

## Original Article

# Effects of long-term low-dose spironolactone treatment in patients with New York Heart Association functional class II heart failure: a 10-year prospective study

Jin-Ling Wu, Dong-Yan Hou, Gui-Ling Ma, Yan-Hong Liang, Hua Wang, Xin Wang, Lin Xu, Wen-Shu Zhao, Zhi-Yong Zhang, Jin Chen, Jia-Mei Liu, Lin Zhang

Heart Failure Center, Department of Cardiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

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**Abstract:** Background: Before 2012, spironolactone has been only recommended for patients with New York Heart Association functional class (NYHA) III-IV congestive heart failure (CHF). This study began in 2004 to test the hypothesis that long-term low-dose spironolactone in CHF patients with NYHA class II are associated with better prognosis. Methods: The present study began in 2004 and ended in 2013, which was divided into two periods: from 2004 to 2008, and from 2009 to 2013. A total of 139 patients with NYHA class II and an ejection fraction of  $\leq 45\%$  were randomly assigned to the spironolactone ( $n=69$ ) or non-spironolactone ( $n=70$ ) group, with a standard treatment regimen from 2004 to 2008. Patients with non-spironolactone began to accept the same treatment as patients in the spironolactone group from 2009 to 2013. Primary outcomes were all-cause mortality, cardiovascular mortality and hospitalization. The secondary endpoint was life-threatening hyperkalemia. Results: From January 2004 to December 2008, all-cause mortality, cardiovascular mortality and hospitalization were significantly lower in the spironolactone (10-20 mg/day) group than in the non-spironolactone group (all  $P < 0.05$ , 15.8% vs. 32.3%, 14.0% vs. 30.6%, 21.1% vs. 37.1%, respectively). From January 2009 to December 2013, there was no difference between the two groups at all end points. The occurrence of serum potassium levels  $> 5.0$  mmol/L was similar between the two groups during the 10-year follow-up. Conclusion: Long-term low-dose spironolactone added to standard treatment in patients with NYHA class II heart failure significantly reduced all-cause mortality, cardiovascular mortality and hospitalization without inducing life-threatening hyperkalemia.

**Keywords:** All-cause mortality, cardiovascular mortality, life-threatening hyperkalemia

## Introduction

Increasing numbers of studies including two randomized controlled trials (RALES and EPHEsus) have confirmed that aldosterone blockade substantially reduces the risk of both morbidity and death among patients with progressive heart failure [1, 2]. These results have led to renewed interest in the role of aldosterone receptor antagonists in the medical management of heart failure. The beneficial effects of aldosterone receptor blocker on left ventricular reverse remodeling in patients with mild-to-moderate systolic heart failure have been reported [3]. More recently, it was reported that eplerenone reduced the risk of both death and hospitalization among patients with heart fail-

ure and mild symptoms in the United States and Canada [4-6].

Since the RALES trial was published, aldosterone receptor blockers have continued to stimulate great interest regarding the treatment of heart failure. However, some studies reported that risk of death within five years of diagnosis continued to exceed 50% [7]. Conversely, recent evidence indicated that the publication of the RALES trial in 1999 was associated with the rapid increase in spironolactone prescription, hyperkalemia-associated hospitalization and in-hospitalization hyperkalemia-associated death [8-10]. It is known that before 2012, spironolactone is only recommended for patients with New York Heart Association functional

class (NYHA) III-IV congestive heart failure (CHF). In fact, the relationship among CHF, the renin-angiotensin-aldosterone system and the sympathetic nervous-catecholamine system are very clear [11-14]; and from the early stage of the disease, it is involved in the pathophysiology of heart failure.

The current study began in 2004 and ended in 2013, with a 10-year follow-up period. This prospective study was designed to investigate the benefit of long-term low-dose spironolactone (10-20 mg/day) to the standard treatment regimen (angiotensin-converting enzyme inhibitor, beta-receptor blocker, hydrochlorothiazide, and/or digoxin) on the mortality and hospitalization of patients with NYHA class II heart failure in mainland China. We would like to prove that long-term low-dose spironolactone added to standard treatment in patients with NYHA class II heart failure could significantly reduce all-cause mortality, cardiovascular mortality and hospitalization without inducing life-threatening hyperkalemia.

### Patients and methods

#### *Study population*

We prospectively studied 139 patients with stable NYHA class II heart failure after treatment with an angiotensin-converting enzyme inhibitor, thiazide diuretics, beta-receptor blocker, and/or digoxin. The inclusion criteria of the study were: (1) 18-80 year-old patients; (2) cardiac dysfunction caused by dilated cardiomyopathy, coronary heart disease or hypertensive heart disease; and (3) the presence of chronic cardiac insufficiency, as defined by a left ventricular ejection fraction (LVEF)<45%.

Patients were excluded for the following conditions: (1) heart rate < 55/min under clear-headed and quiescent conditions; (2) atrioventricular block >1°, sick sinus syndrome, cardiogenic shock, beta-receptor blocker hypersensitivity, and/or obstructive lung disease; (3) hepatic and renal dysfunction (glutamate pyruvate transaminase level 2× above the upper normal-limit, creatinine levels ≥115 μmol/L) and serum potassium level <3.6 mmol/L or >5.0 mmol/L; (4) pregnancy or lactation, or terminal disease with a predicted survival time of <5 years (e.g. malignant tumor).

#### *Study design*

This study complied with the Declaration of Helsinki, and was approved by the Ethics Committee and the Prescription and Therapeutic Committee of Beijing Chao-Yang Hospital, Capital Medical University. All subjects provided written informed consent before participating into the study.

This study was a single center, prospective, randomized controlled trial that began in January 2004 and ended in December 2013. A total of 139 patients with NYHA class II and an ejection fraction <45% were randomly assigned to the spironolactone ( $n=69$ , up to 10-20 mg/day) or non-spironolactone ( $n=70$ ) group with the standard treatment regimen. All 139 CHF patients with dilated cardiomyopathy ( $n=34$ ), coronary heart disease ( $n=41$ ) and hypertensive heart disease ( $n=64$ ) underwent physical examination, chest radiography, electrocardiography and echocardiography. Primary endpoints were all-cause mortality, cardiovascular mortality and hospitalization. The secondary endpoint was life-threatening hyperkalemia.

Data analysis in December 2008 revealed that primary endpoints were significantly reduced in patients in the spironolactone group. According to the rules of the Ethics Committee and the Prescription and Therapeutic Committee of Beijing Chao-Yang Hospital, patients in the non-spironolactone group began to receive the same treatment as patients in the spironolactone group from January 2009 to December 2013.

#### *Administration of medicines*

All patients received the standard pharmacological regimen for CHF (i.e. 12.5 mg/day of hydrochlorothiazide, 2-4 mg/day of perindopril or 25-50 mg/day of losartan, or 0.125 mg/day of digoxin and an initial daily dose of 12.5 mg/day of metoprolol; which was then up-titrated over a 2-4 week period by doubling the twice-daily amount to a target of 100 mg/day). The targets or maximum tolerated dose of heart beat frequency and blood pressure were 55/min and 90/60 mmHg, respectively. Patients in the spironolactone group received low-dose spironolactone (10 mg/day). Spironolactone dose could be increased to 20 mg/day after 4-8 weeks of treatment, and hydrochlorothia-

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**Table 1.** Baseline characteristics of the patients (mean value  $\pm$  SEM)

	Spironolactone group (n=69)	Non-spironolactone group (n=70)	P value
Age (years)	66.7 $\pm$ 1.3	65.5 $\pm$ 1.3	0.523
Sex (man/woman)	34/35	36/34	0.866
SBP (mmHg)	120.6 $\pm$ 1.3	121.3 $\pm$ 1.4	0.693
DBP (mmHg)	78.2 $\pm$ 1.1	75.9 $\pm$ 1.6	0.218
HR (bpm)	93.0 $\pm$ 1.2	94.8 $\pm$ 1.1	0.913
SMWT (m)	305.8 $\pm$ 4.3	301.7 $\pm$ 3.5	0.468
LVEDD (mm)	69.9 $\pm$ 0.8	71.4 $\pm$ 0.7	0.159
LVESD (mm)	55.4 $\pm$ 0.7	55.7 $\pm$ 0.8	0.776
LVEF (%)	32.2 $\pm$ 0.8	32.3 $\pm$ 0.7	0.925
K (mmol/L)	4.4 $\pm$ 0.1	3.8 $\pm$ 0.04	0.563

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SMWT, 6-min walk test; LVEDD, left ventricular enddiastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; K, serum potassium.

zide dose could be increased from 12.5 to 25 mg/day if a patient displayed signs or symptoms of heart failure progression. If hyperkalemia developed at any time, the dose of hydrochlorothiazide and spironolactone could be decreased to the baseline. Other potassium-sparing diuretics were not permitted. Otherwise, patients in both the spronolactone and non-spironolactone groups were strongly advised to reduce their salt intake to approximately 5 g of sodium chloride per day, restrict their intake of food, and control their body weight.

### Follow-up examination

All patients were assigned to designated study investigators and received follow-up examinations for at least ten years after the initiation of the study. Patients were encouraged to schedule interim appointments, and follow-up at least once per month for the first 12 months and every 3-6 months for up to 10 years until 2013. Concurrently, clinical laboratory tests were also performed. Data collected during patient examinations included those for heart rate, blood pressure, weight, the presence of rale during the pulmonary exam, cardiac murmur, the presence of peripheral edema, drug dose, and the presence of any adverse drug reactions from the clinic record system.

### Statistical methods

All data were presented as the mean  $\pm$  SEM. All-cause mortality, cardiovascular mortality

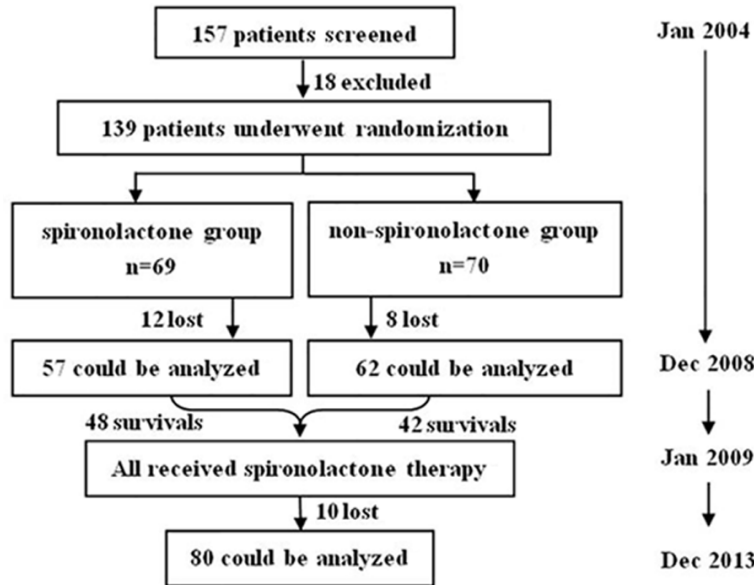
and hospitalization were assessed using Chi-square statistics. The Kaplan-Meier method was used to estimate and plot survival probabilities in the two groups over a 10-year period. Risk factor analysis for death was performed using univariate and multivariate analyses. Metoprolol titration data were fit into a variable slope sigmoidal equation ( $Y = \text{Initial Dose} + (\text{Maximum.Dose-Initial.Dose}) / (1 + 10^{(\text{LogEC50-X}) * \text{Slope}})$ ), in which the independent variable (X) is the log of the time of the dosage value (Y). The LogEC50 denotes the time that corresponds to halfway between the minimum and maximum dosages. Tests of significance were two-tailed. P-values <0.05 were considered statistically significant. Analyses were performed

using the Graph Pad 4.0 software package (San Diego, CA).

## Results

### Clinical characteristics

A total of 157 patients were screened in the study, and all patients received the standard treatment regimen for systolic heart failure. Among these patients, 18 patients were not enrolled, because their LVEF values improved to more than 45% after standard pharmacological interventions. The other 139 patients were randomly assigned to either the spironolactone group (n=69) that received low-dose spironolactone (up to 10-20 mg/day) or the non-spironolactone group (n=70); and were followed-up at heart failure clinics. Twenty patients were lost to follow-up (12 patients in the spironolactone group and eight patients in the nonspironolactone group). One hundred nineteen patients completed the data analysis at December 2008, including 57 patients (57/69, 83%) in the spironolactone group and 62 patients (62/70, 88.5%) in the non-spironolactone group. These two groups were balanced with respect to baseline clinical characteristics (Table 1). From January 2009, all 90 patients who survived in the two groups received the same treatment (standard treatment of heart failure and low dose of spironolactone). Ten patients were lost during the second 5-year follow-up, while the other 80 patients complet-



**Figure 1.** Enrollment and outcomes. A total of 157 patients were screened in the study. Of these patients, 18 patients were not enrolled because their left ventricular ejection fraction values improved to more than 45% after standard pharmacological interventions. One hundred thirty-nine patients were randomly assigned to the spironolactone and non-spironolactone groups. One hundred nineteen patients completed the final data analysis, including 57 patients in the spironolactone group and 62 patients in the non-spironolactone group. From January 2009, all the 90 survival patients in the two groups received the same treatment. 10 patients were lost during the second 5-year follow-up and the other 80 patients completed the final data analysis at December 2013.

ed the final data analysis at December 2013 (Figure 1).

*Primary outcomes*

During the first 5-year follow-up from January 2004 to December 2008, all-cause mortality in the spironolactone group was 15.8% (9/57), which was significantly lower than 32.3% (20/62) in the non-spironolactone group (hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.22-0.97; P=0.0409). Cardiovascular mortality in the spironolactone group was 14.0% (8/57), which was significantly lower than 30.6% (19/62) in the non-spironolactone group (HR, 0.44; 95% CI, 0.21-0.94; P=0.0344). Similarly, the rate of hospitalization for any reason in the spironolactone group was 21.1% (12/57), which was significantly lower than 37.1% (23/62) in the non-spironolactone group (HR, 0.51; 95% CI, 0.26-0.99; P=0.0458). Hospitalization for heart failure was also less common in the spironolactone group than the non-spironolactone group (17.5% vs. 33.9%;

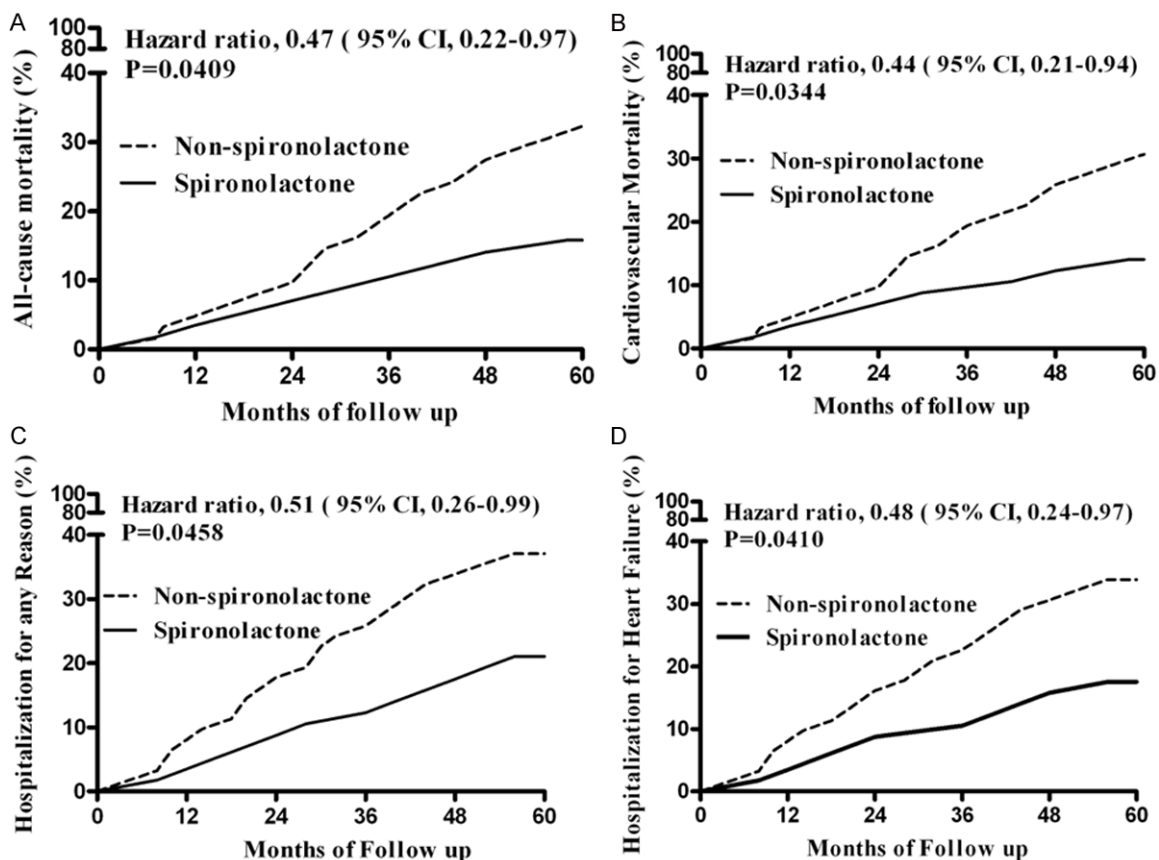
HR, 0.48; 95% CI 0.24-0.97; P=0.0410), as shown in Figure 2. These results suggest that long-term low-dose spironolactone (mean, 16 mg/day) significantly reduces the incidence of mortality and hospitalization in patients with mild heart failure.

However, during the second 5-year follow-up from January 2009 to December 2013, there was no significant difference in all-cause mortality, cardiovascular mortality and hospitalization between the two groups (P>0.05), as shown in Figure 3.

*Echocardiography and six-minute walk test*

During the first 5-year treatment period, low-dose spironolactone therapy, in conjunction with the standard treatment regimen for CHF, was associated with significant reductions in the left ventricular end-systolic diameter and left ventricular end-diastolic diameter. In the spironolactone group, the left ventricular end-diastolic diameter was reduced from 69.9 ± 0.8 mm to 56.0 ± 0.5 mm (P<0.0001), compared with a reduction from 71.4 ± 0.7 mm to 59.9 ± 0.9 mm in the non-spironolactone group (P<0.0001). Similarly, the left ventricular end-systolic diameter was reduced from 55.4 ± 0.7 mm to 37.7 ± 0.5 mm in the spironolactone group (P<0.0001), compared with a reduction from 55.7 ± 0.8 mm to 40.0 ± 0.6 mm in the non-spironolactone group (P<0.0001). Similarly, LVEF markedly increased from 32.2 ± 0.8% to 54.0 ± 1.1% in the spironolactone group (P<0.0001), compared with an improvement from 32.3 ± 0.7 to 49.8 ± 1.3% in the non-spironolactone group (P<0.0001). It is worth noting that patients in the spironolactone group had greater improvements in left ventricular remodeling (P=0.0003 for left ventricular end-diastolic diameter, P=0.0042 for left ventricular end-systolic diameter) and heart function (P=0.0157 for LVEF) than patients in the non-spironolactone group. The same result was

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**Figure 2.** Primary endpoint during the first 5-year follow-up All-cause mortality (A). The rate of all-cause mortality in the spironolactone group was 15.8%, compared with 32.3% in the non-spironolactone group (P=0.0409). Cardiovascular mortality (B). The rate of cardiovascular mortality in the spironolactone group was 14.0%, compared with 30.6% in the non-spironolactone group (P=0.0344). Hospitalization (C). The rate of hospitalization was also lower in the spironolactone group than in the non-spironolactone group (21.1% vs. 37.1%, P=0.0493). Hospitalization for heart failure (D). The rate of hospitalization for heart failure was also lower in the spironolactone group than in the non-spironolactone group (17.5% vs. 33.9%, P=0.0410).

also found in the six-minute walk test, as patients in the spironolactone group walked a longer distance than in patients in the non-spironolactone group after the first five years of follow-up ( $497.0 \pm 7.3$  m vs.  $433.3 \pm 7.5$  m,  $P < 0.0001$ ), as shown in **Table 2**.

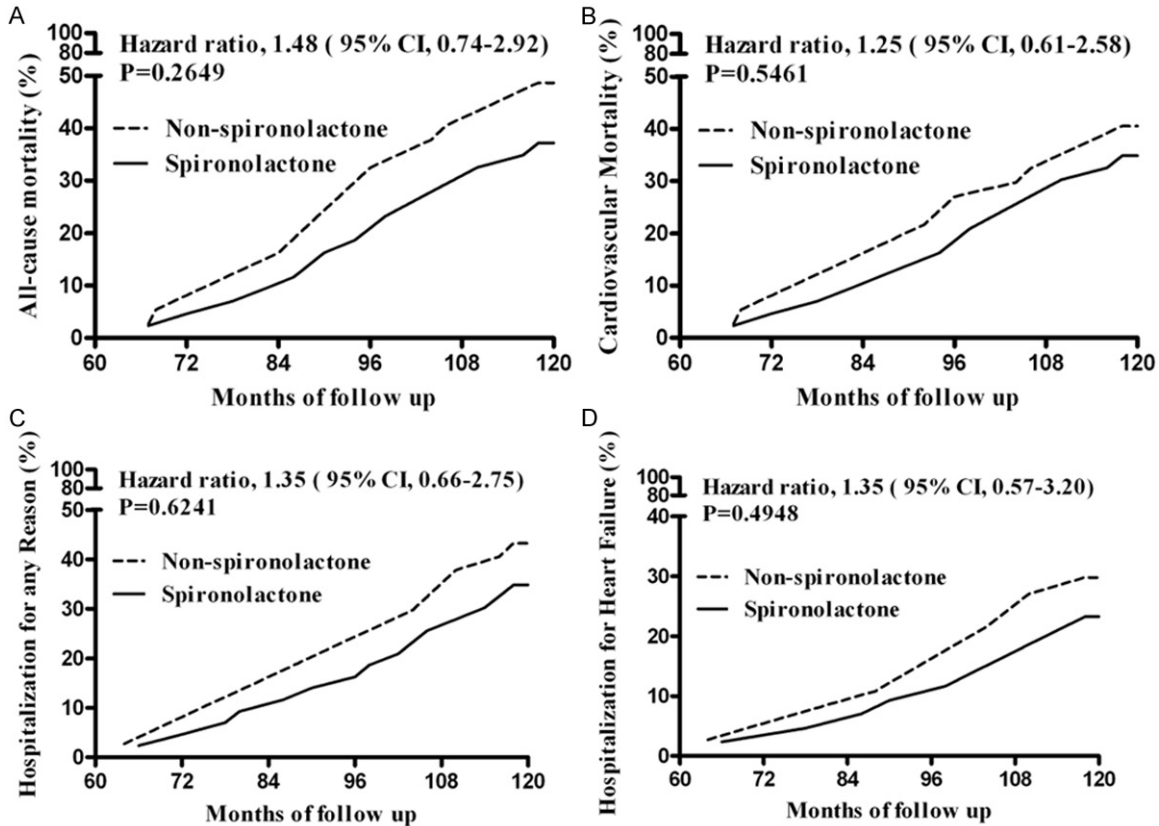
### Univariate and multivariate analysis of all-cause mortality

Univariate and multivariate analysis for all-cause mortality during the first 5-year follow-up period is shown in **Table 3**. Univariate logistic analysis revealed that age  $>70$  years old, spironolactone and metoprolol were significantly associated with all-cause mortality. Multivariate and interactions analysis indicate that spironolactone (odds ratio [OR]=0.35, 95% confidence interval [CI]: 0.14-0.89,  $P=0.028$ ) and age  $\geq 70$

years (OR=4.18, 95% CI: 1.66-10.51,  $P=0.002$ ) were significantly associated with all-cause mortality. These results indicate that death risk was significantly higher in 70 years or older patients than in  $<70$  year-old patients. Spironolactone was associated with a 65% reduction in death risk.

### Relationship between spironolactone and metoprolol

During the first 5-year treatment period, mean metoprolol dose in the spironolactone group was  $38.6 \pm 1.5$  mg bid/day, compared with  $29.0 \pm 1.3$  mg bid/day in the non-spironolactone group ( $P < 0.001$ ). The mean time to maximum titration in the spironolactone group was  $77.3 \pm 2.2$  days, compared with  $99.1 \pm 3.0$  days in the non-spironolactone group ( $P <$



**Figure 3.** Primary endpoint during the second 5-year follow-up. There was no significant difference on mortality and hospitalization between the two groups (P all > 0.05).

**Table 2.** Summary of the echocardiography and six-minute walk test data

	Spironolactone group		Non-spironolactone group	
	Baseline (n=69)	5 Years (n=47)	Baseline (n=70)	5 Years (n= 42)
LVEDD (mm)	69.9 ± 0.8	56.0 ± 0.5*.#	71.4 ± 0.7	59.9 ± 0.9*
LVESD (mm)	55.4 ± 0.7	37.7 ± 0.5*.#	55.7 ± 0.8	40.0 ± 0.6*
LVEF (%)	32.2 ± 0.8	54.0 ± 1.1*.#	32.3 ± 0.7	49.8 ± 1.3*
SMWT (mm)	305.8 ± 4.3	497.0 ± 7.3*.#	301.7 ± 3.5	433.3 ± 7.5*

Abbreviations: LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; SMWT, 6-min walk test. Notes: (1) Data are presented as the mean ± SEM. (2) Left ventricular structure and function were evaluated at baseline and after 5 years by echocardiography. (3) There were significant differences between the 2 groups at 5 years. \* = significant difference between data at 5 years and at baseline. # = significant difference between the spironolactone group and the non-spironolactone group at 5 years.

0.001), as shown in **Figure 4**. The target metoprolol dose of 50 mg bid/day was achieved in 40.4% (23/57) of patients in the spironolactone group, whereas only 12.9% (8/62) of patients in the non-spironolactone group tolerated this amount (P=0.001).

During the second 5-year treatment period, mean metoprolol dose was 35.2 ± 3.0 mg bid/

day in patients in the spironolactone group, compared with 34.4 ± 6.0 mg bid/day in patients in the nonspironolactone group (P=0.91). The target metoprolol dose of 50 mg bid/day was achieved in 35.1% (13/37) of patients in the non-spironolactone group, which significantly increased compared to 12.9% (8/62) of the first 5-year treatment (P=0.018). These results suggest that spironolac-

tone increases efficacy and tolerance to metoprolol.

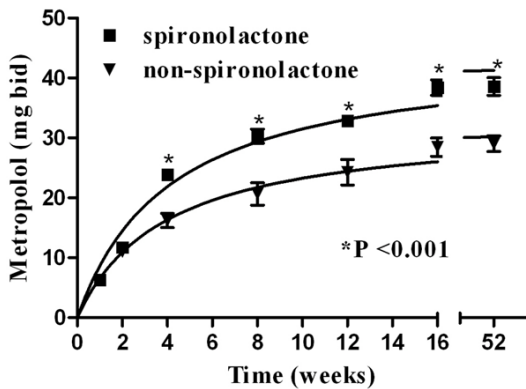
*Safety and adverse effects*

There were no significant differences between the two groups regarding blood pressure, blood glucose and lipid levels, serum sodium concentration, median creatinine level, digoxin con-

**Table 3.** Univariate and multivariate analysis for all cause mortality

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)	1.045	0.999-1.092	0.054			
Age (>70 years)	3.838	1.567-9.403	0.003	4.176	1.659-10.514	0.002
Gender (male)	0.312	0.277-1.506	0.646			
Spironolactone	0.394	0.162-0.958	0.040	0.351	0.138-0.893	0.028
LVEDD at baseline (mm)	1.008	0.939-1.083	0.819			
LVESD at baseline (mm)	1.043	0.972-1.118	0.240			
LVEF at baseline (%)	0.990	0.924-1.060	0.768			
Metoprolol (mg bid/day)	0.965	0.929-1.003	0.072			
Metoprolol (50 mg bid/day)	0.243	0.068-0.868	0.029			
SMWT at baseline (m)	0.995	0.981-1.000	0.460			

Abbreviations: OR, odds ratio; CI, confidence interval; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; SMWT, 6-min walk test.



**Figure 4.** Relationship between spironolactone and metoprolol. During the first 5-year treatment period, the mean metoprolol dose in the spironolactone group was  $38.6 \pm 1.5$  mg bid/day, compared with  $29.0 \pm 1.3$  mg bid/day in the non-spironolactone group ( $P < 0.001$ ). The mean time to maximum titration in the spironolactone group was  $77.3 \pm 2.2$  days, compared with  $99.1 \pm 3.0$  days in the non-spironolactone group ( $P < 0.001$ ).

centration, and liver and kidney function during the 10-year follow-up. At the end of the first 5 year followup, potassium concentration in the spironolactone group significantly increased from  $4.2 \pm 0.1$  to  $4.4 \pm 0.1$  mmol/L ( $P < 0.05$ ), but it remained within normal range. Contrarily, potassium concentration in the non-spironolactone group significantly decreased from  $4.1 \pm 0.1$  to  $3.9 \pm 0.1$  mmol/L ( $P < 0.05$ ), but also remained within normal range. Although the difference between these two groups was significant ( $P < 0.05$ ), it was not clinically important.

It was important that patients receiving long-term low-dose spironolactone treatment did

not die or require hospitalization due to life-threatening hyperkalemia during the 10-year follow-up. During the first 5-year follow-up, hyperkalemia (serum potassium levels  $>5.0$  but  $\leq 5.6$  mmol/L) occurred in five patients in the spironolactone group (8.8%) and in two patients in the non-spironolactone group (3.2%), but this difference was not statistically significant ( $P = 0.37$ ). Similarly, hypokalemia occurred in one patient (1.8%) in the spironolactone group and six patients (9.7%) in the non-spironolactone group ( $P = 0.12$ ). During the second 5-year follow-up, slight hyperkalemia occurred in four patients without hypokalemia.

Slight breast pain was reported in 5.3% (3/57) of the patients in the spironolactone group, and none in the non-spironolactone group, but the difference was not statistically significant. Therefore, spironolactone was tolerated by these patients during the 10-year follow-up period. There was no significant difference between these two groups regarding cough, as approximately 14.0% (8/57) of patients in the spironolactone group and 14.5% (9/62) of patients in the non-spironolactone group developed cough due to perindopril, and these patients were shifted to an angiotensin II receptor blocker, losartan.

**Discussion**

In the present study, we made several novel observations. First, low-dose spironolactone for 10 years in combination with a standard heart failure therapy regimen could significantly reduce the incidence of all-cause mortality, cardiovascular mortality and hospitalization in patients with NYHA class II heart failure. Sec-

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ond, long-term low-dose spironolactone in combination with a standard heart failure therapy regimen is more helpful for the improvement of the left ventricular remodeling and heart function. Third, we have demonstrated for the first time that patients receiving spironolactone are able to tolerate higher doses of metoprolol than patients without spironolactone, suggesting that spironolactone could improve the tolerance and efficiency of metoprolol in mild heart failure patients. Lastly, patients receiving long-term low-dose spironolactone treatment might not die or require hospitalization due to hyperkalemia or hypokalemia over a 10-year period.

In the past decade, aldosterone and the renin-angiotensin-aldosterone system have continued to attract interest as therapeutic targets, especially due to their effects on the cardiovascular system [15]. Some very important clinical trials have demonstrated that aldosterone receptor antagonists spironolactone and eplerenone in combination with standard treatment could significantly decrease the rate of mortality and hospitalization among patients with progressive heart failure and heart failure after acute myocardial infarction [6, 16]. Recently, the EMPHASIS-HF study group reported that compared with placebo, the addition of the selective aldosterone-receptor antagonist eplerenone to the recommended therapy for systolic heart failure in patients with mild symptoms was associated with a reduction in all-cause mortality, cardiovascular mortality, and hospitalization for heart failure [10].

However, all these studies have only been carried out for not more than three years, and long term treatment effects remains unclear. In the current study, we demonstrated that long-term low-dose spironolactone for five years in combination with a standard heart failure therapy regimen significantly reduced the incidence of these same endpoints in patients with NYHA class II heart failure at December 2008.

In this study, long-term low-dose spironolactone and age over 70 years were closely related to all-cause mortality in patients with mild CHF. Age over 70 years was associated with a three-fold increase in death risk. Spironolactone was associated with a 65% reduction of death risk. This may due to the inhibition of the deleterious effects of aldosterone and increased tolerance of metoprolol.

Thus far, there have been no reports of any correlation study between spironolactone and metoprolol. We found for the first time that patients receiving long-term low-dose spironolactone are able to tolerate higher doses of metoprolol than patients without spironolactone, which was due to two reasons. First, spironolactone is a synthetic 17-lactone steroid which is a renal competitive aldosterone antagonist in a class of pharmaceuticals called potassium-sparing diuretics. On its own, spironolactone is only a weak diuretic, but it can be combined with other diuretics (Furosemide was combined in the present study) to effectively reduce water sodium retention in patients with CHF, and improve cardiac function. It is conducive to metoprolol dosage titration. Second, the beneficial effects of spironolactone is the direct inhibition of the RAAS system on left ventricular reverse remodeling in patients with CHF, and this may be helpful to metoprolol to reach the target dose. Therefore, low-dose spironolactone appears to be particularly well-suitable for patients with NYHA class II heart failure, especially for patients requiring continued spironolactone treatment in combination with the standard treatment regimen.

A notable question was whether life-threatening hyperkalemia occurs when spironolactone and angiotensin-converting enzyme inhibitors are used together. It was reported that the publication of RALES was associated with an abrupt increase in the number of prescriptions for spironolactone, and considerable increases were observed in the rates of hospitalization for hyperkalemia and subsequent in-hospital death [12]. Additionally, some studies reported that spironolactone is inexpensive and generally well tolerated, but in some patients, it might provoke life-threatening hyperkalemia when used in combination with angiotensin-converting enzyme inhibitors [17-21].

The findings of this study indicate that low-dose spironolactone significantly reduced mortalities in patients with NYHA class II heart failure after the 10-year follow-up period. This result was similar to the findings of the RALES trial of spironolactone in patients with severe chronic heart failure. However, neither death nor hospitalization attributable to hyperkalemia was observed in the spironolactone group in the current study. Patients in this study took an ini-

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tial dose of 10 mg/day, which was increased to 20 mg/day (mean, 16 mg/day); whereas the RALES trial took an initial dose of 25 mg/day, which was increased to 50 mg/day (mean, 26 mg/day). Therefore, lower doses might explain the low incidence of hyperkalemia during the 10-year follow-up period. Although the differences were not statistically significant, hyperkalemia was more common in the spironolactone group, and hypokalemia was more common in the non-spironolactone group. It appears that the recommended dose of spironolactone (mean, 26 mg/day) might have been indirectly related to hyperkalemic events in other clinical studies [18, 22-24]. Otherwise, our study results revealed that low-dose spironolactone could reduce the incidence of mortality and hospitalization in patients with heart failure without inducing hyperkalemia; and one reason may be related to the use of potassium discharge diuretics at the same time.

In this study, 12 patients in the spironolactone group and eight patients in the non-spironolactone group were lost to follow-up during the first 5-years of treatment. We are not sure on the relationships among all-cause death, cardiovascular death, hospitalization or hyperkalemia, and lost to follow-up. However, serum potassium was normal before lost to follow-up.

In conclusion, this study demonstrates that long-term low-dose spironolactone in combination with standard heart failure therapy could significantly reduced all-cause mortality, cardiovascular mortality, and hospitalization in patients with NYHA class II heart failure. Moreover, we found that patients taking low-dose spironolactone had a better response and tolerance to metoprolol therapy, with greater improvements in left ventricular remodeling and function. Importantly, patients receiving long-term low-dose spironolactone treatment may not die or require hospitalization due to hyperkalemia during the 10-year follow-up period.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Lin Zhang and Jia-Mei Liu, Heart Failure Center, Department of Cardiology, Beijing Chao-Yang Hospital, Capital Medical University, 8 Gong-Ti South Road, Beijing 100020, China. Tel: +86-10-85231066; Fax: +86-10-65951064; E-mail: linzhangdoc@126.com (LZ); jiameiliudoc@163.com (JML)

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