Sodium Restriction Counseling Reduces Cardiac Events in Patients With Heart Failure

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Background: Many heart failure (HF) guidelines recommend sodium restriction for patients with HF, but the outcome of sodium restriction counseling (SRC) for HF patients is still unknown. We wanted to clarify whether SRC reduces cardiac events in patients with HF.

Methods and Results: Overall, 800 patients (77 ± 12 years) who were hospitalized for HF were enrolled. During HF hospitalization, patients received SRC; patients were required to have a salt intake of <6 g/day. After discharge, death or HF rehospitalization events were investigated. During a mean follow-up of 319 ± 252 days, 83 patients died, and 153 patients were rehospitalized for HF. SRC significantly decreased all-cause death (odds ratio, 0.42; 95% confidence interval [CI], 0.23–0.76; $P < 0.01$), especially cardiac death of hospitalized HF patients after discharge. In the multivariate analysis adjusted for age, sex, SRC, body mass index, hypertension, dyslipidemia, β -blockers, and mineralocorticoid receptor antagonist intake, cardiac rehabilitation, and the type of HF, SRC remained a significant predictor of death. Kaplan-Meier analysis showed that SRC significantly reduced deaths and the combined outcome of HF rehospitalization and death. In patients with reduced left ventricular ejection fraction, SRC significantly decreased the mortality rate (odds ratio, 0.27; 95% CI, 0.10–0.71; $P < 0.01$).

Conclusions: SRC reduced the mortality rate after discharge of hospitalized HF patients.

Key Words: Heart failure; Low-sodium diet; Mortality; Nutrition therapy; Sodium restriction counseling

The incidence of heart failure (HF) is increasing worldwide,^{1,2} and the 1-year mortality and HF rehospitalization rates are significantly high.^{3–6} Therefore, new therapies are needed to reduce both the number of HF patients and their deaths after discharge.

Sodium restriction is a major and classical nutrition therapy for patients with HF; most of the major HF guidelines recommend sodium restriction.^{7–9} However, compared with β -blockers, angiotensin coenzyme inhibitors (ACEI) (angiotensin II receptor blockers [ARB]), and mineralocorticoid receptor antagonist (MRA) medications for HF, the evidence for sodium restriction therapy efficacy is still limited.⁷

In Japan, nutrition therapy is clinically performed by registered dietitians as sodium restriction counseling (SRC) for patients with HF. However, reports on SRC outcomes are rare. We hypothesized that SRC reduces HF rehospitalization or death after hospitalization of patients with HF.

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Methods

Patients and Study Design

The study recruited 800 consecutive patients with HF who were hospitalized between 2018 and 2019 at the Gunma Prefectural Cardiovascular Center. After excluding patients who died during hospitalization, 743 patients who were discharged were enrolled.

SRC was conducted by professional nutritionists (registered dietitians) to help HF patients reduce salt intake to <6 g/day after discharge. The counseling session was held once during HF hospitalization, and session lasted at least 30 min. Patients were followed up after discharge to record any deaths or HF rehospitalization events, which were analyzed as outcomes, together with the combined outcome of with or without SRC.

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Transthoracic Echocardiography

Transthoracic echocardiographic data were obtained by an experienced sonographer according to the guidelines reported by Nakatani et al.^{10,11} GE vivid E9 equipped with a 1.75–3.5 MHz transducer was used for the evaluation. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's rule. According to the LVEF, the type of HF was classified as: HF with reduced EF (HFrEF: LVEF<40%), HF with preserved EF (HFpEF: LVEF≥50%), and HF with mid-range EF (HFmrEF: 40%≤LVEF<50%).

Cardiopulmonary Exercise Test (CPET) Protocol and Data Collection

The CPET parameters were evaluated during symptom-limited exercise using a mask, an upright cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan), and ECG equipment (ML-9000; Fukuda Denshi Ltd., Tokyo, Japan). CPET was performed 2–4 h after the patient had consumed a light meal, beginning with 3 min of rest and 3 min of warm-up exercise at 0 W, followed by a continuous increase in work rate (WR) by 1 W every 6 s until exhaustion, as recommended by Buchfuhrer et al.¹² Exhaustion was defined as a gas exchange ratio (carbon dioxide production/oxygen consumption [$\dot{V}CO_2/\dot{V}O_2$]) of >1.10 or a score of 20 points for leg exhaustion on the Borg scale.¹³ Relevant parameters ($\dot{V}O_2$, $\dot{V}CO_2$, and minute ventilation [$\dot{V}E$]) were measured on a breath-by-breath basis using a gas analyzer (MINATO 300S; Minato Science Co. Ltd, Osaka, Japan).

Anaerobic threshold was measured using the V-slope method.¹⁴ Peak $\dot{V}O_2$ was defined as the $\dot{V}O_2$ at peak WR during exercise. The $\dot{V}E$ vs. $\dot{V}CO_2$ slope was defined as the slope of the linear regression line describing the behavior of $\dot{V}E$ during incremental exercise up to the respiratory compensation point on the plot of $\dot{V}E$ as a function of $\dot{V}CO_2$.¹⁵ All CPET parameters were evaluated by consensus among 3 cardiologists.

Estimation of Sodium Intake

Spot urine tests were performed on admission day and after the first outpatient clinic visit (1–2 months after discharge). Data were obtained for 13% of all participants. Estimated salt intake (g/day) was calculated using Tanaka's formula:¹⁶ estimated salt intake (g/day) = $21.98/17 \times [\text{sodium (mEq/L)}/\text{creatinine (mg/dL)}]$ in the spot urine/ $10 \times 24\text{-h}$ estimated creatinine excretion (mg/day)^{0.392} and, 24-h estimated creatinine excretion (mg/day) = body weight (kg) $\times 14.89 + \text{height (cm)} \times 16.14 - \text{age} \times 2.043 - 2,244.45$.

Transtheoretical Model (TTM)

The patients' behavioral stage data were collected using a questionnaire and evaluated by the TTM model.¹⁷ The TTM is divided into 5 stages: "pre-contemplation" (no intention of salt restriction); "contemplation" (intention for salt restriction but not prepared for salt restriction); "preparation" (prepared for salt restriction after discharge); "action" (showing salt restriction behavior within 6 months); and "maintenance" (continuing salt restriction behavior for >6 months). The patients were divided into 2 groups: "non-active stage," which included the pre-contemplation, contemplation and preparation stages, and the "active stage," which included the action and maintenance stages.

Follow-up After Discharge

Hospital records of regular check-ups after discharge of the HF patients were investigated. Mortality was defined as death due to any cause; cardiovascular (CV) death owing to HF, myocardial infarction (MI), cerebrovascular disease, and sudden death. HF hospitalization was defined as major symptoms (breathlessness, orthopnea, fatigue, and ankle swelling) and signs (elevated jugular venous pressure, hepatojugular reflux, 3rd heart sound, and laterally displaced apical impulse) of HF in patients hospitalized to receive intravenous therapy (diuretics, catecholamines, or carperitide).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA). All data are expressed as mean $\pm$ standard deviation, median (25–75th percentiles), or frequency (percentage). Quantitative data were analyzed using Student's t-test, the paired t-test, chi-square test, or Mann-Whitney U test as appropriate. Univariate and multivariable logistic analyses and Kaplan-Meier analysis were used for identifying predictors of death, HF rehospitalization, and the combined outcomes. Statistical significance was defined as $P < 0.05$.

Ethical Considerations

The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Gunma Prefectural Cardiovascular Centre (no. 2020015).

Results

Baseline Clinical Characteristics, Mortality, and HF Events

The patients' characteristics are summarized in **Table 1**. The mean age was 77 ± 12 years, and 58% of the patients were male. The percentage of HFpEF, HFmrEF, and HFrEF was 44%, 14%, and 42%, respectively. The mean LVEF was $45.5 \pm 19.2\%$, and peak $\dot{V}O_2$ was 13.2 ± 3.5 mL/min/kg. SRC was given to 31% ($n=230$) of the participants. Patients undertaking SRC were younger; had a higher body mass index (BMI); had HFmrEF, hypertension, and dyslipidemia; and participated in cardiac rehabilitation after discharge.

Patients were followed up for 319 ± 252 days (median, 295 days; 25th percentile, 83 days; 75th percentile, 503 days), during which 83 patients died (66 CV deaths: 53 HF, 3 MI, 10 sudden deaths), and 153 were rehospitalized because of HF.

SRC With Mortality and HF Events

Patients who underwent SRC had significantly lower all-cause death (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.23–0.76; $P < 0.01$) and cardiac death (OR, 0.33; 95% CI, 0.16–0.68, $P < 0.01$) than patients who did not undertake SRC; however, rehospitalization owing to HF and combined events of death and HF rehospitalization were not significant (**Table 2**). Kaplan-Meier analysis showed that SRC significantly reduced deaths (log-rank X^2 , 11.159; $P < 0.01$) and the combined outcome of HF rehospitalization and death (log-rank X^2 , 4.792; $P = 0.03$) (**Figure 1**).

Relationship of SRC With Mortality and HF Events

The results of the univariate and multivariate analyses for the variables of death are summarized in **Table 3**. After adjustment for age, sex, SRC, BMI, hypertension, dyslip-

Table 1. Patients' Baseline Characteristics

	Overall (n=743)	SRC (+) (n=229)	SRC (-) (n=514)	P value
Age, years	77±12	74±11	79±12	<0.01
Male sex, n (%)	430 (58)	138 (60)	292 (57)	0.42
BMI (kg/m²)	22±5	21.7±5.7	19.8±7.0	<0.01
Smoking history, n (%)	369 (50)	116 (50)	253 (49)	0.79
Heart disease				
DCM, n (%)	108 (15)	36 (16)	72 (14)	0.23
HCM, n (%)	33 (4)	8 (4)	25 (5)	
HHD, n (%)	51 (7)	16 (7)	35 (7)	
Ischemic heart disease, n (%)	180 (24)	53 (23)	127 (25)	
Diastolic dysfunction, n (%)	41 (6)	7 (3)	33 (6)	
Congenital heart disease, n (%)	31 (4)	15 (7)	16 (3)	
Atrial fibrillation, n (%)	76 (10)	21 (9)	56 (57)	
Valve disease, n (%)	178 (24)	57 (25)	121 (24)	
Other, n (%)	45 (6)	20 (8)	25 (5)	
Type of HF				
HFpEF, n (%)	327 (44)	84 (37)	243 (48)	<0.01
HFmrEF, n (%)	102 (14)	45 (20)	57 (11)	
HFrEF, n (%)	308 (42)	100 (45)	208 (41)	
Physical condition				
LVEF, %	45.5±19.2	43.3±18.7	47.2±19.4	0.28
BNP, pg/mL	199 [110–422]	199 [110–418]	196 [110–436]	0.89
Hemoglobin, g/dL	12.4±2.3	12.3±2.3	12.2±2.4	0.33
BUN, mg/dL	29.0±18.4	29.6±19.3	31.0±22.3	0.36
Creatinine, mg/dL	1.3±0.8	1.3±0.7	1.4±1.0	0.16
Anaerobic threshold, mL/min/kg	9.6±2.2	9.9±2.3	9.4±2.1	0.15
Peak oxygen uptake, mL/min/kg	13.2±3.5	13.6±3.8	12.8±3.3	0.20
VE vs. VCO ₂ slope	39.8±9.2	38.1±8.3	40.4±9.8	0.07
Medical history				
Hypertension, n (%)	389 (52)	140 (61)	249 (48)	<0.01
Diabetes mellitus, n (%)	215 (29)	69 (28)	146 (28)	0.63
Dyslipidemia, n (%)	242 (33)	90 (39)	152 (30)	<0.01
COPD, n (%)	59 (8)	20 (9)	39 (8)	0.61
Medications				
ACEI, n (%)	142 (19)	48 (21)	94 (18)	0.39
ARB, n (%)	277 (37)	85 (37)	192 (37)	0.92
β-blocker, n (%)	529 (71)	183 (80)	347 (68)	<0.01
MRA, n (%)	333 (45)	117 (51)	216 (42)	0.02
SGLT2-I, n (%)	77 (10)	31 (14)	46 (9)	0.06
Loop diuretics, n (%)	615 (83)	190 (83)	425 (83)	0.92
Thiazide, n (%)	47 (6)	12 (5)	35 (7)	0.41
Tolvaptan, n (%)	186 (25)	64 (28)	122 (24)	0.22
Digitalis, n (%)	35 (5)	10 (4)	25 (5)	0.76
Participation in outpatient CR, n (%)	86 (12)	54 (24)	32 (6)	<0.01

*Group SRC(+) vs. SRC(-). All data are expressed as mean±standard deviation, median (25–75th percentiles), or frequency (percentage). The data were analyzed using Student's t-test, the chi-square test, and the Mann-Whitney U test, as appropriate. A P value <0.05 indicates statistical significance. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2-I, sodium-glucose cotransporter 2-inhibitor; SRC, sodium restriction counseling; VE, minute ventilation; VCO₂, carbon dioxide production. Type of heart failure (HF); HFpEF, HF with preserved LVEF (LVEF≥50%). HFmrEF, HF with mid-range LVEF (40%≤LVEF<50%).

Table 2. Cardiac Events and Sodium Restriction Counseling

Event	SRC group (n=229)	Non-SRC group (n=514)	OR (95% CI)	P value
All-cause death	14	69	0.42 (0.23–0.76)	<0.01
(Cardiac death	9	57	0.33 (0.16–0.68)	<0.01)
HF rehospitalization	43	110	0.85 (0.57–1.26)	0.43
HF rehospitalization and all-cause death	49	135	0.76 (0.53–1.11)	0.17

Chi-square test, $P < 0.05$ indicates statistical significance. CI, confidence interval; HF, heart failure; OR, odds ratio; SRC, sodium restriction counseling.

Figure 1. Kaplan-Meier curves for event-free survival from death and heart failure rehospitalization (rehosp) after discharge as a function of sodium restriction counseling (SRC). SRC significantly correlated with low rates of death and the combined outcome of death and HF rehosp.

Table 3. Univariate and Multivariate Analyses for Mortality

Variable	Univariate analysis		Multivariate analysis			
	OR (95% CI)	P value	Model 1		Model 2	
			OR (95% CI)	P value	OR (95% CI)	P value
Age	1.029 (1.007–1.052)	<0.01	1.025 (1.002–1.048)	0.03	1.038 (1.011–1.065)	<0.01
Sex	0.880 (0.552–1.404)	0.59	1.066 (0.651–1.746)	0.79	0.972 (0.579–1.610)	0.59
SRC	0.501 (0.295–0.850)	0.01	0.438 (0.235–0.817)	0.03	0.501 (0.295–0.850)	0.01
BMI	0.991 (0.956–1.026)	0.59			1.025 (0.983–1.069)	0.25
Hypertension	0.450 (0.278–0.731)	<0.01			0.453 (0.272–0.754)	<0.01
Dyslipidemia	0.525 (0.300–0.919)	0.02			0.637 (0.357–1.137)	0.31
β -blockers	0.771 (0.471–1.263)	0.31			0.842 (0.496–1.429)	0.84
MRA	0.847 (0.529–1.356)	0.48			0.845 (0.515–1.384)	0.51
CR	0.373 (0.133–1.046)	0.06			0.691 (0.233–2.047)	0.51
Type of HF	0.849 (0.660–1.091)	0.21			0.699 (0.526–0.929)	0.01

$P < 0.05$ was statistically significant. Other abbreviations as in Tables 1,2. Type of HF: HFrEF (LVEF<40%) as number 1, HFmrEF (40%≤LVEF<50%) as number 2, HFpEF (LVEF≥50%) as number 3.

idemia, β -blockers, MRA intake, cardiac rehabilitation, and type of HF, SRC remained a significant predictor (Table 3).

Type of HF and SRC

Only in patients with HFrEF did SRC significantly decrease mortality (OR, 0.27; 95% CI, 0.10–0.71; $P < 0.01$). Kaplan-Meier analysis showed that in patients with HFrEF, SRC significantly reduced mortality during fol-

low-up (log-rank X^2 , 7.671; $P < 0.01$) (Figure 2).

Factors Affecting SRC

Although the percent decrease in estimated sodium intake was not significantly different with or without SRC [SRC(+): 86.3 ± 35.9 vs. SRC(-): 77.4 ± 28.9 %, $P = 0.55$], the estimated sodium intake was significantly decreased after discharge (on admission; 12.1 ± 3.8 vs. follow-up; 9.8 ± 4.3 g/day,

$P < 0.01$) independent of SRC.

On the other hand, Kaplan-Meier analysis showed that patients in the non-active stages of the TTM had significantly decreased mortality rate compared with active-stage patients (log-rank X^2 , 6.048; $P = 0.01$), and SRC(-) (log-rank X^2 , 12.505; $P < 0.01$) (Figure 3).

Discussion

In this study, SRC significantly reduced the mortality rate of patients with HF after discharge, especially in patients with HFrEF. To the best of our knowledge, this is the first report to show that nutritional therapy is significantly effective in patients with HF, especially when delivered by registered dietitians.

The number of HF patients is significantly increasing worldwide and in Japan.^{1,2} The mortality rate of HF is high, and about 25% of patients with HF die within 1 year after discharge. The hospital death rate was 4.7%, and the 1-year mortality rate after HF hospitalization was 23.3% according to 3 large Japanese HF registries.⁵ The rehospitalization rate within 1 year was also high (24.4–27.1%) in the WET-HF,³ ATTEND,⁴ and REALITY-AHF studies.⁶ Moreover, compared with the CHART-1 (2004), CHART-2 study (2010) suggests the percentage of HFpEF was higher than before.¹⁸ In this study, the consecutive HF-hospitalized patients had a mean age of 77 years, and 58% of the patients were male. The hospital death rate was 4.7%, and the 1-year mortality and rehospitalization rates after discharge were 11% and 26%, respectively. The percentage of HFpEF was 44%. These characteristics were consistent with the patient characteristics and outcomes reported by Shiraishi et al. (mean age, 77 years; 56% male patients).⁵

The Japanese Circulation Society (JCS),⁷ European Society of Cardiology (ESC),⁸ and American Heart Association (AHA) HF guidelines⁹ recommend sodium restriction for all the patients with HF. The AHA guideline suggests ≤3 g/day of sodium intake as the target; most Americans eat ≥4 g/day of sodium.⁹ The JCS and ESC guidelines recommend ≤6 g/day of salt intake.^{7,8} Japanese

generally eat higher amounts of salt.¹⁹ In a national report, the mean salt intake in Japan was 10.1 g/day.²⁰ Some countries report a salt intake >10 g/day, and the average salt intake worldwide is 6 g/day.²¹ There are several randomized studies of sodium restriction.^{22–30} Lower sodium intake decreases the rate of acute decompensation HF,^{22,27} and other studies favor sodium restriction because it is associated with a decrease in hypertension due to decreased activity of the renin-angiotensin-aldosterone system (RAAS).^{23–26} However, <2.5 mg/day of sodium intake is harmful in patients with HF,²⁸ and some studies suggest that it is unfavorable because sodium restriction decreases intravascular volume contraction and increase RAAS and neurological hormones.^{29,30} Although many HF guidelines highly recommend sodium restriction for patients with HF, the evidence is still debatable.²³ Because sodium intake is higher in Japan than in many other countries, the effectiveness of sodium restriction therapy may differ.

In this study, patients with HF were given SRC during hospitalization for at least 30 min to encourage a reduction in salt intake to <6 g/day after discharge. Some patients were instructed to cook their meals with their families. Although there are many positive clinical trials on salt restriction,^{22–27} in the real-world, SRC is not a salt restriction clinical trial. SRC consists of salt restriction and counseling. In this study, we observed that in both patients with and without SRC, salt intake after discharge was reduced. Because all patients hospitalized with HF had a diet with <6 g/day of salt and were educated in HF lifestyle modification by the nursing care team during the hospitalization, these effectiveness is assumed. On the other hand, although the patients who had already begun to reduce their salt intake did not improve their mortality rate, those who had no or low motivation for salt restriction did improved their mortality rate after undergoing SRC (**Figure 3**). This suggests that the effects of SRC on the HF patients' behavior were due to the newly realized necessity for salt restriction. Vollone et al have reported that nurses' motivational counsel improves patients' self-care management and its maintenance.³¹ Jonkman et al have also reported that self-care reduced deaths of patients with HF in their meta-analysis. Most counseling was performed by a nurse, physician, or cardiologist, and some studies included telephone call support after counseling.³² In this study registered dietitians performed only one-time counseling based on the TTM, which has been used to change the eating behaviors of patients with type 2 or to generally increase the vegetable and fruit intake of patients.^{17,33,34} When HF patients in the "pre-contemplation" or "contemplation" stage were counseled, the focus was on listening and not making many suggestions. When HF patients in the "preparation" stage were counseled, specific goals were presented. The HF patients in the "action" or "maintenance" stage were counseled to maintain their behavior. Thus, the TTM varies the approach to salt reduction depending on the patient's behavioral stage. Tailoring the TTM-based counseling to the patient's motivational stage leads to continuation of motivational modification for salt reduction.

The study results suggested that adding SRC-tailored TTM by registered dietitians to usual care was the main reason for the motivational modification of salt reduction and improved HF mortality in this study (OR 0.42; 95% CI 0.23–0.76).

In previous reports, sodium restriction studies were only

conducted for HFrEF,^{22,35,36} and occasionally, HFmrEF.²⁶ Machado d'Almeida et al attempted aggressive sodium reduction therapy in patients with HFpEF;³⁷ although HFpEF correlates with hypertension, their results were not significantly different between patients who were managed with sodium restriction and those without. In our study, a significant reduction in deaths after discharge was observed for patients with HFrEF, which is similar to the findings reported in previous studies.

In the multiple logistic analysis (**Table 3**), in addition to SRC, age, hypertension, and HFrEF were the predictors of death. Aging is one of the major predictors of death in patients with heart disease. According model 1 in **Table 3**, the death of patients with HF increases by 3.8% each year. However, SRC decreased the mortality rate by 49.9%, which suggests that SRC is worth 13 (49.9/3.8) years. In model 2, age, hypertension, and HFrEF were significant predictors in addition to SRC. Patients with hypertension had higher systolic blood pressure (114±18 vs. 106±20 mmHg, $P<0.01$) and ACEI/ARB intake (70.2% vs. 39.7%, $P<0.01$) in this study. HF patients with hypotension have a significantly higher risk for mortality,³⁸ and treatment for hypertension is similar to that for HF, including β -blockers or ACEI/ARBs. In this study, higher systolic blood pressure and use of ACEI/ARBs might have affected the hypertension history. In previous studies, patients with HFrEF (LVEF 27±7%, 66±13 years) or HFpEF (LVEF 62±9%, 73±12 years) had similar mortality rates.³⁹ However, in our study, patients with HFrEF (LVEF 26 [19–33]%, 72±13 years) had a higher OR than those with HFpEF (LVEF 60 [55–65]%, 81±10 years). Compared with previous studies, our patients with HFrEF were older. Moreover, they had longer hospitalization periods than the patients with HFpEF (15 [9–23] vs. 13 [8–22] days, $P<0.04$). Patients with HFrEF seemed to have a more severe condition than did patients with HFpEF during hospitalization. These different patient characteristics and conditions might have affected the mortality difference between the patients with HFrEF and HFpEF.

Sodium-glucose cotransporter-2 inhibitors (SGLT2I) have been used to treat HF based on both randomized studies and real-world data.^{40,41} Although there are some randomized studies of sodium restriction therapy,^{22–27} real-world reports are rare. This study showed favorable data for sodium restriction therapy in patients with HF, which supports the reduction in mortality rates after hospitalization in real-world data analyses.

In conclusion, SRC significantly reduced the mortality rate in patients hospitalized with HF, and SRC was the most effective therapy for patients with HFrEF. SRC is an easy, cheaper, and highly efficacious choice for reducing HF mortality. Spreading awareness regarding the effectiveness of SRC might reduce the rate of rehospitalization in patients with HF.

Study Limitation

This was a single-center study with a relatively small number of patients. Future multicenter studies are needed to confirm our findings. However, SRC is much cheaper than any other therapy (2,600 yen [24 dollars/20 euros]) and the reduction in the mortality rate was notable.

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Disclosures

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IRB Information

The study was conducted according to the Japanese ethical rules and was approved by the Ethics Committee of the Gunma Prefectural Cardiovascular Centre (no. 2020015).

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