Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend?

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ABSTRACT

The aim of the present study was to evaluate the effects of a normal-sodium (120 mmol sodium) diet compared with a low-sodium diet (80 mmol sodium) on readmissions for CHF (congestive heart failure) during 180 days of follow-up in compensated patients with CHF. A total of 232 compensated CHF patients (88 female and 144 male; New York Heart Association class II–IV; 55–83 years of age, ejection fraction $< 35\%$ and serum creatinine < 2 mg/dl) were randomized into two groups: group 1 contained 118 patients (45 females and 73 males) receiving a normal-sodium diet plus oral furosemide [250–500 mg, b.i.d. (twice a day)]; and group 2 contained 114 patients (43 females and 71 males) receiving a low-sodium diet plus oral furosemide (250–500 mg, b.i.d.). The treatment was given at 30 days after discharge and for 180 days, in association with a fluid intake of 1000 ml per day. Signs of CHF, body weight, blood pressure, heart rate, laboratory parameters, ECG, echocardiogram, levels of BNP (brain natriuretic peptide) and aldosterone levels, and PRA (plasma renin activity) were examined at baseline (30 days after discharge) and after 180 days. The normal-sodium group had a significant reduction ($P < 0.05$) in readmissions. BNP values were lower in the normal-sodium group compared with the low sodium group (685 ± 255 compared with 425 ± 125 pg/ml respectively; $P < 0.0001$). Significant ($P < 0.0001$) increases in aldosterone and PRA were observed in the low-sodium group during follow-up, whereas the normal-sodium group had a small significant reduction ($P = 0.039$) in aldosterone levels and no significant difference in PRA. After 180 days of follow-up, aldosterone levels and PRA were significantly ($P < 0.0001$) higher in the low-sodium group. The normal-sodium group had a lower incidence of rehospitalization during follow-up and a significant decrease in plasma BNP and aldosterone levels, and PRA. The results of the present study show that a normal-sodium diet improves outcome, and sodium depletion has detrimental renal and neurohormonal effects with worse clinical outcome in compensated CHF patients. Further studies are required to determine if this is due to a high dose of diuretic or the low-sodium diet.

Key words: congestive heart failure, fluid balance, furosemide, low-sodium diet, normal-sodium diet.

Abbreviations: ACE, angiotensin-converting enzyme; AngII, angiotensin II; ARR, absolute risk reduction; b.i.d., twice a day; BNP, brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; BW, body weight; CHF, congestive heart failure; DBP, diastolic BP; EF, ejection fraction; HSS, hypertonic saline solution; NYHA, New York Heart Association; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system; SBP, systolic BP.

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INTRODUCTION

The management of patients with advanced CHF (congestive heart failure) classically consists of sodium restriction, moderate physical activity and a tailored treatment that include digitalis, diuretics and ACE (angiotensin-converting enzyme)-inhibitors [1]. Diuretics, particularly loop diuretics, have long been accepted as the first-line treatment of patients with severe CHF and fluid retention [2,3]; however, a lack of response to diuretic therapy is a common event, particularly in elderly patients with advanced disease. Previously, we have reported [4–6] the safety and tolerability of a combination of high-dose furosemide associated with intravenous infusion of small-volume HSS (hypertonic saline solution) in patients with refractory CHF, and this combination resulted in a significant decrease in hospitalization time compared with the intravenous infusion of a high dose of furosemide as a bolus. In addition, we have observed that patients receiving a normal-sodium diet maintained the achieved NYHA (New York Heart Association) functional class at discharge, a reduction in hospital readmissions for worsening CHF [7,8] and a significant reduction in mortality rate (55 compared with 13 % survival after 48 months) [9,10]. Successively, systematic results on changes in plasma BNP (brain natriuretic peptide) levels and bioelectrical variables occurring in CHF patients before and after treatment showed that patients receiving HSS reached their dry weight more rapidly than those not receiving HSS [11,12].

The aim of the present study was to evaluate the effects of a normal-sodium diet (120 mmol of sodium) compared with a low-sodium diet (80 mmol of sodium), in combination with high-dose furosemide and severe fluid restriction (1000 ml/day), in patients compensated after recently decompensated CHF, on readmissions for worsening CHF (primary end point). In addition, we also evaluated the combination of readmissions and mortality (secondary end point), and plasma BNP and aldosterone levels, and PRA (plasma renin activity) during 180 days of follow-up.

MATERIALS AND METHODS

Patient population

From January 2000 to May 2005, 1244 patients were admitted consecutively to hospital with worsening CHF.

Eligibility criteria

Compensated patients who were hospitalized previously (previous 30 days) for recently decompensated CHF with the following characteristics were included in the study: patients had to have, according to the definition of refractory CHF [13] and according to Framingham criteria and New York Association Functional classification of CHF [14], uncompensated CHF (dyspnoea, weakness, lower limb oedema or anasarca), NYHA functional class IV that was unresponsive to treatment with high doses of oral furosemide up to 250–500 mg/day and/or combinations of diuretics (thiazide, loop diuretic and spironolactone), ACE-inhibitors (captopril; 75–150 mg/day), digitalis, β-blockers and nitrates, and to be under this therapy for at least 2 weeks before hospitalization. The patients were judged unresponsive when they had, during the above treatment, a decrease in urine volume, a constant increase in BW (body weight) and an impairment of clinical symptoms of CHF, as above, in spite of an increase in furosemide and a combination of other diuretics (including thiazide). Additionally, patients had to have a left ventricular EF (ejection fraction) < 35 %, serum creatinine < 2 mg/dl, BUN (blood urea nitrogen) $\leqslant 60$ mg/dl, a decreased urinary volume (< 500 ml/24 h) and low natriuresis (< 60 mmol/24 h), despite receiving established treatments. None of the patients had to take NSAIDs (non-steroid anti-inflammatory drugs). All patients received high-dose furosemide [250–1000 mg, b.i.d. (twice a day)], HSS, a normal-sodium diet (120 mmol) and a decreased fluid intake (1000 ml/day) during hospitalization. When the compensated state was achieved (NYHA class II), patients received oral furosemide (250–500 mg, b.i.d.), a normal-sodium diet (120 mmol sodium) and a fluid intake of 1000 ml/day, according to previous studies [4–11], and the treatment was continued after discharge. Patients were considered clinically compensated when they reached a change in NYHA functional class to at least class II and the accomplishment of an ideal BW, calculated by the Lorenz formula and bioelectrical impedance measurements [11]. Diuretic doses ranged from 250 to 500 mg b.i.d. because these doses allowed maintenance of BW and water balance. The diuretic doses were titrated according to the doses used during hospitalization. In addition, after discharge, patients also received tailored therapy (ACE-inhibitors, digitalis, antialdosterone, β-blockers and nitrates). Only patients in NYHA class II at 30 days after discharge were included in the study and were randomized.

Exclusion criteria

Patients with cerebral vascular disease, dementia, cancer, uncompensated diabetes, and severe hepatic disease 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 (but continued the prescribed treatment), were unable to follow the assigned treatment, did not follow the treatment protocol or attend the scheduled clinical visits, did not adhere to the fluid intake of 1000 ml day, or had a reduction or discontinuation of prescribed treatments. In addition, patients with side effects of ACE-inhibitor treatment (cough), even if

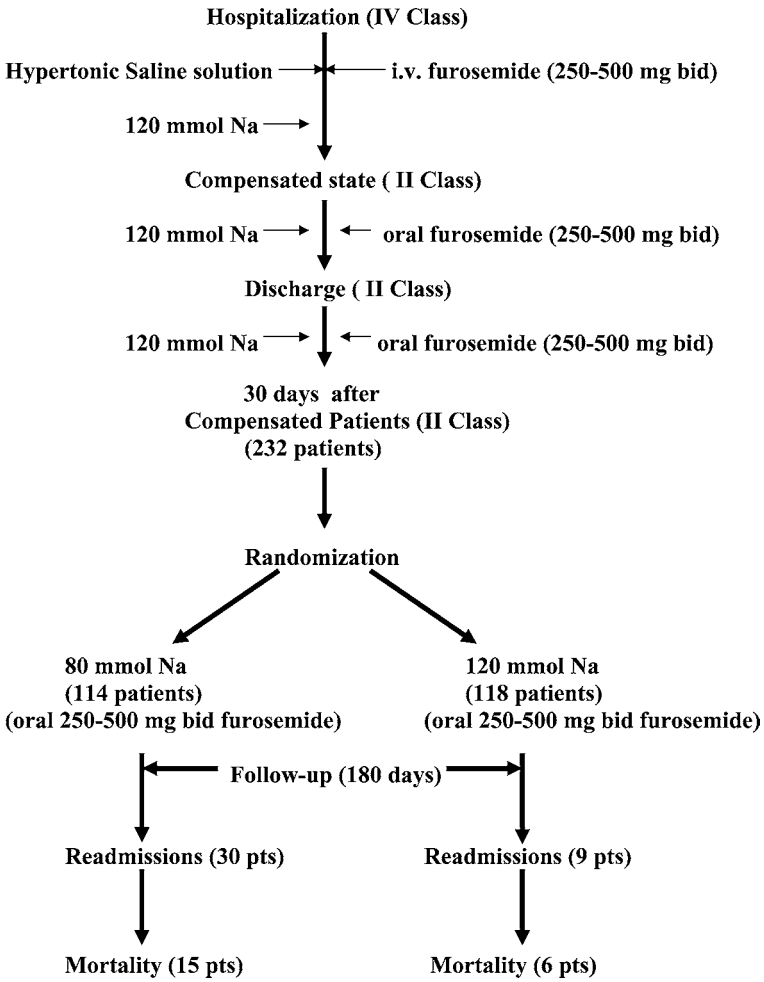

Figure 1 Flow chart of the study

these patients were given ARBs [AngII (angiotensin II)-receptor blockers], were also excluded in order to obtain as homogeneous treatment schedule as possible.

Study protocol and follow-up (Figure 1)

Pre-randomization evaluation

After discharge, patients were controlled with clinical and laboratory evaluations as outpatients every week for the first 30 days, and those at 30 days after the discharge who met the eligibility criteria were included in the study. During the 30-day period after discharge, treatments (where necessary) were corrected according to clinical status and laboratory measurements (decrease and/or increase in diuretics, ACE-inhibitors, digitalis, antialdosterone, β-blockers and nitrates), and, therefore, it was not necessary to correct the assigned treatments during follow-up. In fact, all of the enrolled patients were stable and received the best treatments, which were able to maintain the compensated state obtained after discharge and before randomization. During the follow-up period, other treatments were not added to those administered. Correction of therapy was only carried out in readmitted patients.

Randomization

Only patients adjudged to be compensated according to NYHA class II by an independent external team of at least two physicians blinded to the study protocol were included into the study and randomized into one of two groups: group 1 received a normal-sodium diet (120 mmol of sodium) and continued with oral furosemide (250–500 mg, b.i.d.), and group 2 received a low-sodium diet (80 mmol of sodium) and continued with oral furosemide (250–500 mg, b.i.d.), in addition to the treatment reported above. Both groups received a fluid intake of 1000 ml/day. Randomization was carried out using a preliminary computer algorithm and the assignment of all patients was decided at baseline (at 30 days after discharge) before performing clinical and laboratory measurements.

Written informed consent was obtained from each patient before starting the study. The protocol was approved by Local Ethics Committee.

Evaluation after randomization

After randomization (at 30 days after discharge) and baseline clinical and laboratory assessments, patients were evaluated every week for the first month, every 2 weeks for the next 2 months and then every month for the remainder of the study period. A complete physical examination, with a careful assessment of signs and symptoms of CHF, including measurement of BW (in the morning before breakfast), supine and standing arterial BP (blood pressure) (mean of three measurements) and HR (heart rate), was performed at every follow-up assessment. At baseline (before receiving the normal- or low-sodium diet), fasting blood samples were drawn to determine serum sodium, potassium, chloride, bicarbonate, albumin, uric acid, creatinine, urea and glucose. Plasma aldosterone and BNP levels, and PRA were also determined. A chest X ray, ECG and echocardiogram [to obtain EF according to the modified Simpson' rule, which uses two cross-sectional views (four- and two-chamber apical views)] were also evaluated. All of these parameters were also obtained at 90 and 180 days of follow-up, with the exception of plasma aldosterone levels and PRA, which were measured by RIA in core laboratories at 180 days of follow-up in both groups. In addition, all of the patients with diabetes received insulin therapy; however, oral antidiabetic drugs were discouraged after discharge and follow-up. After randomization, all patients received multiple written standard diets containing 80 mmol of sodium prepared by our dieticians. The group receiving the normal-sodium diet (120 mmol of sodium) received the same diets but with the addition of 40 mmol of sodium/day. In this way, all patients received the same amount of saturated fat, fruit, vegetables etc.

In addition, patients were also contacted every week during follow-up by physicians and dieticians for a telephone interview to determine the adherence to the reduced fluid intake as well as the prescribed diet. Other information was also obtained by regular contact with family doctors, who were informed about the end points of the study. Any of the patients experiencing worsening CHF according to their family doctor were invited to attend hospital for evaluation. Two physicians blinded to the study protocol performed the evaluations to verify the clinical status and if worsening CHF was present.

Statistical analysis

We performed a multiple regression sample size calculation based on a β value of 0.10 (90 % power) and α value of 0.05. Therefore the sample size obtained was 67 for each group, and this number was assumed as a minimum for this study. We estimated a 20 % reduction in readmissions for worsening CHF on the basis of findings from our previous study [9]. Analysis was by intention to treat and according to ARR (absolute risk reduction); we calculated the number needed to treat to prevent one event. We calculated event distributions with the Kaplan–Meier method and compared them by log-rank analysis. Data were analysed using a two-tailed Student's t test to identify differences between groups and ANOVA for repeated measures with Bonferroni post-hoc test correction for intra-group data. Nominal data was analysed by the χ^2 test. $P < 0.05$ was assumed as statistically significant. All calculations were done with SPSS statistical software, and the results are expressed as means $\pm$ S.D.

RESULTS

Of the 1244 patients admitted to hospital for worsening CHF, 76 did not have reduced urinary volume (< 500 ml/24 h) and a low natriuresis (< 60 mmol/l/24 h), 92 patients had severe co-morbidity (see exclusion criteria), 25 patients had side effects of taking ACE-inhibitors, 58 patients required pacemakers, 18 patients had an alcoholic habit, 136 patients had creatinine > 2.0 and/or BUN > 60 mg (on hospital admission), 451 patients were classified as NYHA class III on hospital admission, and 23 patients were in NYHA class III after hospital discharge. All were excluded from the study. A further 79 patients declined to participate in the study either at discharge or at 30 days after discharge, and 54 patients did not follow the prescribed limited fluid intake (1000 ml/day) during the 30-day period after discharge and were therefore also excluded from the study.

As shown in Table 1, 232 patients (88 females and 144 males) with compensated CHF (NYHA class II) of different aetiologies (53–85 years of age) met the entry criteria, agreed to be enrolled and were randomized to receive either the normal-sodium diet or the low-sodium diet. In the group receiving the normal-sodium diet, daily diuresis was maintained during follow-up as at baseline, whereas the group receiving the low-sodium diet had a significant decrease in daily diuresis at 180 days compared with at baseline (Table 2). Patients in the group receiving the low-sodium diet had a significantly decreased daily diuresis at 180 days compared with the patients receiving the normal-sodium diet (Table 2). The same findings were also observed for natriuresis and serum sodium levels (Table 2). Serum potassium levels decreased significantly in both groups, but the value remained within the normal range (Table 2). In addition, the renal function parameters controlled after 90 and 180 days in the group receiving the normal-sodium diet were not significantly different from the baseline values, which was in contrast with the increase in creatinine and BUN values observed in the group receiving the low-sodium diet (Table 2). The group receiving the normal-sodium diet had no significant variation in BW. In both groups, SBP (systolic BP) and

Table 1 Clinical characteristics and aetiology of CHF in the study subjects

AF, atrial fibrillation; CAD, coronary artery disease; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease.

		Patients receiving	
	All patients	Low-sodium diet	Normal-sodium diet
n	232	114	118
Age (years)	72.6 ± 8	73.3 ± 9	72.1 ± 7
Sex (*n*) (female/male)	88/144	43/71	45/73
Diabetes (*n*)	55	25	30
Medication*			
Captopril (*n*)	232	114	118
Carvedilol (*n*)	18	10	8
Digitalis (*n*)	47	23	24
Furosemide (*n*)			
250 mg, b.i.d.	142	73	69
500 mg, b.i.d.	90	46	44
Spironolactone (*n*)	202	99	103
Aetiology of CHF (*n*)			
CAD	110	53	57
HHD	76	37	39
DCM	46	24	22
AF	51	26	25

*Medication: 75–150 mg of captopril/day, 6.25–25 mg of carvedilol b.i.d.; 0.125–0.25 mg of digitalis/day and 25 mg of spironolactone/day.

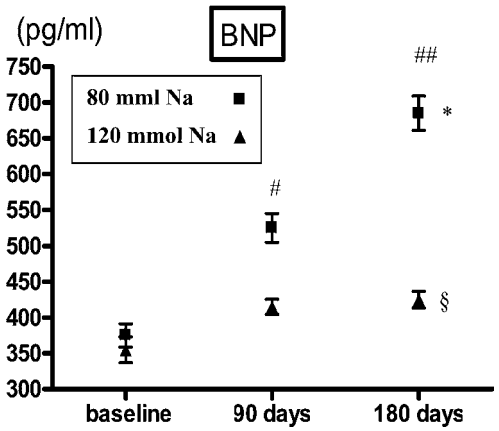

Figure 2 Changes in BNP plasma levels during the study period

*$P < 0.0001$ compared with baseline; §$P < 0.001$ compared with baseline; #$P < 0.001$ compared with the normal-sodium diet at 90 days; ##$P < 0.0001$ compared with the normal-sodium diet at 180 days.

DBP (diastolic BP) were decreased but without any major clinical symptoms (Table 2). A significant ($P < 0.001$) inter-group difference was observed in plasma BNP levels at the end of the study (180 days). The group receiving the normal-sodium diet had significantly lower BNP levels at 90 ($P < 0.001$) and 180 days ($P < 0.0001$) compared with the group receiving the low-sodium diet (Figure 2). In the group receiving the low-sodium diet, aldosterone (normal value, 7–150 pg/ml) increased significantly from 188 ± 171 pg/ml at baseline to 296 ± 224 pg/ml at 180 days ($P < 0.0001$), whereas, in the group receiving the normal-sodium diet, a small, but significant ($P = 0.002$), decrease from 192 ± 160 pg/ml at baseline to 152 ± 102 pg/ml at 180 days was observed. PRA (normal value, 0.2–0.8 ng · ml^{-1} · h^{-1}) was not significantly different ($P = 0.6$) between baseline (3.91 ± 3.71 ng · ml^{-1} · h^{-1})

Table 2 Clinical and laboratory parameters at entry and after 90 and 180 days in the two subgroups

Results are means ± S.D. *$P < 0.001$ compared with low-sodium diet after 180 days. ns, not significant.

	Patients receiving							
	Low-sodium diet				Normal-sodium diet			
	Entry	90 days	180 days	*P* value	Entry	90 days	180 days	*P* value
n	114	106	99		118	114	112	
SBP (mmHg)	126 ± 15	116 ± 11	107 ± 13	< 0.001	125 ± 15	114 ± 11	111 ± 11	< 0.01
DBP (mmHg)	82.0 ± 13	76.0 ± 11	77 ± 9	< 0.001	83 ± 14	78 ± 12	75 ± 11	< 0.001
HR (beats/min)	85 ± 14	83 ± 11	82 ± 12	ns	84 ± 11	76 ± 9	72 ± 8*	< 0.0001
EF (%)	29.3 ± 5	30.1 ± 6	30.2 ± 6	ns	29.5 ± 4	32.2 ± 6	32.5 ± 5	< 0.001
BW (kg)	76.9 ± 15	79.1 ± 13	80.2 ± 13	< 0.001	75.2 ± 14	74.8 ± 15	75.3 ± 10*	ns
Diuresis (ml/24 h)	2560 ± 425	1580 ± 555	1525 ± 565	< 0.0001	2495 ± 635	2250 ± 565	2150 ± 480*	< 0.048
Serum sodium (mol/l)	138.3 ± 5	132.3 ± 4	132.1 ± 5	< 0.001	138.7 ± 7	140.4 ± 3	139.5 ± 6*	< 0.001
Serum potassium (mol/l)	4.6 ± 0.8	3.7 ± 0.4	3.6 ± 0.8	< 0.0001	4.7 ± 0.5	3.9 ± 0.4	3.7 ± 05	< 0.0001
Natriuresis (mol/24 h)	102 ± 11	77 ± 9	76 ± 7	< 0.01	105 ± 14	106 ± 12*	103 ± 11*	ns
BUN (mg/dl)	56.5 ± 3.6	101 ± 12	105 ± 5.8	< 0.0001	58.5 ± 7	67 ± 9	68.4 ± 7.2*	< 0.001
Serum creatinine (mg/dl)	1.55 ± 0.05	1.89 ± 0.3	2.1 ± 0.5	< 0.001	1.56 + 0.2	1.48 ± 0.3	1.45 ± 0.4*	< 0.01
Uric acid (mg/dl)	6.7 ± 2.1	9.8 ± 3.5	10.2 ± 2.3	< 0.0001	6.6 ± 2.5	9.8 ± 3.5	9.9 ± 4.3	< 0.0001

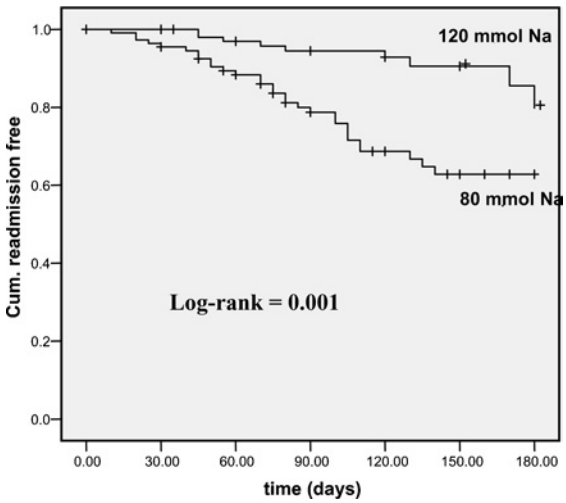

Figure 3 Kaplan–Meyer cumulative event curves for the primary end point (readmissions) in the two groups during 180 days of follow-up

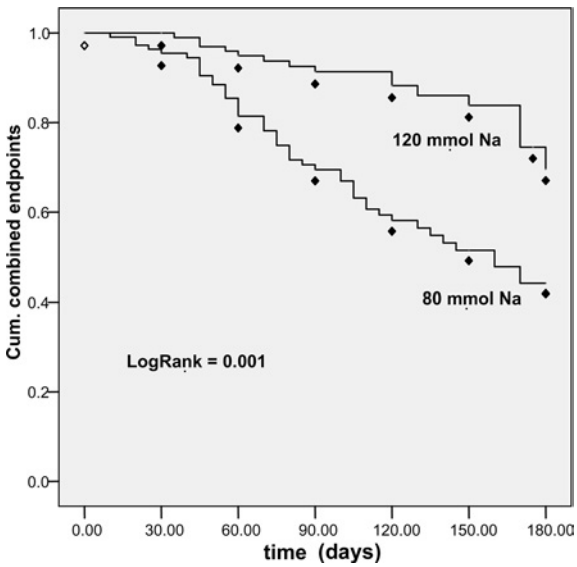

Figure 4 Kaplan–Meyer cumulative event curves for the secondary end point (readmissions + mortality) in the two groups during 180 days of follow-up

and at 180 days (3.65 ± 3.28 ng $\cdot$ ml^{-1} $\cdot$ h^{-1}) of follow-up in the group receiving the normal-sodium diet, whereas a significant ($P = 0.039$) increase from 3.98 ± 3.68 ng $\cdot$ ml^{-1} $\cdot$ h^{-1} at baseline to 5.74 ± 4.12 ng $\cdot$ ml^{-1} $\cdot$ h^{-1} at 180 days was observed in the group receiving the low-sodium diet. In both groups, the baseline values of aldosterone and PRA were similar, but, after 180 days of follow-up, both aldosterone levels and PRA were significantly higher ($P < 0.0001$) in the group receiving the low-sodium diet compared with the group receiving the normal-sodium diet.

Readmission and mortality during follow-up

The group receiving the normal-sodium diet had a significant reduction ($P < 0.05$) in readmission rate (primary end point) compared with the group receiving the low-sodium diet (7.63 compared with 26.32 % respectively), and a significant reduction ($P < 0.001$) in combined mortality and readmissions (secondary end point; 12.71 compared with 39.47 % respectively). During the 180 days follow-up period, nine patients from the group receiving the normal-sodium diet were readmitted for worsening CHF (NYHA classes III/IV) and six patients died (one from sudden death, and five from irreversible CHF). In patients receiving the low-sodium diet, 30 patients were readmitted to the hospital for clinical symptoms of CHF, and they presented at entry a higher functional class than at discharge (NYHA class III/IV). A total of 15 patients died during the 180 day study period in the group receiving the low-sodium diet [four from sudden death, nine from irreversible CHF and two from other causes (neoplastic disease and stroke)]. Figures 3 and 4 show the Kaplan–Meier cumulative-event curves for the primary (hospital readmission) and secondary (combined readmissions and mortality) end points respectively, in the two groups during 180 days of follow-up. Curve analysis showed an evident early (first 30 days) beneficial effect of the normal-sodium diet, which was more consistent during the subsequent months. The readmissions ARR was 18.69 % (95 % confidence interval, 9.29–28.08 %; $P < 0.05$), and the number of patients needed to treat to reduce readmission by one was six. The mortality ARR was 8.07 % (95 % confidence interval, 0.71–15.43; P value was not significant). The readmission and mortality ARR was 26.76 % (95 % confidence interval, 4.67–48.85 %; $P < 0.001$).

No patients received β-blockers at the time of admission to hospital. β-Blockers were also started when patients were compensated during hospitalization and after discharge, but only 18 patients (from both groups) tolerated β-blockers (carvedilol), whereas the other patients had signs of worsening CHF and β-blockers were discontinued. All patients continued with ACE-inhibitors (captopril, 75–150 mg/day) as indicated in Table 1. No patient in either group was excluded during follow-up from the study for renal deterioration (creatinine > 2.0 mg), but only the readmitted patients had an increase in plasma creatine levels > 2.0 mg. Echocardiographic data during follow-up showed a significant slight improvement of EF in patients receiving the normal-sodium diet. All of the enrolled patients had a good compliance with the prescribed treatments; however, 21 patients (12 from group receiving the normal-sodium diet and nine from the group receiving the low-sodium diet) increased their

drink fluid intake (1500 ml) during the first month (during summer), but this protocol violation was subsequently corrected (7 days later). However, patients who were not randomized due to an inability to follow the prescribed fluid intake (i.e. 1000 ml/day) after discharge ($n = 54$), but continued to take oral furosemide (250–500 mg, b.i.d.) and a normal-sodium diet, had a high incidence of readmissions for worsening CHF (30 %) in the first 180 days (results not shown), similar to the group receiving the low-sodium diet.

DISCUSSION

To our knowledge, this is the first investigation to assess the outcome of different doses of sodium intake in medically treated patients with compensated CHF. In the present study, we randomized compensated CHF patients receiving the same treatment during hospitalization and at 30 days after discharge to consume either a low-sodium (80 mmol of sodium) or normal-sodium (120 mmol of sodium) diet. This criterion allowed us to evaluate the effects of a normal level of sodium compared with a low level of sodium in the follow-up period in patients matched for clinical characteristics and treatments. We choose 120 mmol of sodium because epidemiological studies have shown that in Europe and Italy it was estimated that an average of 3.5 g (150 mmol) of sodium is consumed per day [15,16]. Our findings suggest that a normal-sodium diet with a limited fluid intake (1000 ml) when associated with a loop diuretic is able to reduce both hospital readmission for worsening of CHF (primary end point) and neurohormonal activation (plasma BNP and aldosterone levels, and PRA) after 180 days of follow-up. The beneficial effects obtained suggest that a low-sodium diet and free water intake, usually recommended in clinical practice [17–19], might not be the best treatment for these patients and merits further investigation. In addition, the accepted link between sodium intake and cardiovascular events has not been confirmed. In fact, it was shown that high-sodium intake does not induce total body water storage, but causes a relative fluid shift from the interstitial into the cardiovascular space [20]. Conversely, the revised NHANES II (second National Health and Nutrition Examination Survey) study showed an inverse association of sodium with cardiovascular mortality [21], but other studies have contested this link [22]. Unfortunately, the two studies included different populations, a general population in the NHANES II study and a selected population of prehypertensive patients in the TOHP (Trials of Hypertension Prevention) study [23], whereas compensated CHF patients were included in the present study. These findings do not allow conclusive considerations about the management of sodium in cardiovascular diseases. Our present results indicate that renal haemodynamic and neurohormonal responses to sodium intake were tolerated without any excessive sodium and water retention and were associated with lower hospital readmissions for worsening CHF. In the group receiving the normal-sodium diet, only nine patients were readmitted during the follow-up period compared with 30 patient in the group receiving the low-sodium diet. These findings are in contrast with results from previous studies in which untreated and conventionally treated patients with CHF have been shown to accumulate excess sodium and water during dietary sodium loading [24–28]. In view of these clinical results, we hypothesized that normal sodium intake maintains a suitable arterial blood volume that inhibits the neurohormonal activation observed during a low-sodium diet, and improves both renal and hormonal alterations. In fact, the maintained plasma volume expansion determines an increase in diuresis and natriuresis associated with decreased levels of arginine vasopressin, PRA or AngII and aldosterone [29,30]. These findings could indicate, despite the small difference (27 mmol of sodium) in urinary sodium between the two groups, that the large difference in PRA observed could be due to the additive or synergistic effects of a reduction in plasma volume and sodium plasma levels in the group receiving 80 mmol of sodium with a subsequent RAAS (renin–angiotensin–aldosterone system) stimulation. On the contrary, the additive or synergistic effects of plasma volume expansion and the normal plasma sodium levels observed in the group receiving the normal-sodium diet result in an inhibition of the RAAS [31]. In addition, the difference in natriuresis confirmed that all patients followed the assigned diets. Maintenance of normal blood volume depends upon the balance between sodium intake and renal excretion. The reduced tissue perfusion, operating in CHF patients, stimulates the proximal tubule to avidly reabsorb sodium and water, limiting the amount of dilute urine that is generated and excreted. Thus, given the well-documented influence of the renal blood supply on sodium handling and the reversal of the antinatriuresis when renal perfusion is increased in these patients, it appears likely that a renal vascular response participates in sodium retention in patients with advanced CHF [31]. Recently, it has been shown [32,33] that altered sodium intake elicited the same absolute and relative haemodynamic responses in CHF patients as healthy controls. In addition, a suppression of vasoconstrictor hormones was determined in compensated CHF patients receiving high-sodium intake [32–34]. It is possible that regular sodium administration is able to restore fluid balance and to inhibit vasoconstrictor systems. These results suggest that sodium combined with appropriate diuretic therapy, and fluid intake might be beneficial in maintaining a good intravascular volume and, thereby, improving cardiac and renal blood flow. On the contrary, during sodium restriction, sodium- and water-retaining hormonal systems are activated and cardiac

forward flow is impaired [33–35]. In addition, it has been demonstrated that intravascular volume depletion induced by low-sodium intake can compromise renal function, especially if associated with ACE-inhibitors or diuretics [36,37]. Thus not only neuroendocrine activation, but also a compromised cardiorenal function, could result from intravascular volume depletion induced by low-sodium intake. Worsening indices of renal function limit symptomatic and neurohormonal therapy, lead to longer hospital stays and predict higher rates of early readmission and mortality [38–40]. The marked increase and/or normalization in serum sodium levels, observed in patients receiving normal sodium intake, is consistent with vasopressin and RAAS inhibition [41]. The association of a high diuretic dose probably did not allow excessive increases in plasma volume, and the normal sodium intake maintained normal sodium plasma levels, avoiding the effects of hyponatraemia and stimulation of the RAAS. The effects on hyponatriaemia is very important, because its has long been associated with worse outcome [42,43]. It is possible that the intensity of diuretic therapy created an opportunity for the protective benefit from higher sodium intake that would not be realized with lower diuretic doses. In addition, it has been shown that furosemide at therapeutic concentrations exerts a direct venodilator effect [24,44]. The group receiving the normal-sodium diet and oral dose of furosemide, enough to maintain a stable BW, may explain the significant reduction in BNP and aldosterone levels and PRA in comparison with the group receiving the low-sodium diet [29]. The little variation in plasma aldosterone levels and PRA suggest that a normal-sodium diet, fluid restriction and an oral dose of furosemide, enough to maintain a stable BW, did not allow further stimulation of the RAAS and, thus, maintained similar values to those observed at baseline. However, it is possible that the therapeutic effects of this treatment are not only mediated by the direct effects on renal haemodynamics, but also by neurohormonal modulation [34,46,47]. It is possible that the normal-sodium intake also allowed a continued response to diuretics by decreasing intra-renal PGE_2 (prostaglandin E_2) inactivation and improving medullary microcirculation, with a decrease in hyperosmolality and a vasopressin-induced inhibition of PGE_2. [48]. These last two mechanisms could also explain the maintenance of the decrease in BNP levels observed after 90 and 180 days.

Before planning the present study, the effects of lower doses of furosemide (100–250 mg/day) after discharge with a normal-sodium or low-sodium diet and a reduced fluid intake (1000 ml) were evaluated in two groups (15 patients per group) of compensated (NYHA class II) patients (similar to those included in the present study; S. Paterna and P. Di Pasquale, unpublished work). We observed that the group receiving the normal-sodium diet had a rapid worsening of CHF within the first 2 weeks after discharge (ten patients were readmitted for worsening CHF), and the group receiving the low-sodium diet had a dramatic rapid worsening of CHF within the first week after discharge (11 patients were readmitted for worsening CHF) S. Paterna and P. Di Pasquale, unpublished work). These findings suggested that higher doses of loop diuretics were needed to maintain BW and water balance and determined the dose of the diuretic used in the present study. Further studies comparing a normal-sodium diet plus free fluid intake compared with a normal-sodium diet plus reduced fluid intake are necessary.

Limitations of the study

The most important limitation of the study was the brief follow-up, but the interim analysis (as stipulated by the Ethical Committee) after 180 days of follow-up showed a significant decrease in readmissions rate and recommended the discontinuation of the study. These findings were sufficient to suggest that a normal-sodium diet and a reduced fluid intake when associated with a tailored therapy with furosemide may improve outcome in compensated CHF patients.

Another important limitation was the unblinded design. Although we attempted to perform a double-blind study, this was not possible because the patients receiving the prescribed diets perceived the difference in the amount of salt in the two diets. However, to reduce bias, randomization was performed by an external team of physicians blinded to the study protocol, and another set of different physicians, also blinded to the study protocol, performed the evaluation of the programmed controls and evaluated the readmitted CHF patients during follow-up. The laboratory and neurohormonal controls were also performed by physicians blinded to the study protocol. The adherence to diet, fluid intake and doses of furosemide were also controlled by two physicians blinded to the study protocol. All of these physicians communicated the controlled results after the conclusion of the study.

Another limitation was the low rate of β-blocker therapy, but the enrolled patients had compensated CHF (NYHA class II–IV), were unresponsive before hospitalization to conventional treatment (high doses of furosemide, a combination of diuretics, β-blockers, ACE-inhibitors etc.) and, during previous hospitalization, β-blocker treatment was discontinued for repeated episodes of pulmonary oedema. This low rate of β-blocker treatment did not influence the patient outcomes. It is also possible that the intensive follow-up may have affected the outcome, but this was mandatory because of novelty of the study.

In conclusion, the results of the present study suggest a surprising efficacy of a new strategy to improve the chronic diuretic response by increasing sodium intake and limiting fluid intake (1000 ml daily). Our study shows

that the use of high doses of loop diuretics were also not detrimental in the long term, as reported previously [9]. The difference between our studies and those reported previously in the literature are probably due to the association of the normal-sodium diet and the higher dose of diuretic used. In fact, studies reporting detrimental effects of long-term treatment with loop diuretics were performed in CHF patients receiving a low-sodium diet and different diuretic doses [34,49,50]. In addition, all of the readmitted patients were treated with HSS and a high dose of loop diuretics, which resulted in a rapid compensation (< 6 days), especially in patients receiving the low-sodium diet. To date, this counterintuitive approach underlines the need for a better understanding of factors that regulate sodium and water handling in chronic CHF. The observation that a normal-sodium diet improves the outcome in compensated CHF patients and that a high dose of loop diuretics, if associated with normal-sodium diet, does not result in detrimental effects in renal function suggest that sodium depletion has detrimental renal and neurohormonal effects with worse clinical outcome in patients with compensated CHF. Further studies are required to determine whether this is due to the high dose of diuretic used or the low-sodium diet.

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