Table I. Patient characteristics

Characteristics	Total (n = 946)	Spironolactone use (n = 435)	No spironolactone use (n = 511)	P
Age (y [mean ± SD])	66.3 ± 13.7	65.2 ± 14.4	67.3 ± 13.1	.052
Male (%)	72.2	73.3	71.2	.472
BMI (kg/m^2)	22.7 ± 4.2	23.0 ± 4.4	22.4 ± 4.0	.043
Causes of HF (%)				
Ischemic	39.6	38.6	40.5	.554
Dilated cardiomyopathy	36.3	39.3	33.7	.072
Hypertensive	21.6	21.1	21.9	.775
Medical history (%)				
Hypertension	50.7	49.1	52.2	.346
Diabetes mellitus	33.1	33.6	32.7	.790
Hyperlipidemia	28.9	28.5	29.2	.826
Hyperuricemia	51.3	49.2	53.0	.245
Prior stroke	13.8	12.9	14.5	.484
COPD	6.0	6.3	5.8	.734
Smoking	46.6	45.1	47.9	.403
Prior myocardial infarction	34.9	35.3	34.5	.797
Atrial fibrillation	24.3	21.7	26.6	.077
Sustained VT/VF	9.2	11.0	7.6	.068
Procedures (%)				
PCI	20.7	20.8	20.6	.950
CABG	11.9	13.3	10.7	.217
ICD	3.8	3.9	3.7	.879
CRT	2.4	3.4	1.6	.061
Vital signs at discharge				
NYHA functional class	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	.416
NYHA functional class 1or 2 (%)	93.9	94.5	93.3	.468
Heart rate (beat/min)	70.6 ± 12.0	70.6 ± 12.0	70.6 ± 12.0	.988
SBP (mmHg)	113.5 ± 17.1	111.8 ± 17.3	114.9 ± 16.7	.008
DBP (mmHg)	66.2 ± 11.6	65.8 ± 12.1	66.6 ± 11.2	.596
Laboratory data at discharge				
eGFR (mL min^{-1} 1.73 m^{-2})	53.8 ± 24.2	55.9 ± 20.3	52.1 ± 26.9	.017
Serum creatinine ≥2.5 mg/dL	7.9	3.7	11.5	<.001
Hemoglobin (g/dL)	12.9 ± 2.3	13.0 ± 2.1	12.8 ± 2.5	.657
Plasma BNP (pg/mL)	383 ± 534	376 ± 534	388 ± 535	.554
Echocardiographic data				
LV EDD (mm)	61.5 ± 9.4	62.6 ± 9.3	60.6 ± 9.3	.003
LV ESD (mm)	53.0 ± 9.4	54.0 ± 9.4	52.2 ± 9.3	.007
LVEF (%)	27.1 ± 7.3	26.7 ± 7.4	27.5 ± 7.3	.100

Data are shown as percentage or means ± SD.
COPD, Chronic obstructive pulmonary disease; *VT/VF*, ventricular tachycardia/fibrillation; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *ICD*, implantable cardioverter defibrillator; *CRT*, cardiac resynchronization therapy; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *BNP*, B-type natriuretic peptide; *LV*, left ventricular; *EDD*, end-diastolic diameter; *ESD*, end-systolic diameter; *EF*, ejection fraction.

rin were prescribed more in patients with spironolactone use. On the other hand, calcium channel blocker was used more in patients without spironolactone use.

Postdischarge clinical outcomes according to spironolactone use

During the follow-up of 2.2 years after hospital discharge, the rates of adverse outcomes were as follows: all-cause death 17.8%, cardiac death 11.8%, sudden cardiac death 2.2%, rehospitalization due to the worsening HF 33.4%, and all-cause death or rehospitalization 40.0%. The unadjusted rates of cardiac death were significantly lower in patients with spironolactone use (Table III).

After adjustment for covariates in multivariable Cox proportional hazard models, discharge use of spironolactone, which compared to no spironolactone use, was associated with a reduced risk of all-cause death (HR 0.619, 95% CI 0.413-0.928, P = .020) and cardiac death (HR 0.524, 95% CI 0.315-0.873, P = .013) (Table III and Figure 1). However, spironolactone use was not associated with the risk of rehospitalization due to worsening HF and the combined end point of all-cause death or rehospitalization.

Furthermore, in the subgroup of patients with NYHA functional class I or II, discharge use of spironolactone was associated with a reduced risk of all-cause death (adjusted HR 0.605, 95% CI 0.389-0.940, P = .026) and cardiac death (adjusted HR 0.492, 95% CI 0.276-0.876,

Table II. Medication use at hospital discharge

	Total (N = 946)	Spironolactone use (n = 435)	No spironolactone use (n = 511)	P
ACE inhibitor (%)	44.3	44.6	44.0	.861
ARB (%)	45.6	47.4	44.0	.306
β-Blocker (%)	65.9	66.7	65.2	.628
Diuretics (%)	88.1	100	77.9	<.001
Digitalis (%)	28.8	30.3	27.4	.318
Calcium channel blocker (%)	17.1	11.7	21.7	<.001
Nitrates (%)	22.6	22.3	22.9	.827
Antiarrhythmics (%)	20.9	26.9	15.9	<.001
Aspirin (%)	49.2	48.5	49.7	.713
Warfarin (%)	42.9	46.7	39.7	.032
Statin (%)	23.1	23.7	22.7	.722

Table III. Unadjusted and adjusted HRs for outcomes according to spironolactone use

	Number (%)				
Outcomes	Spironolactone use (n = 396)	No spironolactone use (n = 451)	HR	95% CI	P
All-cause death	59 (14.9%)	92 (20.4%)			
Unadjusted			0.746	0.537-1.035	.078
Adjusted for covariates			0.619	0.413-0.928	.020
Cardiac death	36 (9.1%)	64 (14.2%)			
Unadjusted			0.655	0.435-0.986	.041
Adjusted for covariates			0.524	0.315-0.873	.013
Rehospitalization	125 (31.6%)	158 (35.0%)			
Unadjusted			0.902	0.713-1.141	.389
Adjusted for covariates			0.788	0.592-1.048	.101
All-cause death or rehospitalization	150 (37.9%)	189 (41.9%)			
Unadjusted			0.912	0.735-1.130	.398
Adjusted for covariates			0.820	0.632-1.064	.136

The Cox regression model was used in the analysis adjusted for the following covariates; age, BMI, serum creatinine at discharge, systolic blood pressure at discharge, LVEF, and medication use (calcium channel blocker, antiarrhythmic, warfarin). Patients with no spironolactone use were a reference group.

P = .016) compared to no spironolactone use after adjustment for covariates.

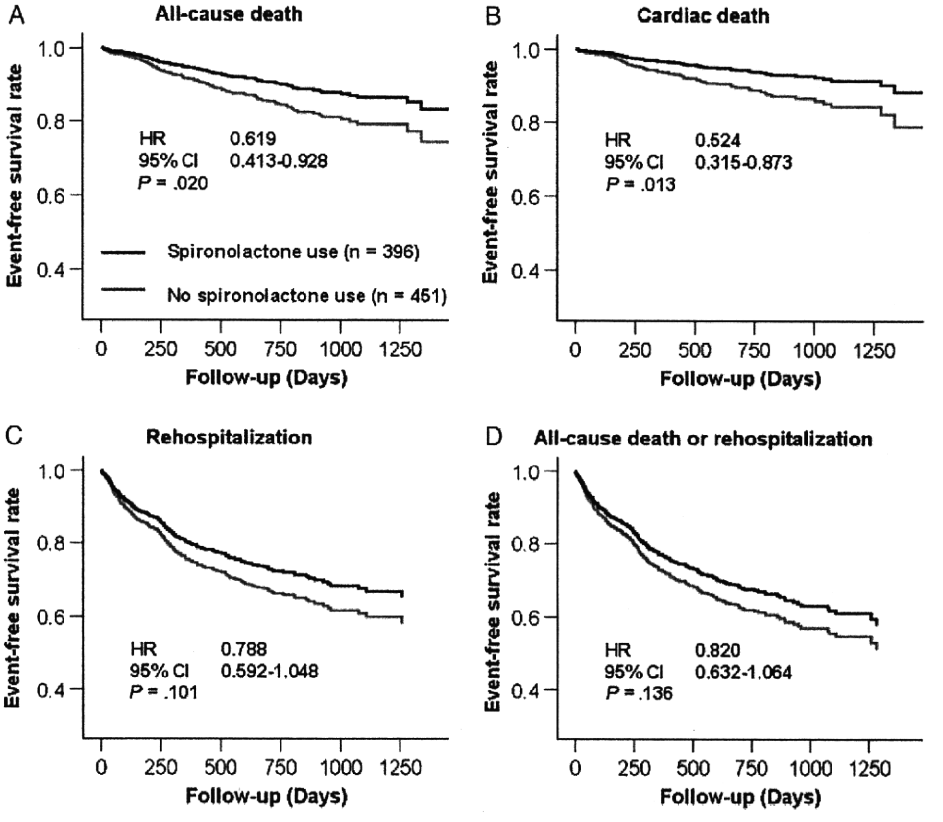
However, in the subgroup patients with serum creatinine ≥2.5 mg/dL (10 patients with spironolactone use and 39 patients with no use), spironolactone use was not significantly associated with the outcomes.

Discussion

The present study suggested that, among patients hospitalized with HF and reduced EF, spironolactone use at discharge was associated with a significant reduction in the risk of cardiac death during the long-term follow-up up to 2.2 years. These findings extended the results of RALES conducted in selected chronic severe HF patients to heterogeneous HF patients with significant survival benefit.

Results from the randomized clinical trial RALES demonstrated that spironolactone significantly improved outcomes in patients with severe HF.[11] RALES enrolled 1,663 patients who had severe HF (NYHA functional class III or IV) and LVEF of no more than 35%. The findings from RALES were further supported by another randomized clinical trial, the EPHESUS, which enrolled 6,632 patients after acute myocardial infarction with LVEF ≤40% and HF.[21] In the EPHESUS, eplerenone, a selective aldosterone antagonist with less adverse effects than spironolactone, reduced the relative risk of death during a mean follow-up of 16 months when added to conventional treatment including ACE inhibitor or ARB and β-blocker. Recent systemic review of 19 randomized clinical trials comprising 10,807 patients demonstrated a 20% reduction in all-cause mortality with the use of aldosterone blockade in clinically heterogeneous groups of patients with LV dysfunction.[22] These studies demonstrated that the addition of aldosterone antagonists in patients with systolic HF and ongoing symptoms despite optimal treatment with ACE inhibition and β-blockers could substantially reduce overall mortality.[23] On the other hand, they found a paucity of evidence on the effects of aldosterone antagonists in patients with diastolic HF or in patients with systolic HF but less severe symptoms.[22]

Figure 1



Kaplan-Meier survival curves free from all-cause death (**A**), cardiac death (**B**), rehospitalization due to worsening HF (**C**), and all-cause death or rehospitalization (**D**) in hospitalized patients with spironolactone use (black lines, n = 396) versus no spironolactone use (red lines, n = 451) at discharge.

More importantly, the patients enrolled in RALES and EPHESUS were recognized as unrepresentative of the general HF population in routine clinical practice. In fact, after the publication of RALES, there was a rapid increase in the rate of prescriptions for spironolactone and in hyperkalemia-associated mortality and morbidity in older patients with HF in Ontario, Canada.[24] This might be explained by the clear difference between the patients in the RALES and those in the "real world" because of the strict inclusion and exclusion criteria that are common to all clinical trials.[25] Furthermore, it may be also due to the recent and rapidly increasing use of β-blockers, which inhibit the release of renin, in patients with HF compared to those enrolled in RALES.[25] Therefore, uncertainty pertaining to the applicability of these findings to the population of patients with HF persists, and it is of critical importance to analyze the registry data of HF patients. The present results extended the previous findings to the "real world" by showing that spironolactone could improve the long-term outcomes in heterogeneous HF patients.

In the present study, >90% of patients had less severe symptom (NYHA functional class I or II) (Table I). The patients with spironolactone use had better renal function and more dilated LV than those with no spironolactone use. According to the European Society of Cardiology and American College of Cardiology/ American Heart Association guidelines, the addition of a low-dose aldosterone antagonist should be considered in all patients with a LVEF ≤35% and severe symptomatic HF (NYHA functional class III or IV) unless contra-indicated or not tolerated.[12,13] Therefore, in hospitalized patients with severe HF, treatment with an aldosterone antagonist has been recommended to be initiated before discharge.[13] However, published data have suggested that spironolactone was widely used with HF without consideration of their functional class or LVEF and optimization of background treatment with ACE inhibitor and β-blockers.[14] Many patients treated with spironolactone are distinctly dissimilar from those in RALES and the effects of therapy in these patients remain unknown. Therefore, the efficacy of aldosterone

antagonist in patients with reduced LVEF but less severe symptoms needs to be tested by an ongoing large-scale clinical trial, the EMPHASIS-HF trial (ClinicalTrials.gov Identifier NCT00133003), which will enroll 2,584 patients with NYHA functional class II symptoms. The present results suggested that spironolactone use could improve the long-term outcomes in patients with systolic HF and even less severe symptoms (NYHA functional class I or II). These findings should reassure clinicians that the use of spironolactone at discharge can provide an opportunity to improve outcomes for HF patients with severe as well as milder symptoms. Several explanations have been postulated for the beneficial effects of spironolactone in HF. First, spironolactone could induce reverse LV remodeling.[26-28] Spironolactone was demonstrated to improve LV function and decrease plasma BNP levels in patients with chronic HF.[26] In addition, it could also improve exercise tolerance in these patients.[27] Second, spironolactone could decrease cardiac fibrosis.[29] The data from RALES demonstrated that serum procollagen type III amino-terminal peptide (PIIINP) levels, markers of cardiac fibrosis, were significantly higher in HF patients and decreased by the treatment of these patients with spironolactone. Third, spironolactone could improve endothelial function in asymptomatic or mild HF patients when added to optimal treatment including β-blocker.[30]

Study limitations

Several limitations inherent in the design of the registry should be considered. First, the documentation of spironolactone use at hospital discharge might not accurately reflect continuation over time or start after discharge. Moreover, we did not collect the information regarding the dose of spironolactone and whether spironolactone was initiated during or before hospitalization. Second, the information regarding the serum potassium concentration was not obtained in our database. Therefore, we could not assess the impact of hyperkalemia in the outcomes in this study. Third, the present study was not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors may have influenced outcomes. Specifically, severer renal dysfunction, inadequate antiarrhythmic therapy including the use of ICD and antiarrhythmics, and disproportionate use of medications such as calcium channel blockers might affect the outcomes in patients with no spironolactone use, although these confounders were corrected in this study. Fourth, we could not evaluate whether the advantage of spironolactone would persist in the subgroup of renal dysfunction (serum creatinine ≥2.5 mg/dL) because the number of patients was so small for this type of analysis. It thus remained to be assessed exclusively in HF patients associated with renal dysfunction. Finally, data were dependent on the accuracy of documentation and abstraction by individual medical centers that participated in this study. Especially, the end points were adjudicated by the participating cardiologists. Moreover, the present study excluded 10.5% of the overall cohort of patients from the follow-up analysis because end points could not be determined. The patients lost to follow-up might influence the overall outcomes. However, the patient characteristics and medication use at discharge were similar between patients with follow-up and those lost to follow-up except for only 2 variables including history of diabetes (32.8% vs 35.4%, $P = .012$) and diastolic blood pressure (65.9 ± 11.4 vs 68.8 ± 12.8 mmHg, $P = .031$).

Conclusions

Among patients hospitalized for HF and reduced LVEF, treatment with spironolactone at discharge was associated with significantly reduced risk of cardiac death. Widespread use of spironolactone could substantially improve the outcomes in the larger numbers of HF patients in routine clinical practice.

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