir RA (2009)	Yes	Yes	No	Yes	Yes	No	Yes	5
Iraqi W (2009)	Yes	Yes	No	Yes	Yes	No	Yes	5
Li MJ (2009)	Yes	No	No	Yes	No	No	No	2
Boccanelli A (2009)	Yes	Yes	No	Yes	Yes	No	Yes	5
Udelson JE (2010)	Yes	Yes	No	Yes	Yes	No	Yes	5
Vizzardi E (2010)	Yes	Yes	No	No	No	No	Yes	3
Kimura M (2011)	Yes	Yes	No	No	No	No	No	2

The modified Jadad scoring system for randomized controlled trials (from Crowther M et al. Blood. 2010; 116:3140-3146):

Question 1. Was the study described as randomized? If yes, score 1 point.

Question 2. If yes to question 1, was an appropriate randomization sequence described and used (eg, table of random numbers, computer generated, etc.)? If yes, score 1 point.

Question 3. If yes to question 1, was an inappropriate method to generate the sequence of randomization used (patients were allocated alternately, or according to date of birth, hospital number, etc.)? If yes, subtract 1 point.

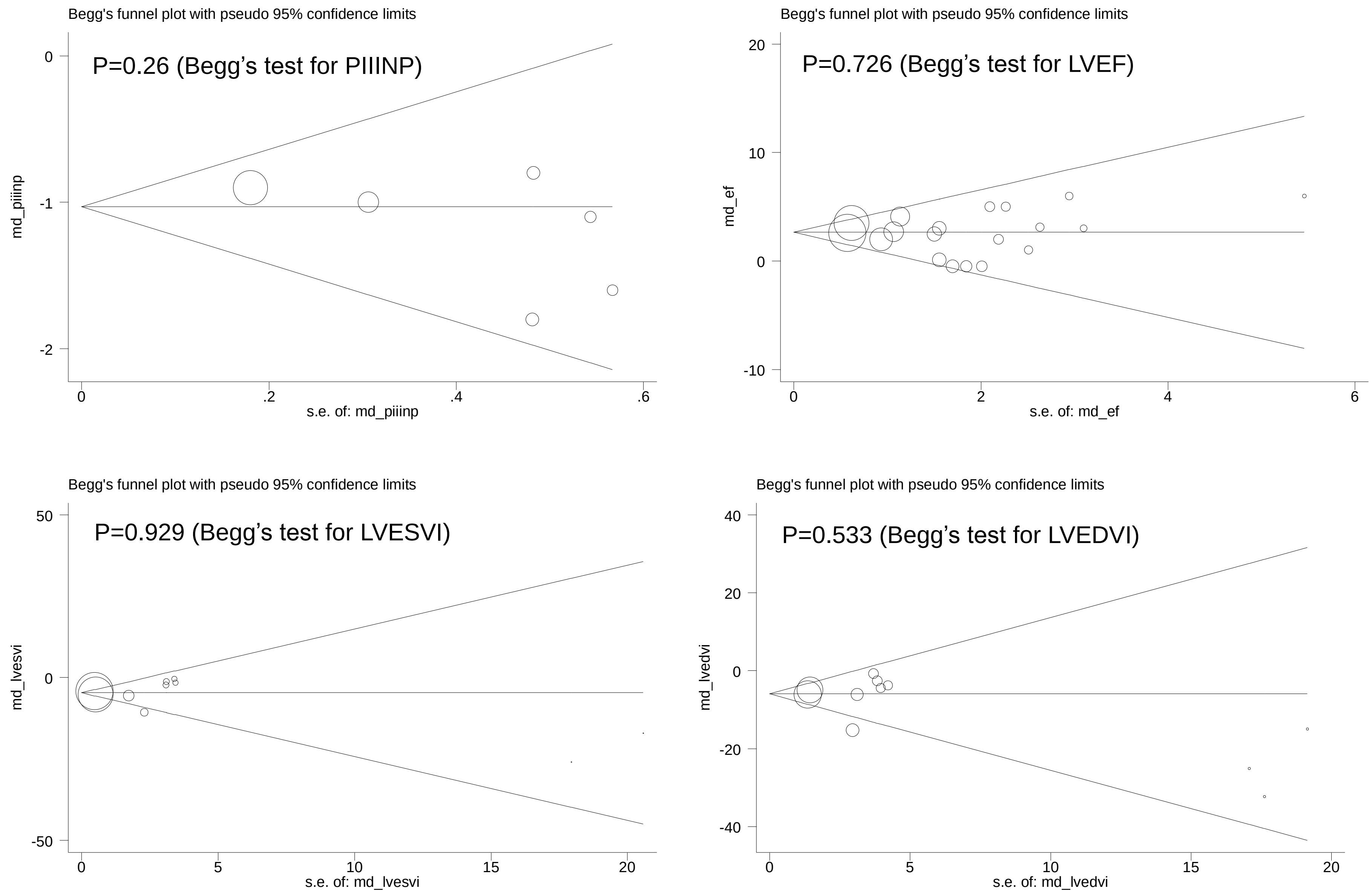
Question 4. Was the study described as double blinded? If yes, score 1 point.

Question 5. If yes to question 4, was an appropriate method of blinding used (eg, identical placebo, active placebo, dummy, etc.)? If yes, score 1 point.

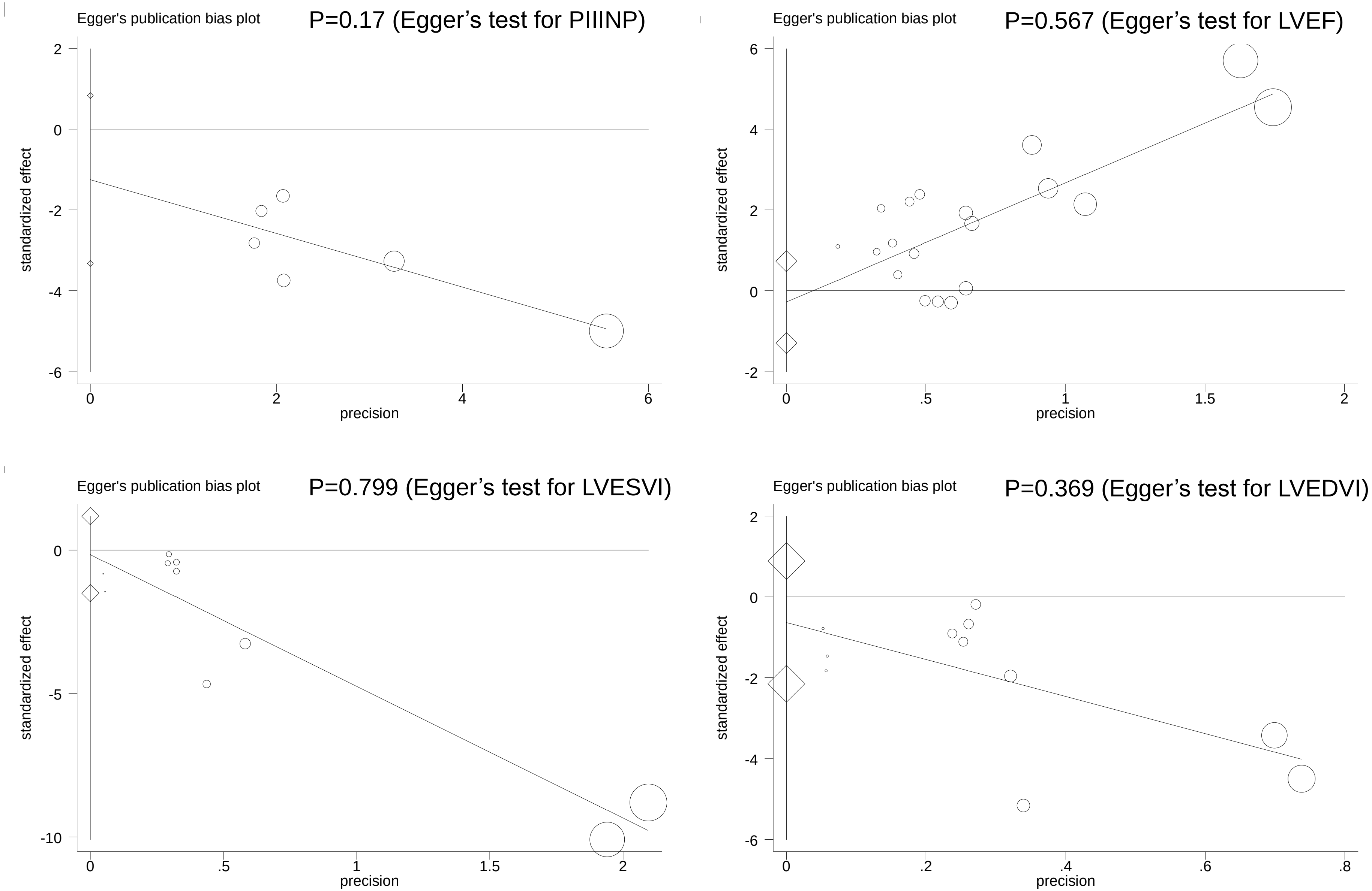
Question 6. If yes to question 4, was an inappropriate method for blinding used (eg, comparison of tablet vs injection with no double dummy)? If yes, subtract 1 point.

Question 7. Were the withdrawals and dropouts described? If yes, score 1 point.

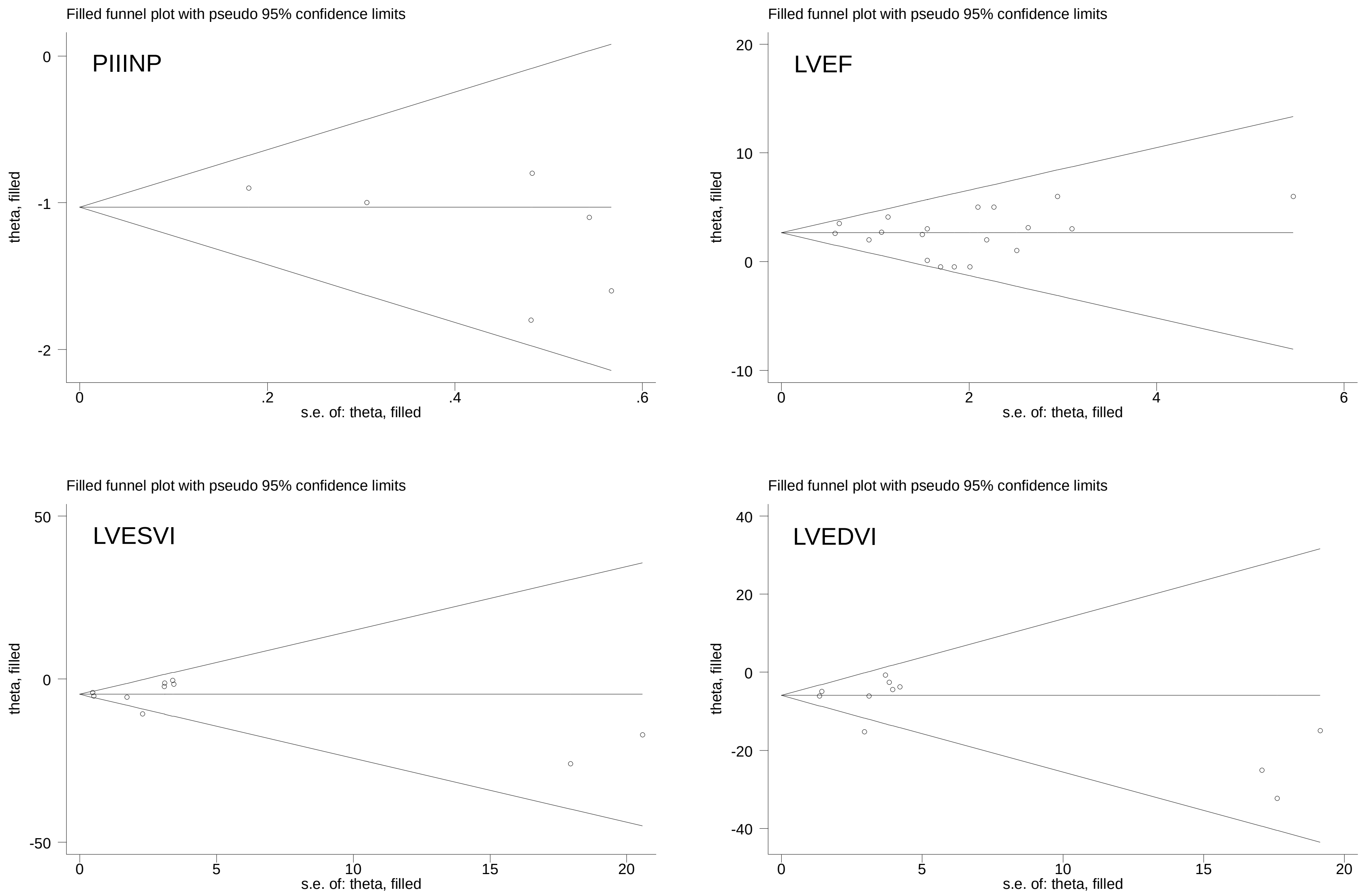
Supplementary Figure S1. Begg's Funnel Plots for Left Ventricular Dysfunction



Supplementary Figure S2. Egger’s Funnel Plots for Left Ventricular Dysfunction



Supplementary Figure S3. Filled Funnel Plots for Left Ventricular Dysfunction



Supplementary Figure S4. Forest Plots for Changes of LVESVI and LVEDVI between MRA Treatment Group and Placebo or Active Control Group in Patients Respectively with HFREF (A and B) and Myocardial Infarction (C and D)