Clinical benefit of spironolactone in patients with acute decompensated heart failure and severe renal dysfunction: Data from the Korean Heart Failure Registry

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Backgrounds We investigated the relationship between spironolactone use and all-cause mortality in acute decompensated heart failure (ADHF) patients with severe renal dysfunction. The clinical benefit of spironolactone in the treatment of heart failure (HF) has been described in several large randomized clinical trials. However, its clinical benefits have not been studied in hospitalized ADHF patients with severe renal dysfunction (estimated glomerular filtration rate [eGFR] <45 mL/min per 1.73 m^2).

Methods and results We retrospectively analyzed data from the Korean Heart Failure Registry. We included 1,035 ADHF patients with severe renal dysfunction. In Kaplan-Meier survival analysis, all-cause mortality in the spironolactone-treated group was significantly lower than that in the nonspironolactone group (18.1% vs 24.9%, respectively, log rank P = .028). However, spironolactone use was not an independent predictor after adjusting other HF risk factors (hazard ratio 0.974, 95% CI 0.681-1.392, P = .884) and after propensity score matching (P = .115). In subgroup analysis, the clinical benefit of spironolactone use was preserved in women, prehospital spironolactone use, the chronic kidney disease stage 3b (eGFR 30-44 mL/min per 1.73 m^2), and the appropriate spironolactone use (eGFR ≥30 mL/min per 1.73 m^2 and K ≤5.0 mmol/L).

Conclusion The spironolactone therapy was not beneficial in ADHF patients with severe renal dysfunction after multivariable adjusting and propensity score matching. However, we reassured the current HF guidelines for spironolactone use and the clinical benefit in chronic kidney disease stage 3b should be assessed in future clinical trial. (Am Heart J 2015;169:713-720.e3.)

Mineralocorticoid receptor antagonism (MRA) with aldosterone-inhibiting drugs such as spironolactone and eplerenone has been shown to reduce mortality and rehospitalization rates in patients with heart failure (HF) with reduced ejection fraction (HFREF) in several randomized clinical trials (RCTs).[1-3] However, there is a disparity in baseline characteristics and prognosis between RCT findings and real-world clinical observations. This incongruity may be due to the fact that the highly selected RCT patients differed from real-world patients.[4] These inconsistencies are especially prominent for MRA therapy in HF patients.[5-7]

In a substudy of severe HF patients from the RALES, the clinical benefit of spironolactone was greater in patients with reduced glomerular filtration rate (GFR) (<60 mL/min per 1.73 m^2) than in those with preserved GFR (>60 mL/min per 1.73 m^2).[8] In addition, current HF guidelines suggest that MRA is contraindicated when creatinine is >2.5 mg/dL or creatinine clearance is <30 mL/min.[9-11] In recent study regarding HF outpatients with severe renal dysfunction

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Table I. Baseline characteristics of ADHF patients with severe renal dysfunction (eGFR <45 mL/min/1.73 m^2) according to all-cause death

		All-cause death		
	Total (N = 1,035)	No (n = 796)	Yes (n = 239)	*P*
Clinical				
Male gender, n (%)	735 (71.0)	578 (72.6)	157 (65.7)	.042
Age, y	70 ± 13	68 ± 13	73 ± 11	<.001
NYHA III/IV, n (%)	819 (79.1)	632 (79.4)	187 (78.2)	.717
Ischemic origin of HF, n (%)	444 (42.9)	332 (41.7)	112 (46.9)	.180
HF adm history, n (%)	316 (30.5)	223 (28.0)	93 (38.9)	.002
Diabetes, n (%)	428 (41.4)	318 (39.9)	110 (46.0)	>.99
HTN (n, %)	579 (55.9)	445 (55.9)	134 (56.1)	>.99
Atrial fibrillation, n (%)	199 (19.2)	155 (19.5)	44 (18.4)	.779
Chronic renal dysfunction, n (%)	228 (22.0)	166 (20.9)	62 (25.9)	.109
Prehospital spironolactone use, n (%)	313 (30.2)	250 (31.4)	63 (26.4)	.149
SBP, mm Hg	133 ± 31	134 ± 32	128 ± 29	.003
Laboratory				
Hb, g/dL	11.4 ± 2.6	12.1 ± 2.6	11.2 ± 2.5	<.001
BUN, mg/dL	34.8 ± 18.8	32.9 ± 18.0	40.9 ± 20.1	<.001
Creatinine, mg/dL	2.33 ± 1.76	2.30 ± 1.83	2.44 ± 1.46	.292
BCR	16.7 ± 7.2	16.2 ± 7.0	18.2 ± 7.5	<.001
Sodium, mmol/L	137.6 ± 5.3	137.9 ± 5.0	136.5 ± 6.1	.002
Potassium, mmol/L	4.54 ± 0.89	4.50 ± 0.87	4.68 ± 0.94	.008
eGFR by MDRD, mL/min/1.73 m^2	30.0 ± 11.2	30.7 ± 11.1	27.7 ± 11.3	<.001
Echocardiographic				
LVEF, %	37.2 ± 15.1	37.3 ± 15.0	36.9 ± 15.6	.707
Discharge medications				
ACEIs/ARBs, n (%)	638 (61.6)	518 (65.1)	120 (50.2)	<.001
β-Blockers, n (%)	436 (42.1)	358 (45.0)	78 (32.6)	.001
Furosemide, n (%)	795 (76.8)	596 (74.9)	199 (83.3)	.007
Spironolactone, n (%)	347 (33.5)	282 (35.4)	65 (27.2)	.019

Values are expressed as mean ± SD or n (%). Abbreviations: *NYHA*, New York Heart Association functional class; *adm*, admission; *Hb*, hemoglobin. *P* values compare mean all-cause death "no" versus "yes" groups by *t* test or χ^2 test.

(estimated GFR [eGFR] <45 mL/min per 1.73 m^2), baseline anemia, a well-known prognostic marker, is not an independent predictor for all-cause mortality.[12] This implies that different pathophysiologic mechanisms affect the prognosis of HF patients with or without severe renal dysfunction. Therefore, we examined the clinical effectiveness of MRA with spironolactone (only available in Korea) in real-world acute decompensated HF (ADHF) patients with severe renal dysfunction from a large cohort of the Korean Heart Failure (KorHF) Registry.

Methods

Study sample and design

The KorHF Registry is a nationwide, prospective, observational, multicenter, online registry that includes the etiologies, clinical characteristics, treatment modalities, morbidity, mortality, and prognostic markers of patients hospitalized for ADHF. We studied 3,200 ADHF patients who were admitted to 24 Korean tertiary hospitals within 24 hours of symptom onset between June 2004 and April 2009.[13-16] The ADHF diagnoses were based on specific symptoms in patient medical histories and signs upon physical examination, according to current guidelines. Detailed data regarding patient characteristics, in-hospital course, and discharge medications were collected from electronic case reports recorded using a Web-based electronic data capture system. The ethics committee at each participating hospital approved the study protocol, which conformed to the tenets of the Declaration of Helsinki. From the initial 3,200 patients, 357 patients without available echocardiographic data and 54 patients without other baseline laboratory data were excluded, as were 1,754 patients without severe renal dysfunction (eGFR > 45 mL/min per 1.73 m^2). Thus, the final analysis included 1,035 patients (Online Appendix Supplementary Figure 1). The clinical end point, all-cause mortality after discharge from the hospital, was collected by reviewing the medical records and by telephone interviews at the end of the study.

Statistical analysis

We calculated eGFR using the Modification of Diet in Renal Disease (MDRD) equation.[17,18] Continuous variables were described using means and standard deviation (SD), and categorical variables were described using numbers or percentages. We compared intergroup differences using the Student *t* test, χ^2 test, and paired *t* test. To adjust for selection bias, we had propensity score matching. A propensity score for the predicted probability of

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