

# Short-Term Effects of Hypertonic Saline Solution in Acute Heart Failure and Long-Term Effects of a Moderate Sodium Restriction in Patients With Compensated Heart Failure With New York Heart Association Class III (Class C) (SMAC-HF Study)

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**Abstract:** *Introduction:* Hypertonic saline solution (HSS) and a moderate Na restriction plus high furosemide dose showed beneficial effects in compensated heart failure (HF), in short and long terms. The study was aimed to verify the effects of this combination on hospitalization time, readmissions and mortality in patients in New York Heart Association (NYHA) class III. *Method:* Chronic ischemic or nonischemic cardiomyopathy uncompensated patients with HF in NYHA III functional class with ejection fraction <40%, serum creatinine <2.5 mg/dL, blood urea nitrogen <60 mg/dL and reduced urinary volume were single-blind randomized in 2 groups: the first group received a 30-minute intravenous infusion of furosemide (250 mg) plus HSS (150 mL) twice daily and a moderate Na restriction (120 mmol); the second group received furosemide intravenous bolus (250 mg) twice a day, without HSS and a low Na diet (80 mmol); both groups received a fluid intake of 1000 mL/d. After discharge, the HSS group continued with 120 mmol Na/d; the second group continued with 80 mmol Na/d. *Results:* A total of 1771 patients (881 HSS group and 890 without HSS group) met inclusion criteria: the first group (881 patients), compared with the second (890 patients), showed an increase in diuresis and serum Na levels, a reduction in hospitalization time (3.5 + 1 versus 5.5 + 1 days,  $P < 0.0001$ ) and, during follow-up (57 + 15 months), a lower rate in readmissions (18.5% versus 34.2%,  $P < 0.0001$ ) and mortality (12.9% versus 23.8%,  $P < 0.0001$ ); the second group also showed a significant increase in blood urea nitrogen and serum creatinine. *Conclusion:* This study suggests that in-hospital HSS administration, combined with moderate Na restriction, reduces hospitalization time and that a moderate sodium diet restriction determines long-term benefit in patients with NYHA class III HF.

**Key Indexing Terms:** Furosemide; Heart failure; Hypertonic saline solution; Sodium. [Am J Med Sci 2011;342(1):27–37.]

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Acutely decompensated heart failure (HF) is one of the most common cardiologic issues in emergency departments. In fact, patients with acute HF represent a varied group that share common features, such as high morbidity and mortality. As a result of growing elderly population, the overall prevalence of HF is increasing.<sup>1</sup> At the same time, advances in outpatient medical therapy allow patients with HF to survive despite advanced stages of hemodynamic impairment. Nearly 5 million Americans are affected by HF, and approximately 550,000 new cases occur every year.<sup>2</sup> Short-term outcomes for patients admitted to the hospital with HF have been fairly constant over the past 2 decades. In-hospital mortality remains approximately 7%, with major adverse events occurring in up to 18% of patients.<sup>3–5</sup> Previously, we showed that relatively small patient populations with advanced HF treated with hypertonic saline solution (HSS) and high intravenous furosemide dose combined with a moderate Na restriction (120 mmol/d) during hospitalization were significantly faster in reducing brain natriuretic peptide (BNP) levels and in dry weight reaching, in comparison with patients treated with high diuretic doses and low sodium diet only; moreover, they had shorter hospitalization stays and a lower readmission rate.<sup>6–12</sup> In addition, the patients receiving, after discharge, the combination of high diuretic doses/moderate Na restriction/water intake restriction (1000 mL/d) seem to require less hospitalizations and to survive better than patients receiving low Na diet (80 mmol/d). The same combination was also effective in reducing neurohormonal activation (BNP, plasma renin activity and aldosterone).<sup>13,14</sup> A further study showed that this combination also improved clinical outcome, did not determine detrimental effects in renal function,<sup>10–14</sup> and that low Na diet was associated approximately with a 10-fold risk of cytokine and neurohormonal plasma level increases.<sup>15</sup> These results stimulated our group to study the effects of the combination of HSS/high doses of furosemide/moderate Na restriction on hospitalization time compared with no HSS/high doses of furosemide/low Na diet combination in patients in III New York Heart Association (NYHA) class and/or stage C (moderate limitation symptoms noted with minimal activity—past or current HF symptoms in association with structural damage to the heart) and the effects of moderate furosemide oral doses/moderate Na restriction versus moderate furosemide oral doses/low Na diet on readmissions and mortality due to cardiac causes in the long term.

**MATERIALS AND METHODS**

The target population for this trial was patients with NYHA class III HF from ischemic or nonischemic origin. The patients signed informed consent and release of medical information forms before enrolment. The ethical committee approved the protocol only as single-blind study.

**Patient Population**

From September 2000 to August 2007, 4728 patients with worsening HF were consecutively admitted to Emergency Medicine and Cardiology Departments of Palermo University, Division of Cardiology, G.F. Ingrassia Hospital—Palermo, Division of Cardiology, Buccheri La Ferla Hospital—Palermo and to second Naples University, Italy.

**Eligibility Criteria**

To be enrolled, patients had to show decompensated HF by chronic ischemic or nonischemic cardiomyopathy, older than 18 years and, according to HF definition,<sup>1</sup> Framingham criteria and New York association functional classification for HF,<sup>2</sup> uncompensated HF (dyspnoea, weakness and lower limb edema), in NYHA III functional class, that was unresponsive to treatment with oral high doses of furosemide up to 250 mg/d, spironolactone, angiotensin-converting enzyme (ACE) inhibitors, digitalis and nitrates; moreover, they had to be under this therapy at least 4 weeks before the study and before hospitalization. The patients were judged unresponsive when they showed, during the aforementioned treatment, a reduction of urine volume, a constant increase of body weight (BW) and an impairment of clinical HF as reported above, despite the increase of furosemide. In addition, they had to have a left ventricular ejection fraction (EF) <40%, serum creatinine <2.5 mg/dL, blood urea nitrogen (BUN) <60 mg/dL and a reduced urinary volume (<800 mL/d) despite the established treatments. None of the patients had to take nonsteroid anti-inflammatory drugs.

**Exclusion Criteria**

Patients with NYHA class > III or < III on admission or with NYHA class III at discharge, with concomitant main comorbidities, as cerebral vascular disease, dementia, cancer, uncompensated diabetes, severe hepatic disease and inability to give informed consent were excluded, as were patients requiring pacemaker implantation and those with an alcoholic habit. Patients were also excluded if they declined to take part in the study protocol. Moreover, patients with side effects for ACE inhibitor treatment (cough), even if these patients were given angiotensin 2-receptor blockers to obtain treatments as homogeneous as possible treatment, were also excluded.

In addition, patients who did not follow the assigned treatment, did not attend the scheduled clinical visits, did not adhere to prescribed diet and the fluid intake of 1000 mL/day or had a reduction or discontinuation of prescribed treatments during follow up were excluded from the study.

Randomization (single blind as suggested by ethical committee; the patients were blinded about the administered treatments) was performed by using sequentially numbered boxes (the numbered boxes were prepared before starting the study by computerized sequence and not by alternating sequence), and the patients' assignment, via a central computerized system, was decided at admission time, before performing complete clinical examination and laboratory measurements. In this way, we randomly assigned the suitable patients either to intravenous high furosemide doses with HSS or to intravenous high furosemide doses without HSS. All patients included in the study underwent, after randomization, a complete physical

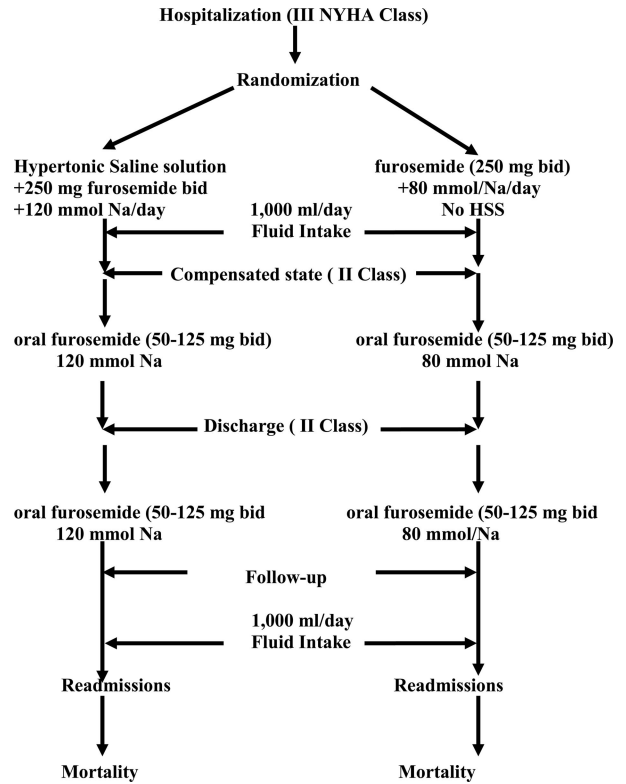


FIGURE 1. Flowchart of the study.

examination, with a careful check of HF signs and symptoms, including measurement of BW (in the morning before breakfast), supine and standing blood pressure [BP (mean of 3 measurements)] and heart rate. Fasting blood samples were drawn to determine serum levels of Na, K, Cl, bicarbonate, albumin, uric acid, creatinine, urea and glycemia on a daily basis during hospitalization, and this was continued until a clinically compensated state was obtained. The total daily output of urine was collected for the measurement of creatinine clearance, urinary Na and K levels. Chest radiograph, electrocardiogram and echocardiogram to obtain EF according to the modified Simpson rule, which uses 2 cross-section views (4- and 2-chamber apical views), were performed before the treatment beginning and again at hospital discharge time. Two observers blinded to the clinical data evaluated the 2-dimensional echocardiographic images. In addition, at entry, after discharge and during follow-up, BNP plasma levels were also controlled.

**Study Protocol**

The recruited patients were divided in 2 groups (single-blind fashion, the patients were blinded about the administered treatments): the first group received an intravenous 30-minute infusion of furosemide (250 mg) plus HSS (150 mL of 1.4%–4.6% NaCl) twice a day and a moderate sodium restriction (120 mmol); the second group received an intravenous infusion of furosemide (250 mg) as bolus twice a day, without HSS and a low sodium diet (80 mmol), and both groups received a fluid intake of 1000 mL/d (Figure 1). The dose of HSS was determined in each patient (first group) according to these schedules: for serum Na values <125 mEq/L, HSS concentration was 4.6%; for serum Na values between 126 and 135 mEq/L, HSS

concentration was 3.5%; and for serum Na values  $>135$  mEq/L, HSS concentration varied between 1.4% and 2.4%, intravenous KCl (20–40 mEq) was also administered to prevent hypokalemia. During the study period, the patients received ACE inhibitors, digitalis and nitrates, as previously reported. During hospitalization, when the patients reached a compensate state (dry status), the first group (HSS group) received the daily dietary sodium of 120 mmol with a fluid intake of 1000 mL/d and oral KCl supplementation, and the treatment was continued after discharge. The patients receiving conventional treatment (without HSS) received and continued a reduced daily dietary sodium intake (80 mmol) and the same fluid intake as HSS group and KCl supplementation. An accurate assessment of BW (in the morning before breakfast) and a measurement of 24-hour urinary volume were performed every day. Serum and urinary laboratory parameters were measured daily until a clinically compensated state was reached: this was considered as a change in NYHA functional class to at least II on clinical judgment and the accomplishment of ideal BW, as calculated by the Lorenz formula<sup>16</sup> and detected by bioimpedance vector analysis.<sup>12,14,15,17</sup> Once the clinically compensated state was reached, the intravenous administration of furosemide (both groups) and HSS (group 1) was stopped and was replaced with oral furosemide administration (50–125 mg twice daily) and oral KCl supplementation, and the best therapy, obtained during hospitalization, was also continued without changes after discharge.

### Follow-Up

During follow-up, the 2 groups continued the treatments according to randomization: the first group continued to receive a moderate sodium restriction (120 mmol/d) associated with a fluid restriction (1000 mL/d) and the furosemide dose as during hospitalization. The second group continued to receive a low sodium diet (80 mmol/d) associated with a restricted fluid intake (1000 mL/d) and the furosemide dose as during hospitalization (Figure 1) along with the best standard therapy (ACE inhibitors, beta blockers, digitalis and nitrates). Furosemide doses used were 50 to 125 mg twice daily because these doses allowed maintenance of BW and water balance, during hospitalization. Only patients discharged in NYHA class  $< III$  and with a dry profile continued the study (1549 patients were in NYHA class II and 378 patients were in NYHA class I). At discharge, all patients underwent a complete physical and laboratory examination, plasma BNP measurements, Doppler echocardiography and ultrasound abdominal examination. In addition, during the study and follow-up periods, other treatments were not added to those administered. After discharge, patients were observed as outpatients, with clinical and laboratory evaluations, every week for the first month, every month for the first 6 months, and thereafter, every 3 months. At every follow-up assessment (about 15 examinations per patient during the follow-up), a laboratory (with 24-hours natriuresis) and clinical and pharmacologic (beta blockers, spironolactone, etc.) evaluation was made, and an electrocardiogram and an echocardiogram were performed. In addition, after discharge, all patients received multiple written standard diets containing 80 mmol of Na prepared by our dieticians and received a diary in which they had to record the amount of daily fluid intake and diet variation. In case of diet variation, patients had to report the amount of the changed or added food. At every programmed control, blinded physicians received the diary, and a new diary was given to patients. The group receiving the normal Na diet (120 mmol) received the same diets but with addition of 40 mmol Na/d, whereas the 80 mmol/d group received a similar composition of placebo. In this way, all

patients received the same amount of saturated fats, fruit, vegetables, etc. Moreover, patients were also contacted during follow-up by physicians and dieticians for a telephone interview to determine the adherence to the restricted fluid intake and the prescribed diet. Other data were also obtained by regular contacts with family doctors, who were informed about the end points of the study. Every patient experiencing worsening HF according to their family physician was called for an in-hospital evaluation and rehospitalized, if indicated. Two physicians blinded to the study protocol performed the evaluations to verify the clinical status and if worsening HF was present. Follow-up was performed on patients enrolled from September 2000 to August 2007, with a minimum period of observation of 31 months (from March 2010). In this period, we analyzed the incidence of readmissions for worsening HF and mortality from all causes (sudden death, progressive left ventricular failure and noncardiac causes).

During the follow-up period, no other treatment was added to those already administered. Treatment corrections were performed only in readmitted patients from both groups.

### End Points

The 2 primary end points were death or first hospitalization for worsening HF. The major secondary end points included death from cardiac causes, hospitalization for cardiac causes, the combined incidence of death from cardiac causes or hospitalization for cardiac causes and a change in the NYHA class. All end points were adjudicated by a blinded critical-events committee.

### Statistical Analysis

The analysis of hospital readmission for worsening HF and mortality (the primary end point) included all patients, according to the intention-to-treat principle and according to relative risk reduction; we also calculated the number needed to treat to prevent 1 event. Kaplan–Meier method was used to construct cumulative survival curves for the 2 groups. The primary comparison between the 2 groups was based on a log-rank test. For analyses of mortality or readmissions (first readmission), data were censored at the time of loss to follow-up or at the time of first readmissions. Data were analyzed using a 2-tailed Student *t* test to identify differences between groups and analysis of variance for repeated measures with Bonferroni posthoc test correction for intra-group data. Nominal data were analyzed by the  $\chi^2$  test. The sample size was calculated on the basis of the estimated reduction in readmissions for worsening HF of 50% on the basis of our previous study.<sup>10–15</sup> The power of the study to detect a difference between treatment groups was set at 95% (with a 2 tailed level of 0.05). Therefore, the sample size obtained was 231 for each group, and this number was assumed as a minimum for this study.

Results are expressed as means + SD, and analysis was performed with the Statistical Package for Social Sciences (SPSS 17; SPSS, Chicago, IL). All tests were 2 sided, and *P*  $< 0.05$  was considered statistically significant.

## RESULTS

Of the 4728 patients consecutively admitted to hospital with worsening HF, 1578 were in NYHA class  $> III$ , 158 in NYHA class  $< III$ , 143 showed cerebral vascular disease or dementia, 61 cancer, 96 uncompensated diabetes, 85 inability to give informed consent and 63 severe hepatic disease, 186 required pacemaker implantation, 43 had previous cardiac resynchronization therapy implantation and 83 an alcoholic habit.

TABLE 1. Clinical characteristics and etiology of HF

	Total	Furosemide with HSS	Furosemide without HSS	P
Patient no.	1927	953	974	ns
Sex (F/M)	714/1213	352/601	362/612	ns
Age (yr)		74.7 ± 11	73.4 ± 13	<0.01
Diabetes	460 (23.9%)	225 (23.6%)	235 (24.1%)	ns
Captopril (75–150 mg/d)	1927 (100%)	953 (100%)	974 (100%)	ns
Carvedilol (6.25–25 mg twice daily)	1338 (69.4%)	659 (69.1%)	679 (69.7%)	ns
Digitalis (0.125–0.25 mg/d)	222 (11.5%)	107 (11.2%)	115 (11.8%)	ns
Furosemide (125 mg twice daily)	717 (37.2%)	363 (38%)	354 (36.3%)	ns
Furosemide (50 mg twice daily)	1210 (62.8%)	590 (61.9%)	620 (63.6%)	ns
Spironolactone (25 mg day)	1636 (84.9%)	811 (85%)	825 (84.7%)	ns
CHF etiology				
CAD	1203 (62.4%)	590 (61.9%)	613 (62.9%)	ns
HHD	637 (33%)	321 (33.6%)	316 (32.4%)	ns
DCM	87 (4.5%)	42 (4.4%)	45 (4.6%)	ns
AF	265 (13.7%)	128 (13.4%)	137 (14%)	ns

HF, heart failure; HSS, hypertonic saline solution; CAD, coronary artery disease; CHF, compensated heart failure; HHD, hypertensive heart disease; DCM, dilatative cardiomyopathy; AF, atrial fibrillation.

Only 37 patients maintained the NYHA class III at discharge, 139 declined to take part in the study protocol and 129 had side effects for ACE inhibitor (cough) and received angiotensin 2-receptor blockers.

Only 1927 patients (women/men: 714/1213), age range 57 to 84 years, with NYHA class III HF of different etiologies met the entry criteria and continued the study in accordance with the study protocol. Both groups were homogeneous and well matched either as general characteristics, clinical and laboratory parameters and HF etiology (Table 1). The patients showed at entry: 1927 dyspnea, 1007 orthopnea, 1927 fatigue on effort, 1831 third heart sound, 465 marked peripheral edema, 1562 moderate peripheral edema, 831 hepatic enlargement, 958 bronchial rales, 397 pleural effusion and 12 pericardial effusion. A prominent improvement in clinical parameters such as dyspnea, lower limb edema and weakness was obtained in all patients studied. In fact, patients (from first group) and patients (from second group) with lower limb edema, pleural and pericardial effusion experienced complete resolution of this state after the treatment (evaluated clinically, by x-ray and echocardiography) that resulted in the rapid relief of dyspnea, weakness and fatigue. A significant increase was observed in daily diuresis in both groups, but in the first group, the diuresis was greater than that in group 2 ( $P < 0.0001$ ). Natriuresis was greater in the first group and serum Na was increased in the first group, whereas in the second group, a reduction in serum Na after therapy was observed. Serum K was decreased significantly, but the value remained in the normal range (Table 2). BW was reduced, and the reduction was proportional to increased urinary volume. At discharge, the changes in NYHA functional class was greater in patients from HSS group, with most of them going from class III to class II (736 patients) or class I (217 patients), whereas in the second group, 813 patients achieved the class II and 161 patients the class I. The second group showed an increase in BUN and serum creatinine. Serum uric acid concentrations were significantly increased after therapy in both groups. No side effects (in particular hearing loss or tinnitus) were observed in patients receiving HSS, whereas these effects were reported in 71 (7%) patients treated with

furosemide only ( $P < 0.0001$ ), without HSS. Both systolic and diastolic values of BP were decreased without important clinical manifestations, and heart rate was corrected to normal values (Table 2). No patient died during hospitalization, and they were discharged from the hospital after 3 to 6 days from admission. The patients not receiving HSS infusion showed a longer hospitalization time than patients receiving HSS infusion (5.5 + 1 versus 3.5 + 1 days),  $P < 0.0001$ . Echocardiographic data showed a slight improvement in EF in patients receiving HSS. Both groups showed a significant reduction in BNP plasma levels (Table 3), but the first group showed lower values than the second group at discharge,  $P < 0.0001$ .<sup>12</sup>

### Follow-Up

One hundred fifty-six patients (8%), 72 (7.5%) from first group and 84 (8.6%) from second group, discontinued the prescribed treatments or were lost during follow-up, ranging from 31 to 83 months (mean, 57 + 15 months) and were excluded from final analysis (Table 4). Only 1771 patients completed the study and were analyzed: 881 from first group and 890 from second group. In the first group (120 mmol Na/d), 163 (18.5%) patients were readmitted to the hospital for clinical signs of HF, and they presented at entry higher functional class than at discharge (NYHA class III–IV). In the second group (80 mmol Na), 305 (34.2%) patients were readmitted to hospital for clinical signs of HF, and they presented at entry higher functional class than at discharge (NYHA class III–IV). In the first group, a total of 114 (12.9%) patients died during the follow-up period: 31 patients by sudden death, 69 patients by irreversible HF and 14 patients died after 4 to 8 months after discharge, but their deaths could not be related to cardiac causes. In the second group, 212 (23.8%) patients died: 149 by irreversible HF and 46 by sudden death, 14 by noncardiac causes and 3 by stroke. The difference between 2 groups was statistically significant,  $P < 0.0001$  (Table 4). Furthermore, the analysis of laboratory and clinical data at 12, 24, 48 months and at the end of study in the survived and not readmitted patients showed that patients from first group had better indices than those from second group (Table 5).

TABLE 2. Clinical and laboratory parameters before (at entry) and after treatment (at discharge)

	Furosemide with HSS			Furosemide without HSS		
	Entry	Discharge	<i>P</i>	Entry	discharge	<i>P</i>
Patient no.	953	953		974	974	
Sex (M/F)	352/601			362/612		
Age (yr)	74.7 ± 11			73.4 ± 13		<0.01
SBP mm Hg)	137 ± 15	112. ± 11	<0.0001	134 ± 16	115 ± 14	<0.0001
DBP (mm Hg)	75. ± 8	65. ± 5	<0.0001	77 ± 7	68 ± 6	<0.0001
HR (beats/min)	88 ± 18	68 ± 6	<0.0001	90 ± 21	70 ± 11	<0.0001
Ejection fraction	33.7 ± 4	37.3 ± 5	<0.0001	34.4 ± 5	36.4 ± 6	<0.0001
Body weight (kg)	82.7 ± 13	73.2 ± 6 <sup>a</sup>	<0.0001	84.5 ± 15	76.6 ± 7 <sup>a</sup>	<0.0001
Diuresis (mL/24 hr)	635 ± 145	2150 ± 565 <sup>a</sup>	<0.0001	690 ± 155	1675 ± 550 <sup>a</sup>	<0.0001
Serum Na (mEq/L)	137.8 ± 8	143.2 ± 4 <sup>a</sup>	<0.0001	138.8 ± 7	135.3 ± 3.9 <sup>a</sup>	<0.0001
Serum K (mEq/L)	4.7 ± 0.7	3.8 ± 0.4 <sup>a</sup>	<0.0001	4.8 ± 0.5	3.6 ± 0.3 <sup>a</sup>	<0.0001
Urinary Na (mEq/24 hr)	73.7 ± 11.4	119 ± 13 <sup>a</sup>	<0.0001	79.1 ± 10	76 ± 5 <sup>a</sup>	<0.0001
Urinary K (mEq/24 hr)	61 ± 21	85 ± 27	<0.0001	63 ± 23	87 ± 28 <sup>a</sup>	<0.0001
BUN (mg/dL)	58.2 ± 3.5	71 ± 13 <sup>a</sup>	<0.0001	56 ± 4	101 ± 12 <sup>a</sup>	<0.0001
Serum creatinine (mg/dL)	1.65 ± 0.05	1.45 ± 0.05 <sup>a</sup>	<0.0001	1.61 ± 0.05	1.91 ± 0.1 <sup>a</sup>	<0.0001
Creatinine clearance	52.5 ± 2.2	55.4 ± 3.3 <sup>a</sup>	<0.0001	52.1 ± 2.3	48.7 ± 2.1 <sup>a</sup>	<0.0001
Uric acid (mg/dL)	6.5 ± 3	8.7 ± 3.3	<0.0001	6.6 ± 3.5	8.8 ± 3.1	<0.0001

Data are expressed as mean ± SD.

<sup>a</sup> *P* < 0.0001.

HSS, hypertonic saline solution; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BUN, blood urea nitrogen.

All the patients maintained the prescribed treatments, the Na diet and the assigned daily fluid intake during the follow-up. Only 98 patients (47 from 120 mmol group and 51 from 80 mmol group) during the first months (during summer) increased fluid intake (1500 mL), and this violation of the protocol was corrected at subsequent control (7 days after). No corrections in treatments were required after randomization and at the assigned visits. The analysis (performed at every visit during follow-up and at end of the study) of diaries given to patients showed a good compliance with assigned diet and fluid intake, and these results were in agreement with concomitant controlled natriuresis. The range of 115 to 130 mmol Na/d and 80 to 90 mmol Na/d was observed in groups assigned to moderate Na restriction and low Na diet, respectively. The range of 1000 to 1200 mL/d fluid intake was observed in both groups. All patients continued the tailored treatments as assessed during hospitalization.

Figures 2 and 3 show curves obtained by Kaplan–Meier method for mortality and readmissions combined endpoint and

for mortality. The curves show that the 120 mmol Na/d group had a significant reduction both in mortality and combined endpoint (mortality plus readmissions) in comparison with low Na diet group; this reduction was already evident in the first months, and the difference was still more significant in subsequent months. At the end of study, we observed 87.1% of survival in 120 mmol Na/d group versus 76.2% in 80 mmol Na/d group. About 69% of patients received beta blockers and 84% spironolactone (25 mg) in both groups. In addition, the

TABLE 3. Clinical results at discharge in both groups

	Furosemide with HSS	Furosemide without HSS	<i>P</i>
Side effects (tinnitus)	0	71 (7.2%)	<0.0001
NYHA class II	736 (77.2%)	813 (83.4%)	<0.29
NYHA class I	217 (22.8%)	161 (16.5%)	<0.006
Hospitalization time (days)	3.5 ± 1	5.5 ± 1	<0.0001
Ejection fraction (%)	37.3 ± 5	36.4 ± 6	<0.0001
BNP (pg/mL)	355 ± 105	385 ± 115	<0.0001
Creatinine clearance	55.4 ± 3.3	48.7 ± 2.1	<0.0001

NYHA, New York Heart Association; BNP, brain natriuretic peptide; HSS, hypertonic saline solution.

TABLE 4. Results of the long-term study: Readmissions and mortality (mean follow-up 57 ± 15 months)

	120 mmol Na/d	80 mmol Na/d	<i>P</i>
Patient no.	881	890	
Sex (F/M)	302/579	315/575	
BNP (pg/mL)	425 ± 175	625 ± 245	<0.0001
Readmissions	163 (18.5%)	305 (34.2%)	<0.0001
Mortality	114 (12.9%)	212 (23.8%)	<0.0001
Sudden death	31 (3.5%)	46 (5.1%)	<0.6
Irreversible HF	69 (7.8%)	149 (16.7%)	<0.0001
Other causes	14 (1.5%)	17 (1.9%)	<0.76
Excluded from final analysis	72 (7.5%)	84 (8.6%)	<0.48
Lost during follow-up	27 (2.7%)	38 (3.9%)	<0.26
Protocol violation	31 (3.2%)	35 (3.5%)	<0.79
NSAID administration	14 (1.4%)	11 (1.1%)	<0.64

Patients excluded from final analysis were lost in the first 3 months after discharge. Patients with protocol violation were excluded between 30 and 45 days from discharge (after repeated corrections), while patients with NSAID administration, were excluded within 30 days from discharge (they refused to discontinue the treatment).

TABLE 5. Clinical and laboratory parameters (12, 24, 48 months and end of the study from discharge) of patients who survived or were not readmitted

	Group	12 Months	24 Months	48 Months	End of the study	P
Patients no.	120 mmol	816	742	636	604	
	80 mmol	788	668	504	373	
SBP (mm Hg)	120 mmol	122 ± 12	116 ± 13	115 ± 9	115 ± 11	<0.0001
	80 mmol	121 ± 13	117 ± 11	116 ± 7	114 ± 12	<0.0001
	P	0.1	0.12	0.041	0.1	
DBP (mm Hg)	120 mmol	68 ± 5	70 ± 7	71 ± 6	68 ± 5	<0.0001
	80 mmol	71 ± 7	73 ± 8	74 ± 8	72 ± 7	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
BW (kg)	120 mmol	74.2 ± 5	74.7 ± 7	75.3 ± 6	75.4 ± 4	<0.003
	80 mmol	76.4 ± 8	78.2 ± 9	81.2 ± 13	81.3 ± 6	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
Diuresis (mL/24 hr)	120 mmol	1875 ± 475	1750 ± 550	1725 ± 425	1750 ± 450	<0.0001
	80 mmol	1450 ± 325	1350 ± 450	1250 ± 350	1150 ± 250	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
Na-s (mEq/L)	120 mmol	139.7 ± 3.5	140.1 ± 3.7	138.5 ± 4.2	137.8 ± 2.3	<0.0001
	80 mmol	133.3 ± 5.2	132.4 ± 3.1	132.7 ± 2.8	131.5 ± 2.5	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
K-s (mEq/L)	120 mmol	3.8 ± 0.2	3.9 ± 0.3	3.7 ± 0.5	3.7 ± 0.2	<0.0001
	80 mmol	3.6 ± 0.3	3.7 ± 0.2	3.6 ± 0.7	3.5 ± 0.3	<0.0001
	P	0.0001	0.004	0.005	0.005	
Na-u (mEq/24 hr)	120 mmol	111 ± 12	113 ± 11	112 ± 13	115 ± 7	<0.0001
	80 mmol	75 ± 7	76 ± 4	74 ± 5	73 ± 4	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
Cr-s (mg/dL)	120 mmol	1.53 ± 0.3	1.57 ± 0.3	1.61 ± 0.4	1.62 ± 0.2	<0.0001
	80 mmol	1.97 ± 0.5	2.2 ± 0.4	2.1 ± 0.3	2.2 ± 0.4	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
BUN (mg/dL)	120 mmol	68.6 ± 7.2	67.2 ± 9.3	71.4 ± 7.2	73.3 ± 5.3	<0.0001
	80 mmol	99.5 ± 6.6	112 ± 6.4	115 ± 5.7	117 ± 3.3	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	
Creatinine clearance	120 mmol	56.5 ± 3.5	53.8 ± 4.1	52.2 ± 5.31	52.3 ± 3.35	<0.0001
	80 mmol	45.7 ± 2.4	44.2 ± 3.2	42.7 ± 3.3	41.5 ± 2.2	<0.0001
	P	0.0001	0.0001	0.0001	0.0001	

BW, body weight; BUN, blood urea nitrogen; Na-s, serum sodium; K-s, serum potassium; Na-u, urinary sodium; Cr-s, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure.

BNP values controlled at the end of follow-up showed a significant increase in second group (625 + 245 pg/mL) in comparison with the first group (425 + 175 pg/mL, *P* < 0.0001). The relative risk reduction was 0.30 (0.21–0.38), and the number needed to treat to prevent 1 event was 8 (6–11).

In addition, we evaluated the nonischemic (hypertensive) subgroup (Figure 4). This subgroup showed an interesting better outcome in patients receiving a moderate sodium restriction compared with patients receiving a low sodium diet.

### DISCUSSION

The study explores the sodium management in patients with HF both in acute phases (hospitalization) and in chronic phases (after discharge) when the patients had reached a compensated state. Although, in the acute phase, the HSS determined a faster resolution of congestive state without determining renal dysfunction or Na reduction and renin angiotensin aldosterone system (RAAS) activation, in the chronic phases (compensated state), a moderate Na restriction allowed to maintain a good renal function, optimal diuresis, compensated

state and normal Na plasma levels, probably by the maintenance of neurohormonal inhibition.<sup>12,13,15,18</sup>

This first step of the study was performed to show that patients with acute HF and fluid retention and treated with combination of high furosemide dose (250 mg twice daily), fluid restriction (1000 mL/d), a moderate Na diet (120 mmol) and the addition of HSS reached a compensated state in a faster way than those treated with combination of high diuretic dose (250 mg twice daily), fluid restriction (1000 mL/d), but with a low Na diet (80 mmol) and without HSS. Indeed, the HSS group had a significant reduction in hospitalization time, lower BNP plasma levels and faster achievement of dry state compared with the “furosemide alone” group. These results were also associated with improved renal function for the HSS group. These results show that the Na management in acute phases of patients with HF plays an important role in maintenance of euvolemic state and avoids plasma volume reduction as it occurs using diuretic treatment and a low Na diet only. In addition, the fluid restriction allowed an equilibrium between fluid intakes and fluid elimination with subsequent better maintenance of a compensated state. In the subse-

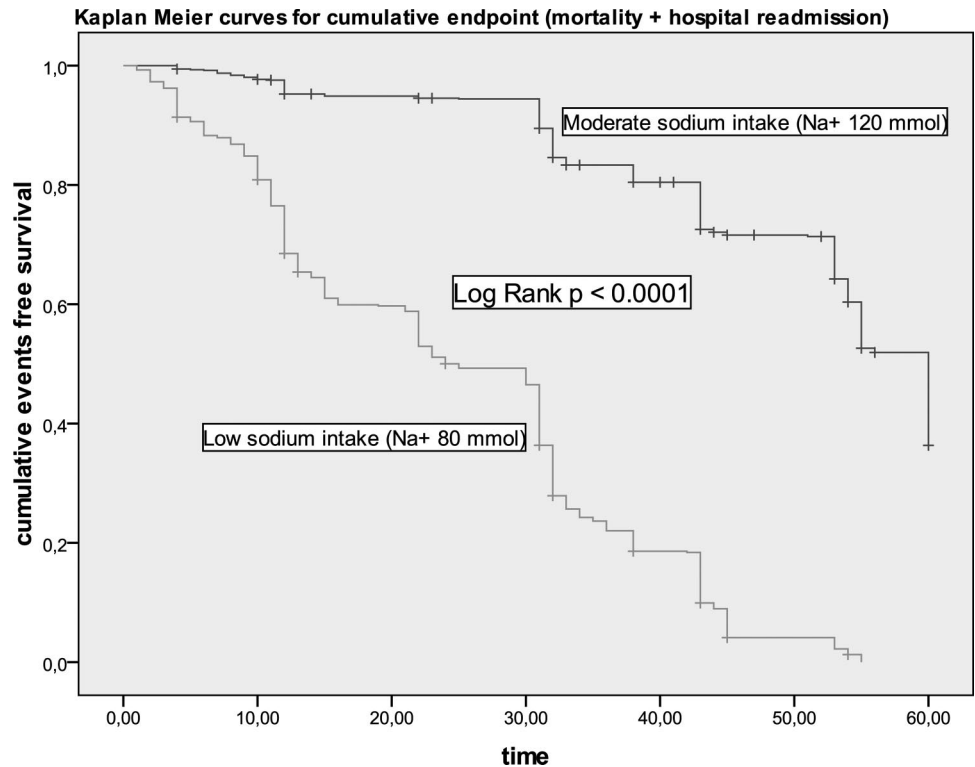


FIGURE 2. The Kaplan–Meier cumulative event mortality and readmissions in the 2 groups during  $57 \pm 15$  months follow-up.

quent step (after discharge), we evaluated the effects of 2 different Na diets (120 mmol/Na/d versus 80 mmol/Na/d) associated with fluid restriction and similar diuretic furosemide doses in the patients from both groups who had reached a compensated state (NYHA class I–II). Decompensated HF is characterized by expansion of venous circulating blood volume and a reduction in effective arterial circulating blood volume. This leads to reductions in arterial filling and renal blood flow that activate the neurohormonal cascade. HSS, through its positive effects on stroke work index, cardiac output, and reduction in renal vascular resistance, may improve intrarenal hemodynamics and reduce some of the neurohormonal factors, leading to Na and fluid retention in the kidneys.<sup>19–23</sup> Moreover, the increased renal blood flow also may facilitate delivery of Na and loop diuretics to the Henle’s loop, and thus, it may enhance the effects of conventional diuretic therapy and help to overcome diuretic resistance. Direct intratubular effects of Na flooding may overwhelm the postdiuretic Na retention, and over the time, they may reduce the diuretic banking phenomenon by which fluid escaping post ascending limb is captured downstream.<sup>24</sup>

The effective treatment of volume overload in patients with decompensated HF and diuretic resistance remains clinically challenging. The administration of small volumes of HSS as an adjunct to loop diuretics may provide a safe and effective therapy for these patients. The mechanisms of this action seem to be centered on renal hemodynamics improvement, explained by direct positive cardiac contractility, and downregulation of vasoconstrictor, antinatriuretic and antidiuretic hormones.<sup>25–27</sup> For more details on diuretic and HSS use, the interested reader is referred elsewhere.<sup>28,29</sup>

This effect may come from HSS potential to preserve the diuretic effectivity of furosemide. HSS may promote vascular refilling and prevent the fall of renal blood flow as induced by the reduction of circulating blood, as observed in

patients receiving diuretics only. The water displacement from extravascular components toward intravascular compartments coincides with the property of HSS to propitiate furosemide’s pharmacodynamic effect on its specific action site, ie, the ascending limb of Henle’s loop.

Further evidences suggest that HSS lowers inflammatory markers, including tumor necrosis factor- $\alpha$  and interleukin-6, in patients with HF.<sup>30–34</sup> High inflammatory cytokines levels are associated with a poor prognosis in HF,<sup>35</sup> and it is possible that HSS administration improves outcomes, partially via an anti-inflammatory mechanism. It seems that the benefit seen in hospital with HSS administration can be longer maintained by liberalizing dietary Na intake. In addition, patients treated with HSS reached a lower and faster reduction in echo-pulmonary capillary wedge pressure compared with the control group during hospitalization, and the effects of both treatments on echo-pulmonary capillary wedge pressure seem well matched with clinical results for both groups.<sup>36</sup>

The HSS brief administration is not enough to directly cause a sustained increase in serum Na levels and to trigger other mechanisms affecting osmolar regulation.<sup>12–15,37</sup> HSS infusion rapidly increases extracellular Na concentration, with a consequent increase in plasmatic volume expansion, instantaneous fluid mobilization into the vascular compartment, and increases renal blood flow. Fluid moved out of erythrocytes and endothelial cells to the extracellular space leads to a reduction in capillary hydraulic resistance.<sup>38</sup> The rapid expansion of extracellular fluid volume is responsible for the decreased plasma and peritubular oncotic pressure that (along with an increased peritubular hydrostatic pressure) enhances urinary Na excretion by a reduction in proximal tubule Na reabsorption.<sup>33,39–41</sup> It is possible that the therapeutic effects of this treatment are mediated not only by direct effects on renal hemodynamics but also by neurohormonal modulation.<sup>12,14,15,30,42–44</sup>

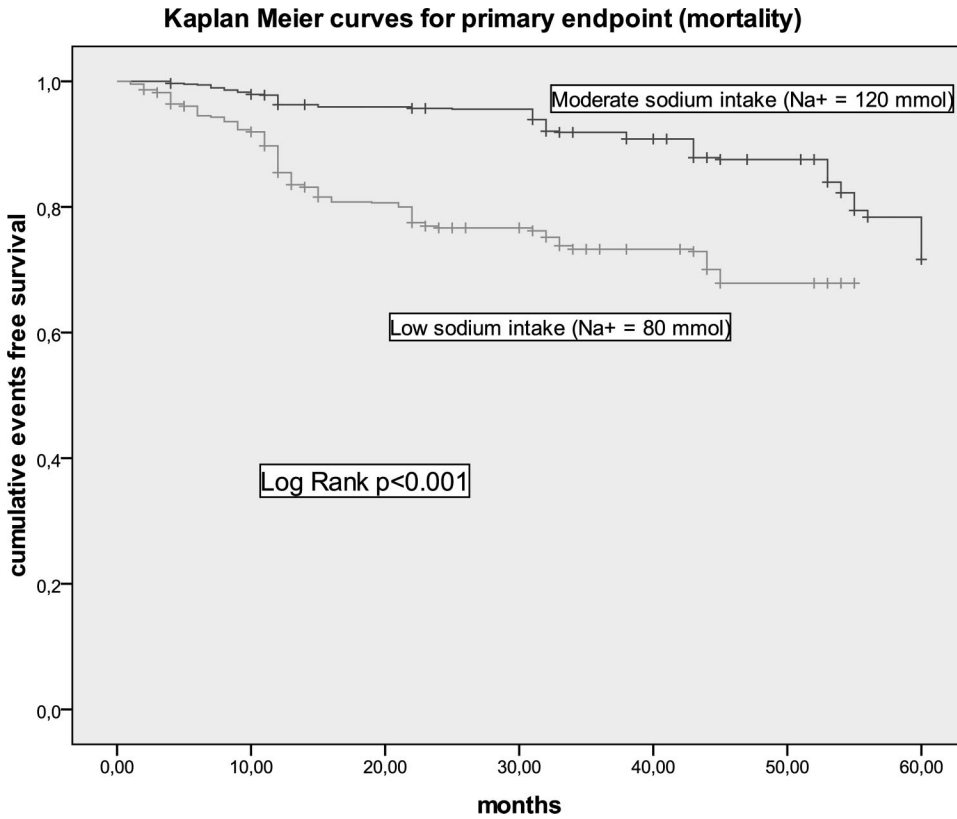


FIGURE 3. The Kaplan–Meier for mortality in the 2 groups during  $57 \pm 15$  months follow-up.

After discharge (chronic phase), the first group continued a fluid intake restriction (1000 mL/d), a moderate Na restriction (120 mmol) and the furosemide doses which allowed to keep BW and water balance during hospitaliza-

tion (50–125 mg twice daily), whereas the second group received the same diuretic doses and fluid intake restriction (as the first group) associated with a low Na diet (80 mmol/d).

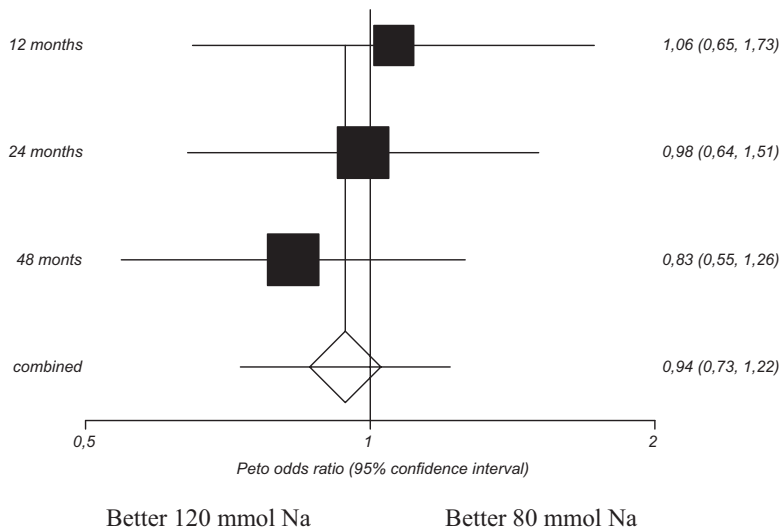


FIGURE 4. Peto Odds ratio plot figure for nonischemic subgroup (hypertensive) patients during a 48-month follow-up according to different sodium diet intake.

Focus is placed on the observed number of events in the two groups (80 vs 120 mmol/Naday). The expected numbers are calculated using the overall event rate in both the experimental and control groups. Because of the way the Peto method calculates odds ratios, it is appropriate when trials have roughly equal number of participants in each group and treatment effects are small. In addition, the figure shows as the effects of a moderate restriction start 12 months after the treatment.



The moderate Na restriction group showed a significant reduction in mortality and readmissions for worsening HF in comparison with the low Na diet group.

In this phase, we explored the effects of moderate Na reduction in comparison with a low Na diet on clinical outcomes in the patients discharged in compensated state. Previously, we showed that a moderate Na restriction improved outcome (readmissions and mortality) and reduced BNP and aldosterone plasma levels and plasma renin activity over 6 months follow-up in patients with compensated advanced HF treated with oral high-dose furosemide and fluid intake restriction, in comparison with a low Na diet. In addition, the renal function parameters in the 120 mmol Na group did not show significant differences from baseline values, in contrast with increased creatinine and BUN values in the low Na group. These data suggest that a moderate Na restriction may be able to maintain the plasma volume and impeding neurohormonal activation.<sup>13–15,18,42–44,45,46</sup> The use of dietary Na in higher doses than conventionally recommended after discharge may further reduce chronic neurohormonal stimulation and stem the adaptive hypertrophy that is seen in the early distal and collecting tubules with chronic diuretic use. This also could improve long-term diuresis and natriuresis in patients with chronic HF. The beneficial effects observed in the long time cannot be related to HSS treatment during hospitalization. It is impossible to think that a brief HSS administration can maintain its effects for the subsequent years. We think that HSS can determine a faster dry state, whereas the long-term results depend from the higher sodium assumption and the association of fluid restriction and diuretic doses. It is likely that a moderate Na restriction was able to maintain fluid balance and inhibit vasoconstrictor systems.<sup>46</sup> On the other hand, the Na and water-retaining hormonal systems are activated in HF, and cardiac forward flow is impaired during Na restriction.<sup>37,45,46</sup> The marked increase and/or normalization in serum Na levels observed in patients with normal Na intake is consistent with vasopressin and RAAS inhibition.<sup>45–49</sup> The origins of HF are rooted in a salt-avid state largely mediated by the RAAS system, whose activation is based on reduced renal perfusion. Stimuli that normally lead to RAAS activation keep working in patients with HF. Treatments that minimize, interfere with, or reverse RAAS activation are integral to the optimal management of HF.<sup>48,49</sup> In addition, it is possible that patients receiving low Na diet and diuretics may have intravascular volume depletion compared with the patients in moderate Na restriction group (probably Na in the first group tends to diminish intravascular volume depletion induced by over-diuresis). This could be an alternative explanation for the improved outcome in the first group during the follow-up. Is salt beneficial or is extensive use of diuretics dangerous? There is not a solely true or a solely false concept, but it is probably the diuretics use in relation to Na intake (or Na intake in relation to diuretics use) that is crucial to get adequate intravascular volumes. Our results seem to justify the effects of Na on plasma volume maintenance, RAAS inhibition and clinical outcome.<sup>46,49</sup> Plasma volume measurements during follow-up could be useful; unfortunately, such measurements are not easily feasible in large-scale studies like this. HF accounts for almost 1 million inpatient admissions per year and represents the first hospitalization reason among the growing elderly population.<sup>2</sup> The National Hospital Ambulatory Medical Care Survey reported 1.5 million emergency department visits in 1999 for nonischemic heart disease, most of them related to HF.<sup>50</sup> An estimated 20% of patients with HF die within the first year from diagno-

sis, according to a 2009 American Heart Association report. This disease was associated with more than 280,000 deaths in 2006. The total cost of healthcare services, medications and productivity loss resulting from HF would be more than \$39 billion per year, according to the American Heart Association. To date, an important controversy exists on sodium diet in general population and patients with HF. High salt intake is often cited as a cause of HF exacerbation and hospital admission.<sup>51,52</sup> Consequently, the American Heart Association/American College of Cardiology recommends that patients with HF should keep a low Na diet, but it acknowledges that this recommendation is based on expert consensus only (evidence C).<sup>53</sup> In fact, there are no definitive clinical studies testing this recommendation.<sup>54–63</sup> Many observational studies have examined the relationship between Na consumption and clinical outcomes, but the results have been conflicting.<sup>53–57,63–67</sup> Recent studies<sup>11–15,45,49,59,61,68</sup> have rekindled the debate, spotlighting a divided scientific community. In fact, 2 recent articles show contrasting results in patients with HF receiving different Na diets, but these articles do not report diuretic doses and fluid intake levels.<sup>52,61</sup> Moreover, the analysis of nonischemic (HF of hypertensive heart disease origin) subgroup showed an intriguing occasional result. In fact, the patients receiving a moderate sodium restriction showed a more favorable outcome in comparison with patients receiving a low sodium diet. The small sample of patients did not allow definitive consideration, but the results suggest further studies (double blind) in larger populations and with a higher EF and lower HF NYHA class. The patients showed a good compliance with Na diet, fluid intake and diuretic dose that was adequately controlled by diary examination, family physician contacts and 24-hour natriuresis checked at the programmed follow-up visits (15 per patient). In addition, at the follow-up controls, beta blocker, ACE-inhibitor and antialdosterone administration was also checked, and no significant variation in doses was observed. In addition, we treated patients with HF with mineral-corticoid blockers before publication of RAALES and EPHESUS trials<sup>69,70</sup> in agreement with our pilot studies.<sup>71–73</sup>

The difference between the current study and the previous ones was the inclusion of patients in NYHA class III only and a lower dose of furosemide. In conclusion, the most striking results of the study were the safety and tolerability of HSS/high furosemide doses/moderate Na restriction combination in the patients with acute HF and that this treatment is also effective in patients with a lower HF class. In addition, the study also shows that the moderate Na restriction, fluid restriction and furosemide combination determined a reduction in mortality and readmissions in the long term. Our counterintuitive approach underlines the need for better understanding of factors that regulate Na and water handling in chronic HF. Furthermore, large-scale trials should be considered to validate the use of HSS for the treatment of this complex clinical problem, and other double-blind studies are required before incorporating this protocol into practice. Albeit encouraging, clinical research on HSS use is actually limited because most of the studies in this area have been performed by a single research group. Two ongoing studies in the United States<sup>74</sup> and in Brazil<sup>75</sup> might help to add more knowledge about the use of this agent in diuretic-resistant HF.

### Limitations of the Study

The major limitation of this study was the single-blind randomization. Ethical committee authorized only single-blind randomization when the study was planned because the treatments used in this study were against the guidelines' recommendations and because of treating patients at high risk. Our patients differ

from HF population usually studied in hospital because of older age, higher BP, higher EF and larger net diuresis (real-world population). However, the patients were strictly selected to test, for the first time in NYHA class III, the effects of combination treatment with HSS plus high doses of furosemide (intravenously) in the short term and, for the first time, a moderate Na restriction plus oral furosemide in the long term; for the same reason, the patients were given single blind treatment.

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