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Effects of renin–angiotensin–aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF

A meta-analysis of 13 randomized controlled trials

Introduction

More than half of patients with heart failure have normal left ventricular (LV) ejection fractions [1]. Previous studies have shown that renin–angiotensin–aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), can significantly reduce all-cause and cardiovascular mortality in heart failure with reduced ejection fraction (HFrEF) [2–5]. It has been proven that RAAS is closely related to ventricular remodeling and may contribute to the progress of heart failure with preserved ejection fraction (HFpEF) [6, 7]. However, the efficacy of RAAS inhibitors on patients with HFpEF remains uncertain. This meta-analysis was designed to assess the role of RAAS inhibitors on mortality, hospitalization, diastolic function, and exercise capacity in patients with HFpEF.

Materials and methods

Search strategy

We searched PubMed, Web of Science, EMBASE, and the Cochrane Library for clinical studies published prior to August 2014. Studies were identified by the following key terms: (1) angiotensin-converting enzyme inhibitor, angiotensin receptor blockade, mineralocorticoid receptor antagonist and their various names, such as captopril, irbesartan, spironolactone; (2) preserved cardiac function heart failure, heart failure with normal left ventricular ejection fraction, heart failure with preserved ejection fraction or diastolic heart failure; and (3) a specialized search formula for filtering randomized controlled trials. We also searched three meta-analyses published previously on RAAS inhibitors and their relevant references [8–10].

Inclusion and exclusion criteria

The inclusion criteria were (1) randomized controlled trial, (2) assessment of the efficacy of RAAS inhibitors for HFpEF (defined as signs or symptoms of heart failure with an EF >40 %), and (3) available end points for mortality, hospitalization, diastolic function (such as E/A velocity ratio) or 6-min walk distance (6MWD). The exclusion criteria were (1) healthy persons enrolled in the control group, (2) lack of a quantitative description of endpoints, and (3) patients receiving heart transplantations. All of the references were imported into Endnote X7.0.2. Duplicate references were excluded by the software.

Data extraction and quality assessment

The information for each eligible trial was abstracted independently by two authors. All inconsistent opinions were resolved by discussions between the two authors. The baseline characteristics (such as age, gender, etiology, blood pressure, and NYHA functional classification), treatment strategy, and outcome data (including all-cause and cardiovascular mortality, hospitalization for all-cause and heart failure, diastolic function, and 6MWD) were systematically extracted into the meta-analysis database by the two authors.

The methodological quality of each included randomized controlled trial (RCT) was evaluated in the light of the Jadad quality scale [11]. Studies with a score greater than or equal to 4 were defined as high quality, and studies with a score less than 3 were defined as low quality. Discrepancies on the methodological quality were resolved by discussions between the two authors.

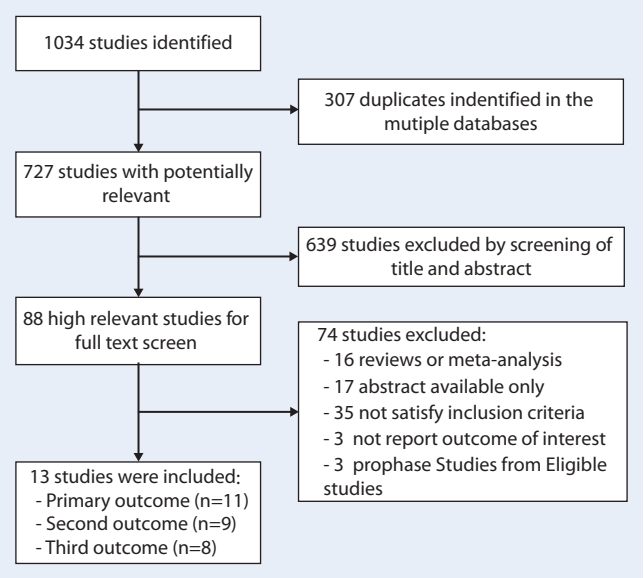

Fig. 1 ◀ Flowchart of the study selection for this meta-analysis

Statistical analysis

We mainly focused on three end points in the included trials. The primary outcome was the clinical end point, including all-cause and cardiovascular-cause mortality, and all-cause and heart failure related hospitalization. The secondary outcome was diastolic function, such as the E/e' index, E/A velocity ratio, and isovolumic relaxation time. The third outcome was the 6MWD.

Our analysis was based on the Cochrane Collaboration Review Manager 5.2 and STATA 11.0 (Stata Corp, College Station, TX, USA). Heterogeneity analysis was conducted by the value of I^2. If the value was less than 50 %, the relative risk (RR) or risk difference (RD) of dichotomous data and WMD or SMD of continuous data were pooled using a fixed-effect model (Mantel–Haenszel method). Otherwise, a random-effects model was used. In addition, subgroup analysis and sensitivity analyses were performed to explore the causes of heterogeneity.

Subgroup analyses, including age, baseline systolic blood pressure, different types of drugs, and follow-up, were conducted in all outcomes. Publication bias was assessed by a funnel plot and Egger's asymmetry test for the small samples of some trials. The hypothesis testing results were considered statistically significant if $p < 0.05$.

Results

Study selection

A flow chart of the study selection process is shown in **Fig. 1**. We originally identified 727 papers, of which 639 were excluded after reading through the titles and abstracts. Another 74 studies were excluded for various reasons by further screening the full text. Finally, we identified 13 RCTs for inclusion in this meta-analysis, including 6 papers on mineralocorticoid-receptor antagonists [12–17], 5 on ARBs [18–22], and 4 on ACEis [18, 23–25].

Baseline characteristics

The baseline characteristics of the 13 RCTs enrolled in this meta-analysis are listed in **Tables 1 and 2**. Of the total 12,532 patients with HFpEF, 6291 were in the intervention group and 6241 were in the control group. The duration of the follow-up ranged from 3.3–49.5 months. The mean age of the patients was 70.9 years, and 52.6 % of the patients were women. Only one study [18] used diuretics as the control group drug, while other studies chose a placebo.

Study quality and heterogeneity

According to the three different outcomes, 11 studies reported primary outcomes (mortality and readmission), nine reported secondary outcomes (diastolic function) and eight reported tertiary outcomes (6MWD). Four studies were identified as low quality according to the Jadad quality scale (Jadad score ≤ 3; **Table 1**). Sensitivity analysis showed that there were no significant differences between the low and high quality studies. The outcomes were stable when each low-quality study was excluded. I^2 analysis was conducted to identify the heterogeneity of the studies. In the secondary outcome of the deceleration time, $I^2 = 52$ %, which indicated moderate heterogeneity in all seven RCTs. The heterogeneity decreased significantly when the low-quality trial was excluded [17]. This fluctuation might be due to its small sample size and open-label design. Whether the low-quality studies were excluded or not, the outcome of deceleration time did not change. In the secondary outcomes of the E/e' index, moderate heterogeneity existed in the nine related RCTs. The heterogeneity was significantly reduced after we excluded the study conducted by Kurrelmeyer et al. In this study, the baseline E/e' index in the intervention group was significantly higher than that in the control group. However, the net reduction of the E/e' index in the intervention group was larger than in the control group, which supported the results of our meta-analysis. Whether we excluded this study or not, the experimental results remained unchanged. There was no significant heterogeneity in other outcomes.

Publication bias

There was no publication bias in this meta-analysis of the primary outcomes according to the funnel plot and Egger's asymmetry test ([26], all-cause mortality, $n = 9$, $p = 0.394$, > 0.05).

Primary outcome

A total of 12,187 patients (6101 in intervention group and 6086 in the control group) were enrolled for all-cause mortality. There were no significant differences in all-cause mortality between the RAAS inhibitors group and the control group (RR 0.99; 95 % CI 0.92–1.07; $p = 0.83$; **Fig. 2**). The ACEi, ARB, and mineralocorticoid-receptor antagonists subgroups showed no significant reductions

in all-cause mortality compared with the control group. Additional results for the subgroups are shown in **Table 3**. There was no beneficial effect on cardiovascular mortality in either the intervention or control group (RR 0.98; 95 % CI 0.89–1.09; $p = 0.75$). The RAAS inhibitors group showed no reduction of all-cause hospitalization compared with the control group (RR 0.99; 95 % CI 0.96–1.03; $p = 0.76$). Heart failure hospitalization was significantly lower in the RAAS inhibitors group compared with the controls (RR 0.89; 95 % CI 0.82–0.97; $p = 0.01$). Although the estimates of the overall RR were significant, none of the eight studies investigating the effects of RAAS inhibitors on the hospitalizations for heart failure in HFpEF patients, when individually studied, showed an association of RAAS inhibitor therapy with a decreased risk of events among HFpEF patients. Subgroup analysis showed that there was no benefit of HF-related hospitalization for the subgroup with a mean age > 70.9 years (RR 0.94; 95 % CI 0.83–1.07;$p = 0.34$) and the ARB subgroup (RR 0.86; 95 % CI 0.64–1.15; $p = 0.30$). The subgroup with a mean age of less than 70.9 years might have been associated with a lower rate of heart failure hospitalization for the treatment of RAAS inhibitors (RR 0.86; 95 % CI 0.76–0.96; $p = 0.009$).

Secondary outcome

The RAAS inhibitors had a significant beneficial effect on the E/e' index compared with controls (MD −1.38; 95 % CI −2.01 to −0.74; $p < 0.0001$; **Fig. 3**). Subgroup analysis revealed that patients in the intervention group with a mean age < 70.9 years (MD −1.38; 95 % CI −2.07 to −0.68; $p = 0.0001$), baseline SBP < 140 mmHg (MD −1.63; 95 % CI −2.39 to −0.88; $p < 0.0001$), and aldosterone receptor blockade (MD −1.53; 95 % CI −2.25 to −0.82; $p < 0.0001$) demonstrated significant benefits for the E/e' velocity ratio (**Table 3**). There were no significant differences on the E/A velocity ratio (MD −0.02; 95 % CI −0.07 to 0.02; $p = 0.31$), isovolumic relaxation time (MD −1.11; 95 % CI −3.97 to 1.75; $p = 0.45$), and deceleration time (MD −2.18; 95 % CI −9.65 to 5.28; $p = 0.57$) between the intervention

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Effects of renin–angiotensin–aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF. A meta-analysis of 13 randomized controlled trials

Abstract

Aim. The purpose of this meta-analysis was to evaluate the effects of renin–angiotensin–aldosterone system (RAAS) inhibitors on mortality, hospitalization, diastolic function, and exercise capacity in heart failure with preserved ejection fraction (HFpEF).

Methods. Thirteen randomized controlled trials (RCTs), totaling 12,532 patients with HFpEF, were selected. All-cause and cardiovascular mortality, all-cause and heart failure-related hospitalization, diastolic function, and the 6-min walk distance were assessed. The risk ratios (RR) of the dichotomous data, weighted mean difference (WMD) of continuous data, and 95 % confidence intervals (CI) were calculated to assess the effects of RAAS inhibitors.

Results. RAAS inhibitors significantly decreased heart failure-related hospitalization (RR 0.89; 95 % CI 0.82–0.97; $p = 0.01$) and improved the diastolic function, as reflected in a reduced E/e' index (MD −1.38; 95 % CI −2.01 to −0.74; $p < 0.0001$). However, there were no beneficial effects on all-cause cardiovascular mortality and all-cause hospitalization. Other diastolic parameters had few changes compared with the controls. The 6-min walk distance was not improved by the use of RAAS inhibitors.

Conclusion. In patients with HFpEF, RAAS inhibitors decreased heart-failure hospitalization and the E/e' index without affecting mortality, all-cause hospitalization, other diastolic function parameters, and the 6-min walk distance.

Keywords

Angiotensin-converting enzyme inhibitors · Angiotensin receptor · Antagonists · Mineralocorticoid-receptor antagonists · Heart failure with preserved ejection fraction

Auswirkungen der Inhibitoren des Renin-Angiotensin-Aldosteron-Systems auf Mortalität, Hospitalisation und diastolische Funktion bei Patienten mit HFpEF. Eine Metaanalyse von 13 randomisierten kontrollierten Studien

Zusammenfassung

Ziel. Ziel dieser Metaanalyse war es, die Auswirkungen der Inhibitoren des Renin-Angiotensin-Aldosteron-Systems (RAAS) auf Mortalität, Hospitalisation, diastolische Funktion und körperliche Belastbarkeit bei Herzversagen mit konservierter Ejektionsfraktion (HFpEF) zu evaluieren.

Methoden. Dreizehn randomisierte kontrollierte Studien (RCTs) mit insgesamt 12.532 HFpEF-Patienten wurden ausgewählt. Die kardiovaskuläre und Gesamtmortalität sowie die durch Herzversagen bedingte Hospitalisation, diastolische Funktion und die 6-min-Gehstrecke wurden beurteilt. Das relative Risiko (RR) der dichotomen Daten, die gewichtete mittlere Differenz ("weighted mean difference", WMD) der kontinuierlichen Daten und das 95% Konfidenzintervall (CI) wurden berechnet, um die Auswirkungen der RAAS-Inhibitoren zu untersuchen.

Ergebnisse. RAAS-Inhibitoren senkten Herzversagen-bedingte Hospitalisation signifikant (RR 0,89; 95% CI 0,82–0,97; p=0,01) und verbesserten die diastolische Funktion, wie ein reduzierter E/e'-Index (MD −1,38; 95% CI −2,01 bis −0,74; p<0,0001) zeigt. Jedoch gab es keine positiven Auswirkungen auf die kardiovaskuläre und Gesamtmortalität und Gesamthospitalisierung. Bei anderen diastolischen Parametern gab es im Vergleich zur Kontrollgruppe nur geringe Abweichungen.

Schlussfolgerung. Bei Patienten mit HFpEF reduzierten RAAS-Inhibitoren die Hospitalisation wegen Herzversagens sowie den E/e'-Index, ohne die Mortalität, Gesamthospitalisationsrate, andere diastolische Funktionsparameter und die 6-min-Gestrecke zu beeinflussen.

Schlüsselwörter

Inhibitoren des Angiotensin-konvertierenden Enzyms · Angiotensin-Rezeptor · Antagonisten · Mineralokortikoid-Rezeptor-Antagonisten · Herzversagen mit konservierter Ejektionsfraktion

Table 1 Study characteristics

First author (year)	Treatment	Control	Age (year)	Female, n (%)	SBP (mmHg)	Definition of HFPEF (LVEF, %)	Sample Size (T/C)	Follow-up (months)	Outcomes	Jadad score
Cleland JG (2006) [24]	Perindopril	Placebo	75.00	472 (55)	139.00	40	424/426	26.2	All-cause/CV mortality and hospitalization	6
Deswal A (2011) [14]	Eplerenone	Placebo	70.37	3 (6.8)	130.17	50	21/23	6	All-cause/CV mortality, hospitalization and diastolic function	3
Edelmann F (2013) [13]	Spironolactone	Placebo	67.00	221 (52)	135.00	50	213/209	12	All-cause mortality, hospitalization and diastolic function	7
Kitzman DW (2010) [23]	Enalapril	Placebo	69.51	60 (85)	143.51	50	35/36	12	All-cause/CV mortality and hospitalization and diastolic function	6
Kurrelmeyer KM (2014) [15]	Spironolactone	Placebo	71.35	48 (100)	135.05	50	24/24	6	All-cause/CV mortality, hospitalization and diastolic function	5
Mak GJ (2009) [17]	Eplerenone	Placebo	79.55	24 (55)	142.73	45	24/20	12	All-cause mortality and diastolic function	1
Massie BM (2008) [19]	Irbesartan	Placebo	72.00	2491 (60)	136.50	45	2067/2061	49.5	All-cause/CV mortality and hospitalization	5
Mottram PM (2013) [16]	Spironolactone	Placebo	62	19 (63)	151.50	50	2067/2061	6	Diastolic function	5
Parthasarathy HK (2009) [20]	Valsartan	Placebo	62.13	75 (49)	NA (< 130)	40	70/82	3.3	All-cause/cardiovascular mortality and diastolic function	4
Pitt B (2014) [12]	Spironolactone	Placebo	68.70	1775 (52)	130.00	45	1722/1723	39.6	All-cause/CV mortality and hospitalization	7
Yip GW (2008)[a] [18]	Irbesartan + diuretics	Diuretics	74.06	66 (62)	145.00	45	56/50	12	All-cause/CV mortality, hospitalization, and diastolic function	3
Yip GW (2008) [18]	Ramipril + diuretics	Diuretics	73.47	56 (59)	144.05	46	45/50	12	Mortality, hospitalization and diastolic function	3
Yusuf S (2003) [22]	Candesartan	Placebo	67.15	1212 (40)	136.15	40	1514/1509	8.5	CV mortality and hospitalization	7
Zi M (2003) [25]	Quinapril	Placebo	78	48 (56)	NA (130–140)	40	36/38	6	All-cause mortality and hospitalization	3

SBP systolic blood pressure, *LVEF* left ventricular ejection fraction, *T/C* treatment group/ control group, *CV* cardiovascular, *NA* means the exact value is not mentioned, but a range of the value is given.
[a]This study used ACEi and ARB as intervention groups, respectively.

Table 2 Patient characteristics

	Pitt B (2014)	Edelmann F (2013)	Deswal A (2011)	Kurrelmeyer KM (2014)	Mottram PM (2013)	Yip GW (2008)	Yip GW (2008)	Massie BM (2008)	Kitzman DW (2010)	Mak GJ (2009)	Parthasarathy HK (2009)	Yusuf S (2003)	Cleland JG (2006)	Zi M (2003)
LVEF (%)	56	67	62.31	62.7	67.5	67.42	67.11	59.5	65	63.45	71.04	54.05	64.5	58.63
Etiology (%)														
Hypertension	91.35	92	NA	83.33	NA	82	81	88.42	73.24	90.91	88.82	0.64	0.79	0.3
CAD	58.72	40	56.82	35.42	NA	NA	NA	25.1	NA	NA	NA	NA	NA	NA
MI	25.92	NA	NA	NA	NA	NA	NA	23.47	NA	NA	NA	0.44	0.27	NA
AF	35.24	5	13.64	25	NA	16	13	29.29	NA	59.09	12.5	0.29	0.2	0.35
DM	32.45	17	61.36	375	3.33	19	21	27.47	12.68	27.27	17.76	0.28	0.21	0.15
PCI or CABG	23.6	NA	NA	NA	NA	NA	NA	13.28	NA	NA	NA	0.17	0.12	NA
Dyslipidemia	60.17	65	NA	NA	46.67	10	7	NA	NA	29.55	NA	NA	NA	NA
Stroke	7.69	NA	NA	NA	NA	NA	NA	9.67	NA	NA	NA	0.09	NA	NA
NYHA (%)														
I–II	67	86	59	375	NA	70	69	21	79	NA	NA	61	77	78
III–IV	33	14	41	62	NA	30	31	79	21	NA	NA	39	23	22

LVEF left ventricular ejection fraction, *CAD* coronary artery disease, *MI* myocardial infarction, *AF* atrial fibrillation, *DM* diabetes mellitus, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *NA* not available.

and the control groups. Subgroup analyses on age, baseline systolic blood pressure, follow-up, and drug types showed no significant differences between the intervention and control groups in each subgroup (**Table 3**). Although subgroup analysis on the deceleration time showed that patients with a mean age ≥ 70.9 years had significant reductions in the deceleration time, the outcome showed no significant difference between the intervention and the control groups when we excluded the low-quality studies (Jadad score = 1).

Third outcome

There were 1,598 patients in eight studies who were enrolled to conduct 6MWD. No significant changes in 6MWD were observed in the RAAS inhibitors group compared to the control group (MD 0.65; 95 % CI −8.07 to 9.36; $p = 0.88$; **Fig. 4**). Subgroup assessments on age, baseline SBP, follow-up, and drug types also showed no significant differences between the two groups (**Table 3**).

Discussion

This was the first study that used RCTs and mineralocorticoid-receptor antagonists to assess the efficacy of RAAS inhibitors in patients with HFpEF. This meta-analysis mainly evaluated three outcomes, of which the latter two had not yet been considered: (1) primary outcome: RAAS inhibitors might reduce the rate of heart failure related hospitalization, but had no significant effect on reducing all-cause or cardiovascular mortality and all-cause hospitalization; (2) secondary outcome: RAAS inhibitors had a significant effect on improving the E/e' velocity ratio compared with the controls. However, the results from this meta-analysis were still not sufficient to prove the effectiveness of RRAS inhibitors on the other diastolic function parameters; and (3) tertiary outcome: RAAS inhibitors could not increase 6MWD in patients suffering from HFpEF, which indicated little effect of the RAAS inhibitors on improving the cardiopulmonary function.

The diagnostic criteria for HFpEF are still controversial, especially in terms of the EF cut-off criteria [27]. According to

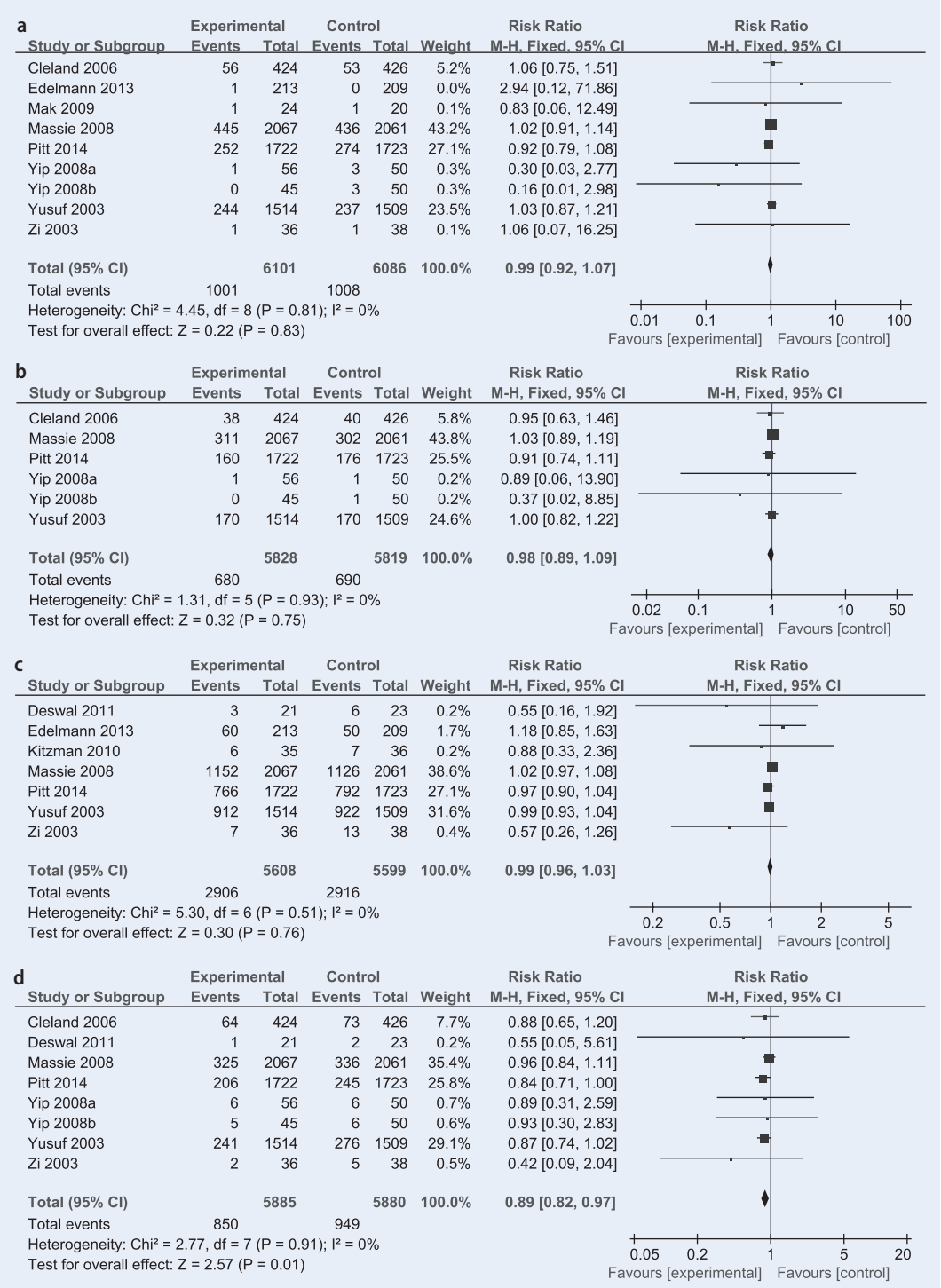

Fig. 2 ◀ Forest plots of the primary outcome. **a** Forest plot of RR for all-cause mortality between RAAS inhibitors group and controls. **b** cardiovascular (*CV*) mortality. **c** All-cause hospitalization. **d** Heart failure related hospitalization

the current guidelines, patients with EF between 40 and 50 % are defined as an intermediate group. Their features, therapy models and prognoses seem to be similar to patients with HFpEF, who were identified by an EF > 50 % [28]. In our meta-analysis, when different cut-offs (45 and 50 %) were used in the subgroup analyses, the results were similar to our original conclusion (**Table 3**). Thus, this meta-analysis included studies using EF ≥ 40 % as the EF cut-off criterion of HFpEF.

Several factors play important roles in the pathophysiology of HFpEF. One of the mechanisms is increased myocardial stiffness and ventricular remodeling [7, 29], which may lead to diastolic LV dysfunction, as reflected in extended isovolumic relaxation times and LV filling decelerations [30]. Compared to patients with HFrEF, those with HFpEF are more likely to be older, female, and have a lower event rate of coronary artery disease and a higher incidence of atrial fibrillation [31]. The activation of RAAS makes an important contribution to the progress of HFpEF [6]. Theoretically,

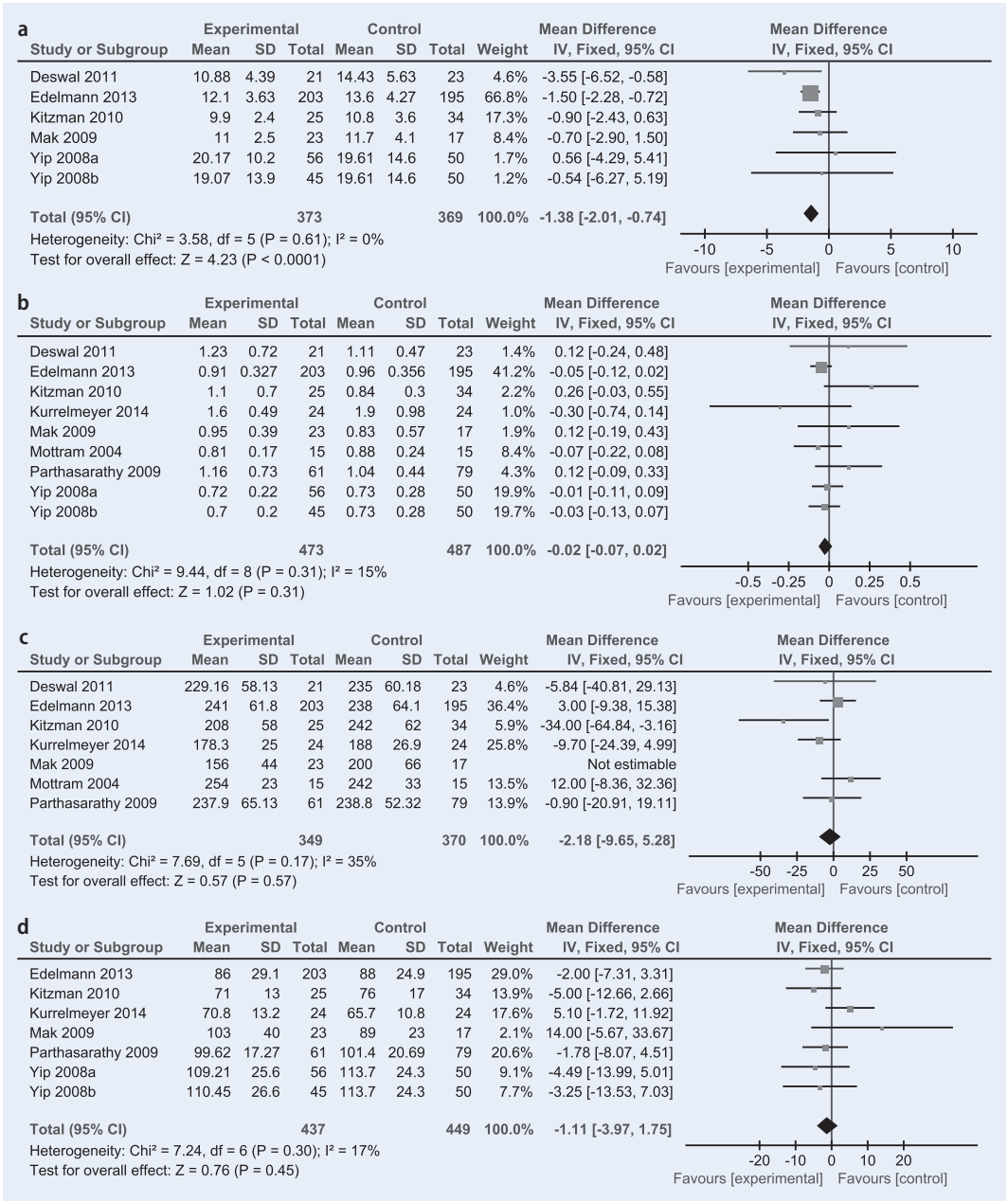

Fig. 3 ◀ Forest plots of secondary outcome. **a** Forest plot of MD for E/e' index between RAAS inhibitors group and controls. **b** E/A velocity ratio. **c** Deceleration time. **d** Isovolumic relaxation time. The RAAS inhibitors has a significant beneficial effect on E/e' index (MD −1.38; 95 % CI −2.01 to −0.74; $p < 0.0001$). There is no significant effect on E/A velocity ratio, deceleration time, and isovolumic relaxation time. *E/A velocity ratio* ratio of early to late transmitral flow; *E/e' index* ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity

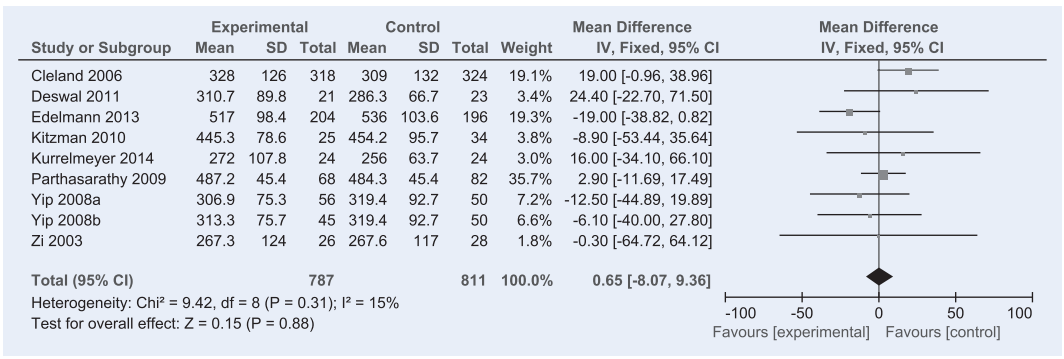

Fig. 4 ◀ Forest plot of third outcome. There is no significant effect on exercise capacity between the two groups (MD 0.65; 95 % CI −8.07 to 9.36; $p = 0.88$)

RAAS inhibitors might reduce myocardial remodeling and might improve patients' symptoms and prognosis. However, apart from HF related rehospitalization and the E/e' velocity ratio, most outcomes from our meta-analysis show few changes using RAAS inhibitors in patients suffering from HFpEF, despite a blood pressure reduction. There may be several rea-

Table 3 Subgroup Analysis

Subgroup	All-cause mortality	CV mortality	All-cause hospitalization	HF hospitalization	E/A	IVRT	Deceleration time	E/e'index	6MWD
	RR (95 %CI)	RR (95 %CI)	RR (95 %CI)	RR (95 %CI)	MD (95 %CI)	MD (95 %CI)	MD (95 %CI)	MD (95 %CI)	MD (95 %CI)
Age (year)									
≥ 70.9	1.01 (0.91, 1.13)	1.02 (0.88, 1.17)	1.01 (0.96, 1.07)	0.94 (0.83, 1.07)	−0.02 (−0.08, 0.05)	1.46 (−3.27, 6.20)	−13.4 (−26.1, −0.73)[a]	−1.37 (−2.97, 0.22)	8.81 (−4.77, 22.39
< 70.9	0.97 (0.87, 1.09)	0.95 (0.83, 1.10)	0.98 (0.94, 1.03)	0.86 (0.76, 0.96)[a]	−0.03 (−0.09, 0.03)	−2.59 (−6.17, 1.00)	0.84 (−8.10, 9.79)	−1.38 (−2.07, −0.68)[a]	−5.07 (−16.43, 6.30)
SBP (mmHg)									
≥ 140	0.40 (0.12, 1.37)	UN	UN	UN	−0.00 (−0.06, 0.06)	−0.08 (−3.57, 3.41)	−9.56 (−24.94, 5.82)	−0.74 (−1.93, 0.45)	−9.31 (−30.04, 11.42)
< 140	1.00 (0.92, 1.08)	0.99 (0.89, 1.09)	0.99 (0.96, 1.03)	0.89 (0.82, 0.97)[a]	−0.05 (−0.12, 0.02)	−3.22 (−8.21, 1.76)	−2.24 (−10.55, 6.07)	−1.63 (−2.39, −0.88)[a]	2.79 (−6.82, 12.39)
Follow-up (months)									
> 8.5	0.98 (0.90, 1.07)	0.98 (0.87, 1.10)	1.00 (0.96, 1.05)	0.91 (0.82, 1.01)[b]	−0.02 (−0.07, 0.02)	−2.65 (−6.29, 0.99)	−5.97 (−16.92, 4.98)	−1.27 (−1.92, −0.62)[a]	−3.03 (−14.67, 8.61)
≤ 8.5	1.03 (0.87, 1.21)	UN	0.98 (0.92, 1.04)	0.86 (0.74, 1.01)[b]	−0.01 (−0.12, 0.10)	1.38 (−3.24, 6.01)	−2.22 (−12.04, 7.60)	UN	5.35 (−7.81, 18.50)
Drug									
MRA	0.92 (0.79, 1.08)	UN	0.98 (0.91, 1.05)	0.84 (0.71, 1.00)[a]	−0.05 (−0.11, 0.01)	1.26 (−2.84, 5.36)	−2.30 (−10.42, 5.83)	−1.53 (−2.25, −0.82)[a]	−9.13 (−26.29, 8.03)
ACEI	1.01 (0.72, 1.42)	0.93 (0.61, 1.42)	0.68 (0.37, 1.26)	0.92 (0.83, 1.02)[b]	−0.00 (−0.09, 0.09)	−4.38 (−10.5, 1.77)	UN	−0.88 (−2.36, 0.60)	9.18 (−6.39, 24.75)
ARB	1.02 (0.92, 1.12)	1.02 (0.90, 1.14)	1.00 (0.97, 1.05)	0.86 (0.64, 1.15)	0.01 (−0.07, 0.10)	−2.61 (−7.85, 2.64)	UN	UN	0.30 (−13.01, 13.61)
LVEF cut-off (%)									
EF ≥ 45	0.97(0.89, 1.07)	0.98 (0.87, 1.11)	1.00 (0.96, 1.05)	0.91(0.82, 1.01)	−0.03 (−0.07, 0.02)	−0.94 (−4.15, 2.27)	−4.35 (−12.21, 3.50)	−1.38 (−2.01, −0.74)	−9.2 (−22.42, 4.01)
EF ≥ 50	UN	None	1.09 (0.81, 1.46)	UN	−0.04 (−0.10, 0.02)	−0.63 (−4.31, 3.05)	−2.39 (−10.44, 5.66)	−1.49 (−2.17, −0.81)	−9.09 (−25.11, 6.92)

MRA mineralocorticoid receptor antagonists, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CV* cardiovascular, *SBP* systolic blood pressure, *RR* relative risk, *MD* mean difference, *E/A* ratio of early to late transmitral flow, *E/e'* ratio of peak early transmitral ventricular filling velocity to early diastolic tissue doppler velocity, *IVRT* isovolumic relaxation time, *DT* deceleration time, *6MWD* 6 min walk distance, *UN* only one study in the subgroup which is inappropriate for subgroup analysis.

[a]significant differences between the intervention and the control group.

[b]The intervention group has a tendency to improvement, compared with the control group.

sons for the absence of effectiveness. First, changes in structure remodeling and arterial stiffness are not associated with a decrease in blood pressure by the use of ACEi [32]. Second, the treatment period may not be long enough to achieve an improved diastolic function. Ten studies had a mean follow-up periods of ≤ 12 months, while only three studies had an observable mean follow-up periods > 12 months. Subgroup analysis indicated that a longer follow-up with medication might be more effective than short-term medication. Third, myocardial remodeling and vascular stiffening are increased with aging and hypertension [33, 34]. Subgroup analysis showed that younger patients might obtain benefits from RAAS inhibitors. Thus, age and blood pressure might be associated with the effectiveness of RAAS inhibitors, as reported previously [1]. An earlier study reported that patients with heart failure and high systolic blood pressure might have lower mortality with antihypertensive treatments [35]. Patients with a SBP ≥ 160 mmHg had a significantly lower mortality compared with those with a SBP ranging from 120 to 140 mmHg. In our meta-analysis, the baseline mean systolic blood pressure in nine studies varied between 130 and 140 mmHg, indicating the limited benefit of RAAS inhibitors to those with relatively low blood pressure. However, the results of the subgroup analysis also revealed that compared to the control group, the subgroup with a SBP < 140 mmHg had significant improvements on the E/e' index, while the subgroup with a SBP ≥ 140 mmHg did not. This scenario could be attributed to the fact that the gap between these two subgroups' mean systolic blood pressure was not obvious (**Table 1**). Until now, it was been possible to conclude whether patients with a lower SBP may benefit more from RAAS inhibitors than those with a higher SBP.

According to the enrolled studies, the other parameters related to diastolic function were not sufficient to conduct the meta-analysis. Previous studies noted that tissue Doppler imaging, including the E/e' index, was regarded as more relevant to diagnose diastolic dysfunction [36, 37] and that the mean lateral E/e' index was considered to be the best parameter to as-

sess diastolic dysfunction in patients with HFpEF [38, 39]. However, only one study reported a mean lateral E/e' [15], while the other studies used the average E/e' index to assess diastolic dysfunction. Thus, we included all of the studies that reported the E/E' index for this meta-analysis on diastolic function rather than only those with the mean lateral E/e' index.

Subgroup analysis showed that the effects of the three types of RAAS inhibitors were inconsistent. Aldosterone receptor blockade reduced heart failure rehospitalization and improved the E/e' index significantly, while the ACEi subgroup had a tendency to decrease HF-related hospitalization, with no significant differences in the E/e' index compared with the control group. The ARB subgroup showed no effect in reducing HF rehospitalization in contrast to the control group. There was only one study demonstrating diastolic function with the use of ARBs, which was inappropriate in number to conduct subgroup analysis. These results may be explained by the use of the other RAAS inhibitors. In the I-PRESERVE study [19], 40 % of the patients received ACEi and 29 % received spironolactone. Kitzman DW et al. [23] mentioned that they could not exclude the patients receiving ARB from their research. In the CHARM study [22], 19 % of the patients took ACEi and 11 % took spironolactone. The use of other RAAS inhibitors may lead to crossover effects and different results. Second, this condition can also be interpreted as an 'aldosterone breakthrough'. In clinical trials using ACEi or ARBs as the intervention, some patients' plasma aldosterone levels decreased at first and then elevated over a long period of time, which was called 'aldosterone breakthrough' [13, 40]. A long stimulation period using aldosterone on the mineralocorticoid receptor system could promote cardiovascular remodeling and further progress heart failure [41, 42]. It has been reported that aldosterone receptor blockade reduced extracellular matrix turnover and the myocardial collagen content, which were associated with the progress of heart failure [43, 44]. Although ACEis or ARBs suppressed angiotensin-II-mediated aldosterone release, there were still several patients' whose plasma aldosterone level increased, which influenced the total treatment outcome.

Study limitations

There are several limitations in our meta-analysis. First, the inclusion of studies with a follow-up of less than one year may lead to an excessively low estimation of mortality and hospitalization. Among the 13 included studies, six studies had a follow-up of less than 1 year, with one study having a 3.3 month follow-up. The inclusion of these studies may lead to bias in the findings. However, according to the results of the subgroup analysis, among the seven studies with more than 8.5 months of follow-up, the intervention group showed more improvement on HF hospitalization and a significant improvement of diastolic function compared with the control group. Further studies are recommended to include studies with a follow-up duration of longer than 1 year. Second, the sample sizes of the enrolled studies with the second outcome were small. Further studies with large samples of diastolic function are needed to investigate the effect of RAAS inhibitors on diastolic dysfunction in patients with HFpEF. Third, we did not review the functional effects on the cardiopulmonary exercise testing, such as peak oxygen consumption and quality of life, because these parameters were only reported by a few studies. As a convenient and effective method to test exercise capacity, 6MWD was reviewed in our meta-analysis, which failed to show any significant improvements in the RAAS inhibitor groups. A final limitation is the difficulty of having uniform doses of the RAAS inhibitors in all of the studies, which may affect the balance of drug action. Insufficient RAAS inhibitor treatment may reduce the effect of the drugs [32].

Conclusion

This meta-analysis shows that RAAS inhibitors could significantly reduce heart failure-related hospitalization and improve the E/e' index in patients with HFpEF. Further large-scale randomized controlled trials, especially on diastolic function, are needed to confirm the effects of RAAS inhibitors in patients with HFpEF.

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Compliance with ethical guidelines

Conflict of interest. Qi Zhang, Yanhong Chen, Qian Liu, Qijun Shan state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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