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Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction

A meta-analysis of randomized clinical trials

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Abstract

Background: Recent studies have shown the efficacy for using spironolactone to treat heart failure with reduced ejection fraction (HFrEF), but the efficacy of spironolactone for heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) is unclear. This meta-analysis investigated the efficacy and safety of spironolactone in patients with HFmrEF and HFpEF.

Methods and results: We searched several databases including PubMed and the Cochrane Collaboration, for randomized controlled trials (RCTs) that assessed spironolactone treatment in HFmrEF and HFpEF. Eleven RCTs including 4539 patients were included. Spironolactone reduced hospitalizations (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.73–0.95; $P = .006$), improved New York Heart Association functional classifications (NYHA-FC) (OR, 0.35; 95% CI, 0.19–0.66; $P = .001$), decreased the levels of brain natriuretic peptide (BNP) (mean difference [MD], −44.80 pg/mL; 95% CI, −73.44–−16.17; $P = .002$), procollagen type I C-terminal propeptide (PICP) (MD, −27.04 ng/mL; 95% CI, −40.77–−13.32, $P < .001$) in HFmrEF and HFpEF. Besides, it improved 6-minute walking distances (6-MWD) (standard weighted mean difference [SMD], 0.45 m; 95% CI, 0.27–0.64; $P < .001$), decreased amino-terminal peptide of procollagen type-III (PIIINP) (SMD, −0.37 μg/L; 95% CI, −0.59–−0.15; $P = .001$) in HFpEF only. The risks of hyperkalemia ($P < .001$) and gynecomastia ($P < .001$) were increased.

Conclusion: Patients with HFmrEF and HFpEF could benefit from spironolactone treatment, with reduced hospitalizations, BNP levels, improved NYHA-FC, alleviated myocardial fibrosis by decreasing serum PICP in HFmrEF and HFpEF, decreased PIIINP levels and increased 6-MWD only in HFpEF. The risks of hyperkalemia and gynecomastia were significantly increased with the spironolactone treatment.

Abbreviations: 6-MWD = 6-minute walking distance, Aldo-DHF = aldosterone receptor blockade in diastolic heart failure, AMI = acute myocardial infarction, BMI = body mass index, BNP = brain natriuretic peptide, CI = confidence interval, CNKI = China National Knowledge Internet, E/A ratio = the ratio of early to late diastolic transmitral flow, E/e' = early diastolic mitral valve blood flow velocity and the early diastolic mitral valve ring motion velocity, HF = heart failure, HFmrEF = heart failure with mid-range ejection fraction, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure patients with reduced ejection fraction, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, MD = mean difference, MMP-9 = matrix metalloproteinase-9, MRAs = mineralocorticoid receptor antagonists, NYHA-FC = New York heart association functional classifications, OR = odds ratio, PICP = procollagen type I C-terminal propeptide, PIIINP = amino-terminal peptide of procollagen type-III, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RAAS = renin-angiotensin-aldosterone system, RCTs = randomized controlled trials, RR = risk ratio, SMD = standard weighted mean difference, TOPCAT = treatment of preserved cardiac function heart failure with an aldosterone antagonist trial.

Keywords: efficacy, heart failure with mid-range ejection fraction, heart failure with preserved ejection fraction, safety, spironolactone

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1. Introduction

Heart failure (HF) is a complex set of clinical syndromes associated with abnormal heart structure or function that results in impaired ventricular ejection function or filling.[1] The HF includes a wide range of patients, from those with normal left ventricular ejection fraction (LVEF), typically considered as ≥50%, heart failure with preserved ejection fraction (HFpEF) to those with reduced LVEF typically considered as <40%, heart failure with reduced ejection fraction (HFrEF).[2] Patients with an LVEF in the range of 40 to 49% now are defined as HF with mid-range ejection fraction (HFmrEF).[2,3] Over the next decade, HFmrEF and HFpEF are expected to become a dominant cause of HF worldwide, which result in high morbidity and mortality due to the lack of effective proven therapies, making it a provocative and important health problem.[4]

Mineralocorticoid receptor antagonists (MRAs) are the effective potassium-sparing diuretics[5], they can reduce mortality and improve symptoms in patients with HFrEF by improving left ventricular remodeling, mainly by inhibiting the metabolism of myocardial muscle fibers, reducing cardiac myocyte necrosis, and modifying the myocardial inflammatory response inhibition mechanism.[6] The clinical efficacy of MRAs in patients with HFrEF has been proven in the randomized controlled trials (RCTs) and has been recommended in guidelines for the management of HFrEF.[7–10] But the management and prognosis of HFmrEF and HFpEF remain largely unchanged.[11] Diastolic dysfunction may play a vital role in the pathophysiological mechanisms involved in HFmrEF and HFpEF, mainly associated with the compensation reaction out of heart in the activation of renin-angiotensin-aldosterone system (RAAS) and the increasing of ventricular remodeling.[12,13,14] Therefore, blockade of aldosterone may alleviate the ventricular remodeling and improve left ventricle performances, subsequently improve the prognosis in the patients with HFmrEF and HFpEF.

Recently, some systematic review[15] and meta-analyses[16–18] investigated the use of MRAs in patients with HF with LVEF ≥40%, but the results remained controversial and some of those outcomes were presented with significant heterogeneity. Compared with eplerenone and finerenone, spironolactone is the most wildly used MRAs. The active metabolite of spironolactone, canrenone has a relatively long serum half-life (10–35 h for the spironolactone vs. 4–6 h for eplerenone). Spironolactone is also the cheapest MRAs in the clinical practice.[19] However, the study focusing on spironolactone is absent, which could avoid the heterogeneity of different medicines.[20] Therefore, the study aimed to investigate the effectiveness and safety of spironolactone in the patients with LVEF ≥40% (HFmrEF and HFpEF).

2. Methods

This meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).[21,22]

2.1. Literature search

A systematic search was conducted using PubMed, EMBASE, Cochrane Collaboration Central Register of Controlled Trials, Clinical Trials Databases, and the China National Knowledge Internet (CNKI); the following key words were searched: "spironolactone", "aldactone", "antisterone", "diastolic heart failure", "heart failure", "HFpEF", "heart failure with normal ejection fraction", and "diastolic dysfunction", "heart failure with mid-range ejection fraction", "HFmrEF". We screened the literature and conducted a concurrent quality evaluation of articles, available through June 2018, assessing spironolactone treatment in patients with HFmrEF and HFpEF.

2.2. Literature screening and quality evaluation

The inclusion criteria were as follows: First, RCTs in humans. Second, patients with HFmrEF and HFpEF. Third, spironolactone treatment compared to placebo or standard conventional therapy. Studies were excluded from further analysis if firstly, not RCTs; secondly, the follow-up time was unavailable; or thirdly, the research design did not meet the Cochrane Handbook guidelines for RCTs.[23]

Two authors (Xiang and Shi) independently extracted the data according to the inclusion or exclusion criteria; disagreements were resolved by discussion with a 3rd investigator. The Cochrane risk of bias assessment tool were used to assess the risk of bias.[23] The PRISMA flow diagram described the full search strategy. Information of the year of publication, 1st author, patient characteristics, intervention strategies, follow-up times, mean ages was reviewed (Table 1). Hyperkalemia was defined as a potassium level >5.5 mmol/L.[18] Readmissions were defined as additional hospitalizations for all cardiovascular events. The mortality was defined with death from cardiovascular causes.[20]

3. Outcomes

Mortality and hospitalizations were the primary clinical outcomes. The functional capacity and serum indicator outcomes included: First, changes in functional capacity using the New York Heart Association functional classifications (NYHA-FC) and 6-minute walking distance (6-MWD) test. Second, changes in serum collagen turnover (procollagen type I C-terminal propeptide [PICP] and amino-terminal peptide of procollagen type-III [PIIINP]), which reflect myocardial fibrosis intensity.[24,25] Third, changes in brain natriuretic peptide (BNP) levels as a quantitative marker of HF.[25] The effects of spironolactone on diastolic function indexes included: changes in the ratio of early diastolic mitral valve blood flow velocity to the early diastolic mitral valve ring motion velocity (E/e') and changes in the ratio of early to late diastolic transmitral flow (E/A).[20] Spironolactone's effects on cardiac structure and function indexes included LVEF changes and changes in the left ventricular end-diastolic dimension (LVEDD). Adverse events associated with spironolactone use were also evaluated.

3.1. Statistical analysis

All statistical analyses were conducted using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity tests were performed using the Chi-square test and I^2 statistic test. If the value was less than 50%, the relative risk (RR) or odds ratio (OR) of the dichotomous data and mean difference (MD) or standard weighted mean difference (SMD) of continuous data were pooled using a fixed effects model (Mantel–Haenszel method); otherwise, a random effects model was used. For data analysis, NYHA-FC were divided into 2 levels: grades I and II were incorporated into one level, grades III and IV were incorporated into a 2nd level to allow a dichotomous data analysis.[23] A sensitivity analysis was conducted to determine the influence of individual trials on the overall, pooled results. In the

Table 1

Basic characteristics of clinical trials included in the meta-analysis.

Author, Year	Patient clinical characteristics	LVEF	Country	Number	Intervention: dose (mg/d)	Control group	Follow-up (months)	Mean age, y
Amil, 2015[33]	HFmrEF and HFpEF	≥45%	USA, Russia, and Georgia	935	Spironolactone 25 mg/d; n=121	Placebo; n=118	12-18	70.19
Bertram Pitt, 2014[11]	HFmrEF and HFpEF	≥45%	USA, Canada, Argentina, Brazil, Russia, Georgia	3445	Spironolactone 25 mg/d; n=1722	Placebo; n=1723	39.60	68.70
Karla 2014[28]	HFpEF	≥50%	USA	48	Spironolactone 25 mg/d; n=24	Placebo; n=24	6	71.35
Vatankulu, 2013[31]	HFmrEF and HFpEF with AMI	≥40%	Turkey	186	Spironolactone 12.5 or 25 mg/d; n=104	Placebo; n=56	6	56.40
Kosmala, 2013[27]	HFpEF with BMI >30 Kg/m^2	≥50%	Australia	113	Spironolactone 25 mg/d; n=58	Placebo; n=55	6	58
Edelmann, 2013[5]	HFpEF	≥50%	Germany and Australia	422	Spironolactone 25 mg/d; n=213	Placebo; n=209	12	67
Kosmala, 2011[24]	HFpEF with metabolic syndrome	≥50%	Australia	79	Spironolactone 25 mg/d; n=40	Placebo; n=39	6	59
Kayrak, 2010[26]	HFmrEF and HFpEF with AMI	≥40%	Australia	110	Spironolactone 25 mg/d; n=55	Standard conventional Therapy; n=55	6	56.25
Liu, 2006[32]	HFpEF with hypertension	≥50%	China	78	Spironolactone 25 mg/d; n=40	Standard conventional therapy; n=38	6	63.49
Roongsmtong, 2005[30]	HFmrEF and HFpEF	≥45%	USA	28	Spironolactone 25 mg/d; n=14	Placebo; n=14	4	71.55
Mottram, 2004[29]	HFpEF with hypertension	≥50%	Australia	30	Spironolactone 25 mg/d; n=15	Placebo; n=15	6	61.50

LVEF = left ventricular ejection fraction, HFmrEF = heart failure with mid-range ejection fraction, HFpEF = heart failure with preserved ejection fraction, BMI = body mass index, AMI = acute myocardial infarction.

current work, studies were included according to search terms as defined by the latest guidelines.[7] Therefore, patients with LVEF ranged 40 to 50% were also recruited in some of the previous HFpEF clinical trials. Subgroup analyses were conducted for the RCTs which included only patients with LVEF≥50%. Subgroup analyses also explored potential sources of heterogeneity among the included studies when necessary; the results were presented as forest graphs.

4. Results

Eleven RCTs[5,11,24,26–33] were included, involving a total of 4539 HFmrEF and HFpEF patients. Three[24,26,31] studies included 375 patients with myocardial disease, including metabolic syndrome and myocardial infarction, 2[29,32] other studies included 108 patients with hypertension, and the remaining included 4056 patients with multiple or unclear etiology. Six studies enrolled 770 patients with LVEF≥50%,[5,24,27–29,32] other 3769 patients had LVEF ≥40% or ≥45%. All the RCTs used spironolactone in the intervention group; the controls included placebo (n=9)[5,11,24,27–31,33] or standard conventional therapy (n=2).[26,32] All of those studies had follow-up periods longer than 4 months (Table 1). Among those studies, the study by Amil et al in 2015 was a substudy of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), where patients were separately consented to participate in the echocardiographic, 935 patients were suitable for quantitative analysis and included in this study.[33] The parameters of echocardiographic were included, but we didn't count the duplicated patients.

4.1. Quality assessment

We used the Cochrane risk of bias and the "Risk of Bias" tool in Review Manager 5.3 to perform quality assessments. The randomized experimental scheme was shown in all studies.[23] Four studies[24,27,29,33] clearly described the randomization methods; one study[30] did not describe the study's allocation and concealment procedure and another[31] did not describe the characters of participants and study personnel blinding methods (Fig. 1).

5. Clinical outcomes

5.1. Mortality and hospitalizations

The mortality was defined with death from cardiovascular causes, reported in 3 studies[11,26,31] with overall 3715 patients. There was no significant differences in mortality between spironolactone and control group in HFmrEF and HFpEF (RR, 0.72; 95% confidence interval [CI], 0.31–1.69; $P=.45$). The fixed effects model was used ($P=.24$, $I^2=29\%$) (Fig. 2**A**). Overall hospitalizations were reported in 2 studies[5,11] including 3845 patients. The results showed that spironolactone decreased the readmission of patients with HFmrEF and HFpEF (OR, 0.84; 95% CI, 0.73–0.95; $P=.006$) (Fig. 2**B**). The fixed effects model was used due to the low heterogeneity observed ($P=.21$, $I^2=35\%$).

5.2. Functional capacity and serum indicator

An evaluation of the NYHA-FC involving 527 patients from three studies[5,24,28] showed that spironolactone improved the NYHA-FC of patients with HFmrEF and HFpEF (OR, 0.35;

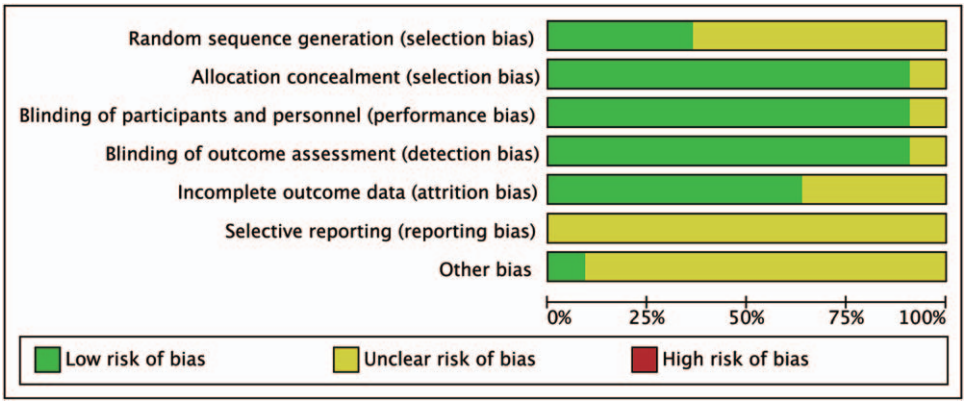

Figure 1. Quality assessment of each included study.

95% CI, 0.19–0.66; $P=.001$) (Fig. 2C). The 6-MWD was reported in three studies with 497 HFpEF subjects.[5,28,32] Spironolactone treatment of HFpEF patients showed significant improvement in 6-MWD (SMD, 0.45 m; 95% CI, 0.27–0.64; $P<.001$) (Fig. 2D).

Three studies[24,27,30] including 220 patients reported the PICP changes. Four studies involving 270 patients[24,26,27,32] reported PIIINP changes, which only enrolled the patients with HFpEF. Spironolactone treatment was associated with a significant decrease in PICP levels in patients with HFmrEF and HFpEF

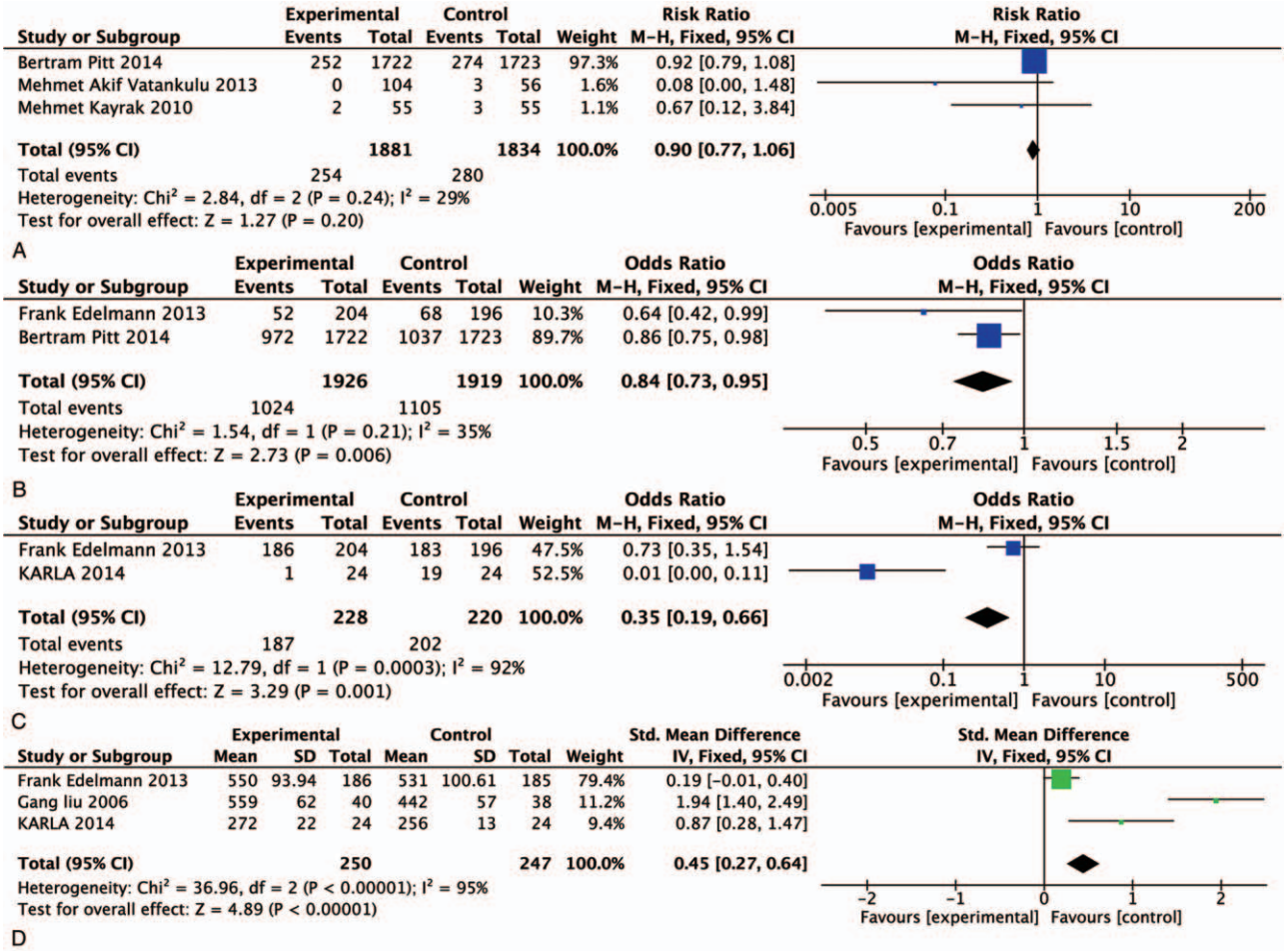

Figure 2. Forest plot of hospitalizations and functional capacity outcomes. (A) Mortality. (B) Hospitalizations. (C) New York Heart Association functional classifications (NYHA-FC). (D) Six-minute walking distance (6-MWD). All were assessed using fixed effects analyses. Squares indicated the risk ratio, odds ratio, or standard weighted mean difference; the horizontal lines indicated the 95% confidence intervals for each included trial. The statistical weight of a trial in the meta-analysis was proportional to the size of each square; diamonds indicated pooled risk ratios and 95% confidence intervals, with the center indicating the point estimate and the left and the right ends indicated the 95% confidence interval.

(MD, −27.04 ng/mL; 95% CI, −40.77 to −13.32; $P<.001$) (Fig. 3**A**). Similarly, treatment was associated with decreased serum PIIINP in HFpEF (MD, −0.37 μg/L; 95% CI, −0.59 to −0.15; $P=.001$) (Fig. 3**B**).

Four studies involving 516 patients[5,27,30,32] included BNP levels (MD, −44.80 pg/mL; 95% CI, −73.44 to −16.17; $P=.002$) (Fig. 3**C**). In a subgroup analysis, the BNP reduction was only significant in the studies from United States (MD, −47.54 pg/mL; 95% CI, −54.37 to −40.71; $P<.001$) both for HFmrEF and HFpEF, but not in the studies from other regions (MD, −48.84 pg/mL; 95% CI, −119.40 to 21.71; $P=.17$). There was no significant differences between subgroups ($P=.97$, $I^2=0$).

5.3. Echo indexes of diastolic function

The E/e' velocity ratio was reported in 6 studies[5,24,27,28,31,33] with 999 subjects. Nine studies reported E/A ratios in 1164 patients.[5,24,26,27,29–33] Subgroup analyses were performed between LVEF ≥ 50% and LVEF ≥ 40%, E/e' velocity ratio (SMD, −0.1; 95% CI, −0.22 to 0.01; $P=.46$) or the E/A ratio (SMD, 0.08; 95% CI, −0.11 to 0.27; $P=.39$) did not differ between spironolactone and control groups, neither in HFmrEF nor HFpEF. No significant differences was observed between subgroups (E/e', P = 0.18, $I^2=44.4\%$; E/A, $P=.67$, $I^2=0$) (Fig. 3**D**, **E**).

5.4. Echo indexes of cardiac structure and systolic function

The LVEF were reported in five studies[5,24,26,31,33] that included 1010 enrolled patients, and the LVEDD was presented in 6 studies[5,24,26,27,29,31] including 914 patients. A subgroup analysis did not show a significant difference between those treated with or without spironolactone in HFmrEF and HFpEF, in terms of LVEF (SMD, 0.08; 95% CI, −0.11 to 0.27; $P=.42$) or LVEDD (SMD: 0.03 mm; 95% CI, −0.21 to 0.27; $P=.81$). It didn't show significant subgroup differences (LVEF, $P=.88$, $I^2=0\%$; LVEDD, $P=.34$, $I^2=0\%$) (Fig. 4**A**, **B**).

5.5. Safety and adverse events

In these studies, spironolactone increased serum potassium levels (MD, 0.25 mmol/L; 95% CI, 0.18–0.33; $P<.001$). Subgroup analyses showed spironolactone increase the risk of hyperkalemia (OR, 2.56; 95% CI, 1.54–4.27; $P<.001$) and gynecomastia (OR, 7.82; 95% CI, 3.82–16.01; $P<.001$) both in HFmrEF and HFpEF patients, with no subgroup differences observed (hyperkalemia, $P=.67$, $I^2=0\%$; gynecomastia, $P=.78$, $I^2=0\%$).(Fig. 4**C**, **D**, **E**)

6. Discussion

The present meta-analysis including eleven RCTs with 4539 patients to evaluate the efficacy and safety of spironolactone in patients with HFmrEF and HFpEF, which is different with previous meta-analysis about the MRAs treatment including spironolactone, eplerenone, or finerenone together. It avoided the heterogeneity from different MRAs. The main findings of this study were that spironolactone significantly reduced hospitalizations and myocardial fibrosis through decreasing serum PICP, improved NYHA-FC and BNP levels in HFmrEF and HFpEF. Besides, spironolactone could also decrease the levels of PIIINP and increase 6-MWD compared with control group in HFpEF. However, no benefit was observed for mortality and diastolic function, neither HFmrEF nor HFpEF.

The results of previous clinical studies about the efficacy of spironolactone on HFmrEF and HFpEF remain controversial. The Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial in 2014[5] indicated that spironolactone could improve left ventricular diastolic function but not affect hospitalizations or exercise capacity. But the improvement of diastolic function was not significant in the study of Vatankulu in 2013,[31] and TOPCAT trial in 2014,[11] which only showed the improvement in the hospitalization due to heart failure. The present meta-analysis showed that spironolactone significantly reduced the primary clinical outcome hospitalizations, while the improvement of left ventricular diastolic function was not significant. Besides, HFmrEF as the gray area, the present meta-analysis also suggested a potential benefit for HFmrEF patients with spironolactone treatment. Therefore, we believe the present study may provide some new insights to this area.

The present study also showed that spironolactone significantly reduced the serum indicators PICP in HFmrEF and HFpEF, reduced PIIINP in HFpEF only. This due to the RCTs, which reported the PIIINP outcome, all enrolled patients with LVEF ≥50%. This was consistent with the results of most randomized clinical trials[24,28,27] and previous MRAs meta-analysis.[16–18] The changes in PICP and PIIINP levels were associated with decreased levels of matrix metalloproteinase-9 (MMP-9), which played an important role in the degradation and generation of extracellular matrix.[25] The PICP and PIIINP were known to delay or prevent ventricle remodeling, which was a known predictor of poor outcome, and was a major determinant of heart failure progression.[6] The PIIINP could also improve HF symptoms and prevent further patient deterioration.[25] Therefore, HFmrEF and HFpEF patients with myocardial fibrosis or myocardial hypertrophy may benefit from the treatment with spironolactone.

The BNP is a useful indicator of the severity of left ventricular dysfunction (i.e., LVEF or ventricular systolic and diastolic volumes) and cardiovascular outcomes, such as hospitalizations.[7] Treatment with spironolactone lower the plasma levels of BNP may due to the decreased left ventricular filling pressure via decreased retention of water and sodium, and attenuated left ventricular remodeling.[34] Subgroup analysis indicated a significant reduction in BNP levels with spironolactone treatment in HFmrEF and HFpEF patients from the USA while not in the other regions. Similar results were reported in the TOPCAT trial in terms of the HF hospitalization: patients from 'the Americas' (Canada, USA Argentina, and Brazil) showed a marked response to treatment of spironolactone whereas patients from Eastern Europe (Russia and Georgia) did not.[14] A possible interpretation was that in the present study the majority of patients (85.27%) came from other regions, there may exist heterogeneity of different race.

In the present study, spironolactone treatment had no effect on mortality in HFmrEF and HFpEF patients. The result was consistent with the meta-analysis in 2015 which showed that all-cause mortality was not improved by MRAs.[18] Shah showed that spironolactone treatment could decrease the mortality of HFpEF patients.[15] However, Solomon indicated that spironolactone treatment did not reduce the primary endpoints of cardiovascular death, HF hospitalizations, or aborted cardiac arrests in patients with HFpEF in the TOPCAT trial.[35] The possibility of without change in mortality may be due to the short-term follow up duration (10/11 of the included studies with follow-up durations ≤12 months). The present study also showed no change in diastolic function with spironolactone

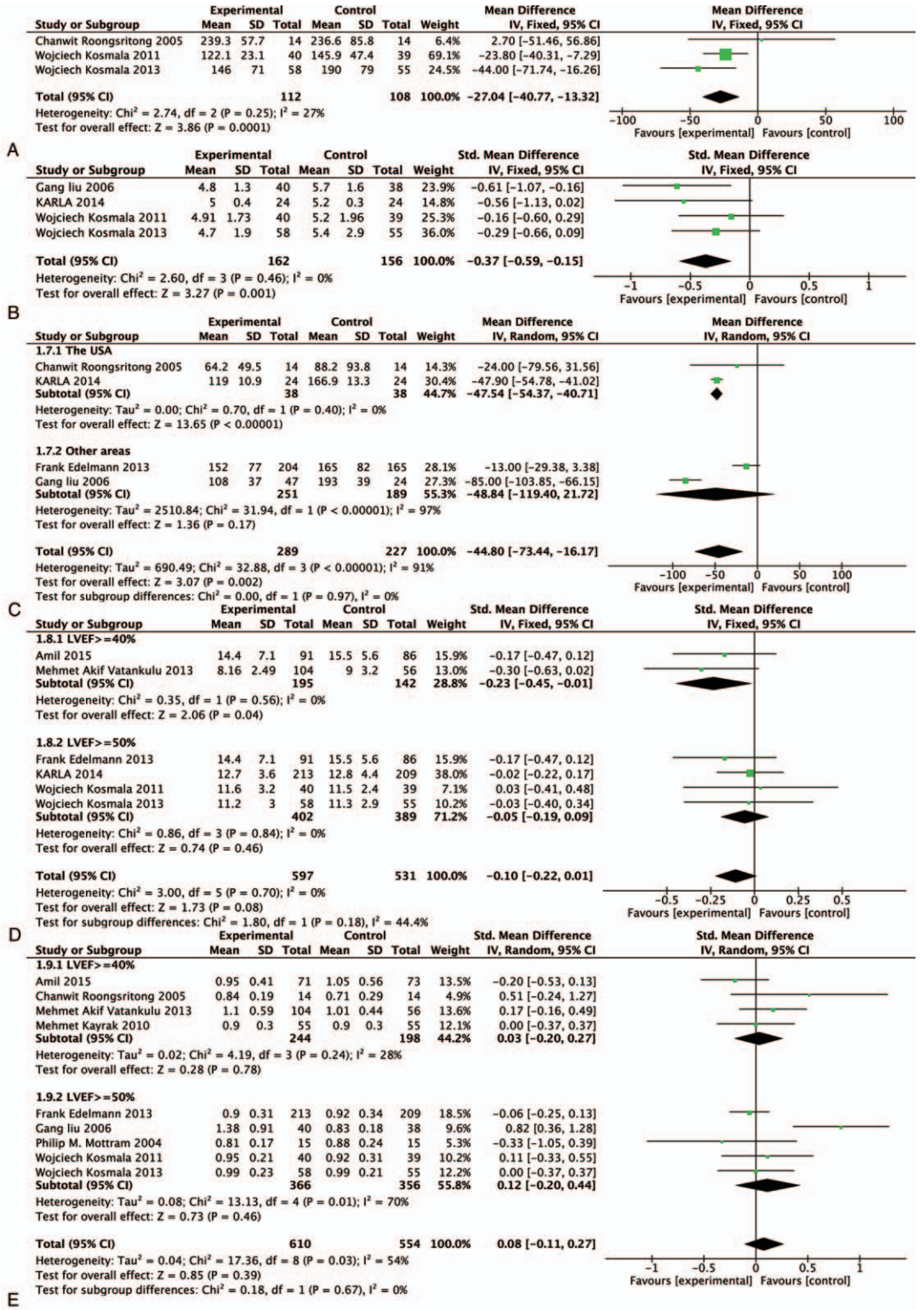

Figure 3. Forest plot of serum indicator outcomes and Echo indexes of diastolic function. (A) Procollagen type I C-terminal propeptide. (B) Amino-terminal peptide of procollagen type-III. (C) Brain natriuretic peptide (BNP). (D) Early diastolic mitral valve blood flow velocity and the early diastolic mitral valve ring motion velocity (E/e'). (E) The ratio of early to late diastolic transmitral flow (E/A ratio). The BNP and E/A ratio analysis involved a random effects model; the other three employed fixed effects analyses. The squares indicated the mean difference or standard weighted mean difference and the horizontal lines indicated the 95% confidence intervals (CI) for each trial included. The statistical weight of a trial in the meta-analysis was proportional to the size of each square; diamonds indicated pooled risk ratios and 95% CI, with the center indicating the point estimate and the left and the right ends representing the 95% CI. LVEF: Left ventricular ejection fraction.

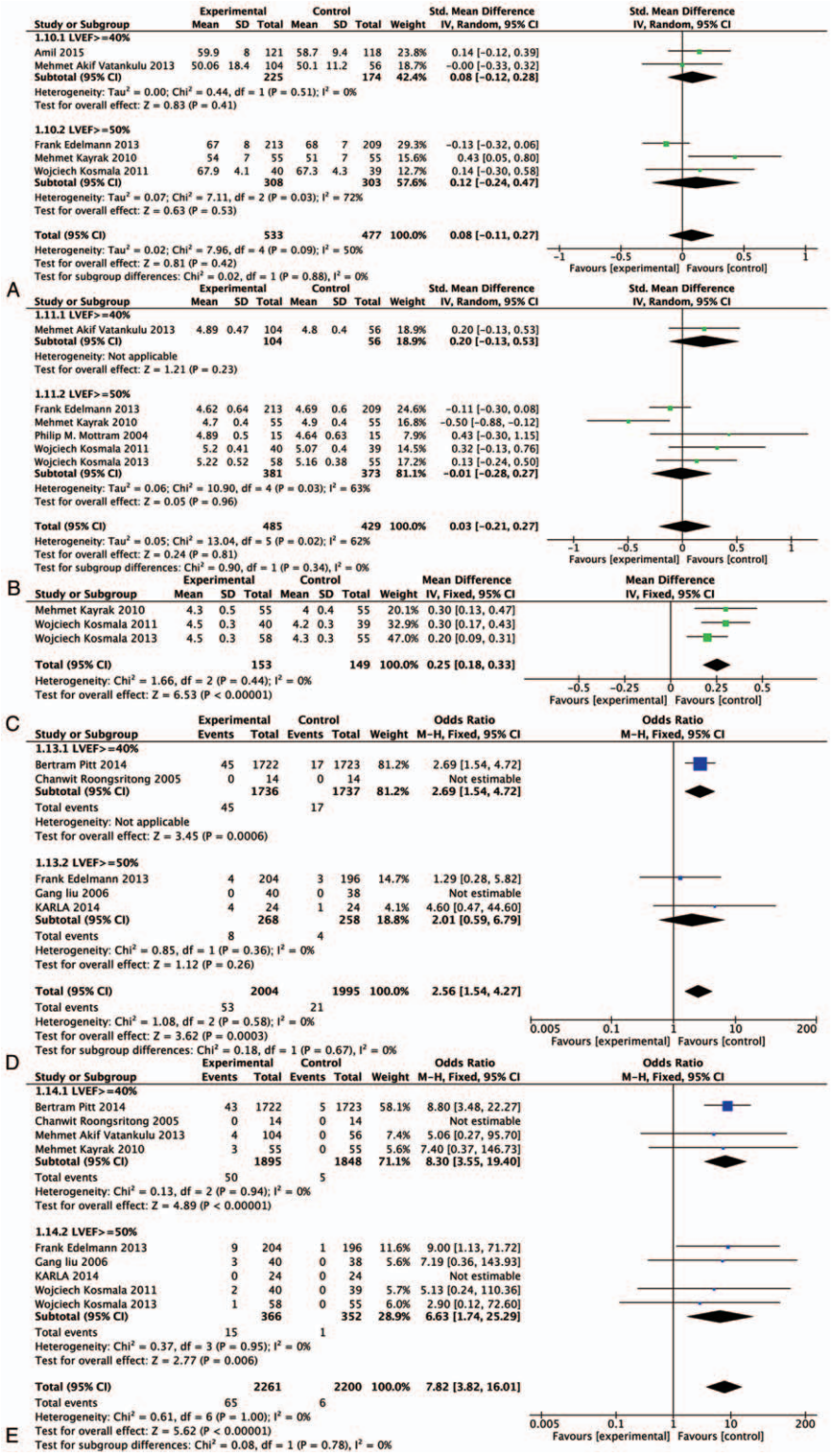

Figure 4. Forest plots for echo indexes of cardiac structure and function and adverse events. (A) Left ventricular ejection fraction (LVEF). (B) Left ventricular end-diastolic dimension (LVEDD). (C) Serum potassium. (D) Hyperkalemia. (E) Gynecomastia. The LVEF and LVEDD analysis used random effects analyses, the others employed fixed effects model analyses. The squares indicated the mean difference, standard weighted mean difference or odds ratio and the horizontal lines indicated the 95% confidence intervals (CI) for each included trial. The statistical weight of a trial in the meta-analysis was proportional to the size of each square; diamonds indicate pooled risk ratios and 95% CI, with the centers indicating the point estimates and the left and the right ends representing the 95% CI. LVEF: Left ventricular ejection fraction.

treatment. This was different with the results of Kosmala, which demonstrated improvements in the E/e' velocity ratio with spironolactone treatment in LVEF≥50% patients.[24,27,36] Moreover, the results of E/A ratio also differed from Amil 2015,[33] Frank Edelmann 2013,[5] Mottram 2004[29] which indicated spironolactone could decrease the E/A ratio, to Roongsritong 2005,[30] Vatankulu 2013,[31] Kayrak 2010,[26] Liu 2006[32] which showed increase in the E/A ratio. The potential reasons of the discrepancy should be the sample size various.

For 6-MWD, previous meta-analysis[16] showed that MRAs failed to increase 6-MWD in patients with LVEF≥40%. In contrast, the present study showed substantial evidence of improving 6-MWD in HFpEF and NYHA-FC in HFmrEF and HFpEF associated with spironolactone treatment. In the present study, the NYHA-FC and 6-MWD showed considerable heterogeneity among studies, with I^2 values >70% (NYHA, $I^2=97\%$; 6-MWD, $I^2=95\%$). A sensitivity analysis failed to show the influence of individual trials on the overall pooled results. We found that the potential heterogeneity among the studies[5,11,24,28,32] could result from differences in the manifested diseases, study countries, and patient ages.

The present study also showed that the potential side effects of hyperkalemia and gynecomastia. It is recommend that caution should be exercised when MRAs are used in HFrEF patients with impaired renal function and in those with serum potassium levels >5.0 mmol/L.[7] The present study demonstrates that the serum potassium monitoring also should be concerned in HFmrEF and HFpEF patients. Spironolactone is high affinity but is not specific for the mineralocorticoid receptor also binds to progesterone and androgen receptors, accounting for its well-known side effects such as breast pain and gynecomastia, erectile dysfunction in males and menstrual irregularities in premenopausal females.[19]

There were some limitations need to be noted. First, among the 11 studies, only 1 reported a long-term follow-up period (39.6 months)[5], whereas the remaining studies had follow-up durations of ≤12 months. Second, the large variances in sample sizes among the studies meant that we had to perform several SMD calculations. Third, most studies involved patients treated with a single dosage of spironolactone (25 mg/d); only one was performed with different doses (12.5 or 25 mg/d). This meant that we were unable to describe a relationship between the spironolactone effects and its dosage. Fourth, in the study, 6/11 RCTs used an LVEF cut off of ≥50%, other 5/11 RCTs used an LVEF ≥40%. Patients with LVEF between 40 and 50% were included in the previous "HFpEF" studies, without evaluated as a separate entity. There may exist considerable inconformity with the updated guideline.[7,8] But, our meta-analysis does suggest a potential spironolactone treatment both benefit for HFmrEF and HFpEF patients, especially for those with myocardial fibrosis, elevated BNP or poor heart functional capacity. Further long-term randomized trials should be conducted to determinate the effects of spironolactone on mortality and diastolic function in HFmrEF and HFpEF, separately.

7. Conclusions

Patients with HFmrEF and HFpEF could benefit from spironolactone treatment, with reduced hospitalizations, BNP levels, improved NYHA-FC, alleviated myocardial fibrosis by decreasing serum PICP in HFmrEF and HFpEF, decreased PIIINP levels and increased 6-MWD in HFpEF. The risks of hyperkalemia and gynecomastia were significantly increased. The serum potassium monitoring should be concerned.

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