Changes in thirst intensity during optimization of heart failure medical therapy by nurses at the outpatient clinic

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Abstract

Background: Thirst can be aggravated in patients with heart failure (HF), and optimized HF medication can have positive impact on thirst.

Objectives: To describe changes in thirst intensity and determine factors associated with high thirst intensity during optimization of HF medication.

Methods and Results: Patients with HF (N = 66) who were referred to an HF clinic for the up-titration of HF medication were included. Data were collected during the first visit to the clinic and at the end of the treatment program. Prior data analysis, thirst was dichotomized by the median VAS score, dividing patients into two groups: low thirst intensity (0-20 mm) and high thirst intensity (>20 mm on a visual analog scale of 0-100 mm). In total, 67% of the patients reported a higher thirst intensity after the HF up-titration program. There was no difference in thirst intensity between the patients who reached target doses and those who did not. Plasma urea (odds ratio [OR] 1.33; 95% confidence interval [CI] 1.07–1.65) and fluid restriction (OR 6.25; 95% CI 1.90–20.5) were independently associated with high thirst intensity in patients with HF.

Conclusions: Thirst intensity increased in two-thirds of the patients during a time period of optimization of HF medication. Fluid restriction and plasma urea levels were associated with high thirst intensity.

Key words: heart failure, medical therapy, outpatient clinic, thirst intensity

Introduction

Thirst is described as a “deep-seated sensation or desire for water that cannot be ignored and causes a powerful behavioral drive to drink water.”¹ Thirst can be increased in patients with chronic heart failure (HF) and has been described as a problem that causes distress in daily life.²⁻⁶ HF is an irreversible and progressive condition that causes troublesome symptoms, such as dyspnea and fatigue.⁷⁻⁹ In addition to these HF-specific symptoms, patients can also suffer from increased thirst intensity and thirst distress.²⁻⁴ Thirst intensity is defined as the severity of thirst and is sometimes accompanied by dry mouth, while thirst distress refers to what degree the patient is bothered by thirst or its associated discomfort.³

Previous findings have shown that 19% of HF patients reported persistent thirst over a period of 18 months after discharge from a HF hospitalization.¹⁰ Increased thirst can be caused by fluid restriction, which is part of the HF self-care management to reduce congestive symptoms in HF.^{3,5-7,11-13} Thirst is associated with higher serum urea, a larger number of HF symptoms, and male gender.¹⁰ The severity of thirst in patients with HF is also associated with anxiety and is higher in patients who are in the highest New York Heart Association classes (NYHA, classes III-IV).²

The renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system are highly activated in HF and are associated with the development of HF symptoms.⁷ Angiotensin II (AT II) is a part of the RAAS and increase of the concentration of AT II has been associated with increased thirst intensity in animal studies and also in human studies with patients with chronic renal failure.¹⁴⁻¹⁸ Interruption of these neurohumoral processes is the basis for the medication of HF.⁷ Optimization of the medication of HF is an important goal of HF clinics.^{7,19-21} Because the optimized HF medication should decrease neurohumoral activation, and in particular when considering the relationship between the AT II and thirst, we hypothesized that thirst intensity would be lower in patients who reach target doses of

beta-adrenergic blockers and RAAS blockers.

An understanding of the severity of thirst and its relationship to possible factors associated with thirst might help to develop future interventions aimed to prevent or alleviate troublesome thirst in patients with HF. The main objectives of the study were to (i) describe changes in thirst intensity in patients with HF during the up-titration of HF medication; (ii) compare thirst intensity in patients who reach target doses of HF medication with those who do not reach target doses; and (iii) determine the factors associated with high thirst intensity.

Methods

Design

A prospective observational study was conducted between September 2012 and August 2014 involving two hospitals with HF clinics in Sweden.

Sample

HF patients with signs and symptoms of HF were referred by a cardiologist to the outpatient HF clinics for the up-titration of HF medication (Fig. 1). The up-titration program also included information about HF, HF self-care behavior and medication. Both clinics followed similar protocols for the up-titration program.⁷

Inclusion criteria were mean left ventricular ejection fraction (LVEF) $\leq 50\%$ and age ≥ 60 years. Patients were excluded if they had an additional condition or disease associated with possible risk of increased thirst. These were: diabetes type 1, diabetes type 2 with insulin treatment; advanced kidney disease with dialysis; palliative end-of-life care; and pulmonary disease treated with oxygen.

Measurements

Thirst

A visual analog rating scale (VAS, 100 mm) was used to assess thirst intensity.²² Patients were asked to grade their thirst intensity — ranging from no thirst on the left (0) to worst possible thirst on the right (100) — by marking a cross on the line. The VAS has been validated for patients with HF and used in studies about thirst in HF.^{2,11,22} Because thirst intensity was not normally distributed, we dichotomized it. The median score of thirst intensity at exit was used to differentiate patients with high and low thirst, and the median value of thirst at exit was used because there is no standard cut point for thirst intensity. This basis was used to divide patients into a low thirst intensity group (< 21 mm) and a high thirst intensity group ($\geq$ 21 mm).

Thirst distress was measured using the Thirst Distress Scale for patients with HF (TDS-HF).^{23,24} This five-point Likert scale consists of nine statements about thirst. The patients were asked to rate each statement from 1 (strongly disagree) to 5 (strongly agree). The total score ranges from 9 to 45, with higher scores indicating higher thirst distress. The TDS-HF is newly developed and found a valid and reliable tool for measuring thirst distress in patients with HF.^{23,24} The internal consistency of the TDS-HF was high for this study sample (Cronbach's alpha 0.92).

Demographic and clinical variables

Sociodemographic and clinical characteristics, and data on medical therapy were collected from the patients' medical records or from interviews. HF medication is presented as classes of 1) RAAS blockers: a) angiotensin-converting enzyme inhibitor (ACE-inhibitor), including ramipril and enalapril, b) angiotensin receptor blocker (ARB), candesartan and losartan, c) mineralocorticoid receptor antagonist (MRA), spironolactone, and of 2) Beta-blockers:

metoprolol, atenolol, and bisoprolol.^{7,25} Data on furosemide was also collected. Additional data were collected on medical therapy that is known to increase thirst, such as opioids, antihistamines, omeprazole, benzodiazepam, and antidepressants. Information about ongoing fluid restriction and the amount of fluid restriction was collected by asking the patients.

Blood and saliva samples were used to analyze biochemical parameters known to be associated with thirst, the severity of the HF condition and of stress. Freezing point depression method was used to measure serum osmolality (coefficient of variation [CV] 3%; Advanced 2020 Multi-Sample Osmometer, Advanced Instruments Inc., Norwood, MA). Enzymatic reaction with conductivity detection was used to analyze plasma urea, potentiometry ISE of plasma sodium, and the Jaffé method to analyze plasma creatinine (CV 3-7%; DXC800, Beckman-Coulter, Brea, CA). Radioimmunoassay was used to quantify the plasma aldosterone and saliva cortisol concentrations (CV 10-11%; Wizard 1470 gamma counter, Perkin-Elmer/Wallac, Waltham, MA). An electrochemical luminescence immunoassay was used to measure levels of N-terminal of the prohormone brain natriuretic peptide, NT-proBNP (CV 8%; Modular E, Roche Diagnostics, Basel, Switzerland). All analyses were performed at the certified Study Center of Laboratory Medicine at Karolinska University Hospital, Stockholm, Sweden.

To grade the feeling of being anxious (experiencing worry or nervousness) and feeling depressed (a state of unhappiness or despondence), two questions were developed for the study because no similar short questionnaire was available. Patients were asked to rate on a five-point Likert scale (1 = strongly disagree to 5 = strongly agree) whether they felt anxious and depressed during the last few days. The face validity of the questionnaire was assessed by five patients who considered the questions relevant and clear.

Self-care behavior

HF self-care was measured using the European HF Self-Care Behavior Scale (EHFScBS-9).²⁶ Self-care is a process of maintaining health through health promoting practices and managing illness.²⁷ EHFScBS-9 measures the behaviors that patients with HF perform to maintain life, healthy functioning, and well-being.²⁶ The questionnaire has nine items rated on a five-point Likert scale (from 1 to 5). The scores were computed to the new reversed and standardized scores (0-100).²⁸ Higher scores indicate better ability for self-care behavior. The questionnaire is available in Swedish and is considered as a valid and reliable tool.²⁶ In this study, the EHFScBS-9 had a Cronbach's alpha of 0.73.

Procedures

Study nurses enrolled the patients and collected data. Baseline data were collected during their first visit, and additional data were collected at the end of the up-titration program (exit) at the HF clinic at daytime (Fig. 1). The patients completed questionnaires at baseline and exit about thirst intensity, thirst distress, and self-care behavior, and whether they were feeling depressed or anxious. They were also asked to provide blood and saliva samples, which were taken after they responded to the questionnaires. Patients rested for 10 minutes prior the blood and saliva sampling in the clinic examination room, which were collected within one hour after responding to the questionnaires. The saliva sample was collected before the blood sampling.

The local Ethics Committee approved the study (2012/42-32 Stockholm, Sweden), which complied with the Declaration of Helsinki. Written information about the study and signed consent preceded the data collection.

Data analyses

The data are presented as mean (SD), median (interquartile range [IQR]), or n (%). Changes in thirst intensity between baseline (y_1) and exit (y_2) were calculated by using delta (Δ): $\Delta = y_2 - y_1$. Concentrations of NT-proBNP were logarithmized to achieve a normal distribution.

Univariate analyses were performed to identify the variables associated with thirst intensity. Differences at baseline and exit were studied with the paired t test (continuous normally distributed), the Wilcoxon test (continuous skewed), and the McNemar's test (binominal variables). Differences between the patients with low and high thirst intensity were analyzed with the independent samples t test (continuous normally distributed), Mann-Whitney U test (continuous skewed), and chi-square test (categorical).

Multivariable logistic regression analysis was conducted with a backward method to identify the factors associated with high thirst intensity at exit. A P value of $<.05$ was considered to be significant. The data were analyzed with the use of Statistical Package for Social Sciences (SPSS) version 22 (SPSS, Chicago, Illinois).

Results

Sample characteristics

The included patients ($N=69$) were predominantly male ($n=57$, 83%), and the mean (SD) age was 73 ± 7 years. In total, 32 patients (46%) were classified as NYHA class III or IV with plasma NT-proBNP 1930 (median, IQR 1045-3258) ng/L and a mean LVEF of $32 \pm 9\%$.

Of the 69 patients, 27 patients (39%) had been hospitalized for HF less than six months prior. Forty patients (58%) had new onset HF and 29 patients (42%) had pre-existing HF. The number of days for the up-titration of the HF medication was 43 (median, IQR 27-70). The etiology for HF was ischemic heart disease ($n=24$), hypertension ($n=17$), and atrial fibrillation ($n=5$). Eleven HF patients (16%) had other etiology (cardiomyopathy, valvular disease, or

chemotherapy-caused), while the etiology was unknown for 12 patients (17%). The most common comorbidities were diabetes type 2 with diet or oral treatment (n=14) and pulmonary disease (n=7).

Education about self-care for HF was provided to 67 patients (97%) at baseline. In total, 33 patients (48%) had fluid restriction, and the mean fluid restriction volume reported by the patients was 1515 ± 152 ml/day. A few patients with HF had been prescribed other medical therapy known to increase thirst, such as omeprazole in 9 patients (12%), opioids in 2 patients (3%), and antidepressants in 1 patient (1%).

Three patients could not complete the exit visit due to worsening HF conditions, and they were excluded from the analysis (Fig. 2). Their thirst intensity at baseline was lower (VAS 0 to 13 mm) than for most of the patients who remained in the study.

Thirst intensity and changes

For the total sample, the median thirst intensity was 14 (IQR 6-36) (VAS, 0 to 100 mm) at baseline and 21 (9-41) mm at exit. The change in thirst intensity from baseline to exit for all patients was +5.5 (median, IQR -5.5 to 18.5) mm. Thirst intensity increased in 44 patients (67%), while thirst intensity decreased from baseline to exit in 22 patients (33%). There was a significant difference in the thirst intensity change between the patients who increased vs. decreased during the study (median +13 [IQR +5 to 27] vs. -26 [-40 to -5] mm; $P < .001$).

There was no statistically significant difference in thirst intensity at baseline between patients in the high thirst intensity group and the low thirst intensity group (Table 1). Thirst intensity at exit in the high thirst intensity group was median 39 [30-61] mm, and in the low thirst intensity group 9 [5-14] mm $P < .001$. The change in thirst intensity from baseline to exit was greater for patients in the group with high thirst intensity compared with patients in the low thirst intensity group (median +18 [+9 to 36] vs. -3 [-33 to 5] mm; $P < .001$).

Heart failure medication, fluid restriction and thirst intensity

Of patients who were prescribed ACE-inhibitors (n=48) 73% reached the target dose according to the guidelines, and for those prescribed Beta-blockers (n=63) 41% reached the target dose (Table 2). There were no differences in thirst intensity between the patients who reached their target doses and those who did not (Table 2). For those patients having fluid restriction (n=28) thirst intensity was significantly higher compared with those patients who did not have fluid restriction (n=38) at exit (median 37 [IQR 19-54] vs. 13 [6-26] mm; $P=.001$).

Factors related to thirst intensity

A univariate analysis showed that patients with high thirst intensity more often had fluid restriction (n=21 vs. 7; $P<.001$) and higher plasma urea (median 9 [7-11] vs. 7 [IQR 5-8] mmol/L, $P=.002$). They also were more often in NYHA class III or IV (n=16 vs. 7; $P=.02$) (Table 1). Patients with high thirst intensity also had higher thirst distress (median score 21 [14-25] vs. 12 [10-18]; $P=.001$) and a higher concentration of NT-proBNP (2300 [787-4310] vs. 1260 [349-2860] ng/L; $P=.03$), and more often had diuretic doses ≥ 40 mg per day at exit (n=18 vs. 10; $P<.05$).

The stress marker saliva cortisol increased from baseline to exit in patients with high thirst intensity (median 20 [12-26] to 26 [19-37] nmol/L; $P=.001$) (Table 1). More patients in the high thirst intensity group compared with the low thirst intensity group increased in NYHA class (n=4 vs. 0; $P=.039$) and got more anxious (n=15 vs. 7; $P=.037$). Moreover, fluid restriction was ended less often in patients with high thirst intensity (n=1 vs. 7; $P=.024$) and additional patients had fluid restriction prescribed (n=4 vs. 0; $P=.014$).

Univariate variables showing a difference of $P<0.05$ were entered into the multivariable logistic regression analysis. Having fluid restriction (OR 6.02; $P=.003$) and higher plasma

urea (OR 1.33; $P=.01$) were independently associated with high thirst intensity (Table 3). There was no association between thirst intensity at baseline and thirst intensity at exit. No multicollinearity was found for any of the variables in the regression (variance inflation factor range 1.2-2.2).

Discussion

This is the first study to investigate thirst intensity changes and thirst intensity-related factors in patients with HF during the HF up-titration program. The main finding was that high thirst intensity in patients with HF is strongly associated with fluid restriction, independent of disease severity or HF medication. The baseline thirst intensity for all patients was rather low (VAS, median 14 [IQR 6-36] mm), but 67% of patients increased in thirst intensity during the up-titration period. This is in contrast to the study hypothesis that optimized HF medication would lower thirst intensity. We did not find any effect on thirst intensity by reaching the target doses.

Fluid restriction can be seen as self-care in patients with HF, but this can increase the thirst.^{3,5,6,11,29} Thirst intensity was significantly higher in patients with fluid restriction compared to those without in the present study. In guidelines, fluid restriction is recommended to be reasonable to patients with advanced HF to relieve symptoms and congestion.^{7,13} In practice, patients are often advised to restrict their volume of fluid to 1.5-2.0 L/day, but more recent recommendations propose a use of a weight-based fluid restriction (30 mL/kg body weight or 35 mL/kg if body weight >85 kg), which may cause less thirst.^{7,11,13} Routine fluid restriction is not recommended to patients with mild to moderate HF symptoms.^{7,13} Coaching might help those patients who need to follow fluid restriction for example by exchanging ideas with the patients about how best to spread out fluid intake over the course of the day.³⁰ Both resources and policy are needed to optimally educate patients,

but also health care providers need to optimally advocate the evidence-based pharmacological and non-pharmacological therapy.^{31,32}

Thirst increased in 67% of the patients, but our study revealed that thirst intensity at baseline was not associated with thirst intensity at exit. This finding is consistent with a previous study reporting on temporary thirst in patients with HF.¹⁰ In that study, it was also found that patients who were once thirsty were more likely to become thirsty again. There are naturally personal perspectives of symptom experiences, which must be taken into account when developing interventions to relieve thirst.⁸ Clinicians need to assess and evaluate thirst intensity in patients with HF, as thirst can be or become a troublesome symptom. Information about the severity of thirst can also address a low fluid intake if patients continue with fluid restriction without having need for it.

The concentration of plasma urea was also higher in the patients with high thirst intensity. The highly activated neurohormones in HF cause vasoconstriction of the afferent arterioles.³³ This action leads to a reduction in renal perfusion and increase in water and urea reabsorption, resulting in an increased urea.³³ Plasma urea may provide a comprehensive assessment of cardiorenal interactions and is a prognosticator of mortality, rehospitalization, and the adverse effects of diuretics.³³⁻³⁵ Although the concentration of plasma urea in our study was not very high, it has been shown that even mild to moderate elevations in urea can be predictive in patients with HF.³³ HF patients with high thirst intensity may have higher neurohormonal activation reflected by the plasma urea.

We also found that the patients with more severe HF, reflected by higher plasma NT-proBNP and more often classified as NYHA III-IV, also had higher thirst intensity. Another interesting finding in this study was that patients who had increased thirst intensity during the study also increased in the stress-related biomarker cortisol, which might be caused by the high sympathetic activity in HF. Several of the patients with high thirst intensity reported that

they felt more anxious and depressed as well. This is consistent with a previous study, which showed that thirst intensity was higher in HF patients with anxiety.²

Dehydration is a known cause of increased thirst in healthy persons, and the concentration of serum osmolality was slightly higher than normal in our study.^{14,15} A large number of the study patients had fluid restriction, which contributes to a low fluid intake and thereby increases the risk of dehydration. But there was no association between the osmolality and high thirst intensity in patients with HF. Dehydration can also be caused by high doses of diuretics, and in our results we could see that patients with high thirst intensity were more often prescribed higher doses of diuretics. However, thirst is not considered a good test to indicate dehydration in people older than 65 years.³⁶

Nurses and cardiologists should make patients with HF aware that they can become thirsty when they have fluid restriction. Interventions to prevent troublesome thirst in patients with HF at outpatient clinics could include a standardized plan with (i) screening for patients with thirst, (ii) assessment of thirst intensity and thirst distress, (iii) screening for patients with thirst and fluid restriction and evaluate the usefulness of fluid restriction in consultation with a cardiologist, and (iv) individual self-care management to alleviate troublesome thirst.

The majority of the study participants were men, which limits the generalizability to all HF patients. Because there is no cut-off value for low and high thirst intensity in patients with HF, the median value of the sample was used. This is a commonly used method, but it can create future problems when comparisons between studies are being made. Not all of the patients were at target doses of HF medication, which can make the results difficult to interpret and draw conclusions from. Another limitation is the somewhat short up-titration period, giving an uncertainty with regard to the expected attenuated neuroactivation. In

addition, we did not have information on the patients' true fluid intake, only the self-reported restricted fluid volume.

Conclusions

Thirst intensity increased in two out of three patients during the up-titration of HF medication in outpatient HF clinics. Important factors associated with high thirst intensity were fluid restriction and a higher concentration of serum urea. This study confirms the need for clinicians to assess thirst intensity and to carefully consider the necessity of fluid restriction in patients with HF.

What's new and important

- Thirst intensity increased in 67% of the HF patients during the HF medical therapy up-titration program. Optimization of HF medication did not have an impact on thirst intensity.
- Clinicians should be aware that current thirst intensity may not predict the trajectory of thirst. Even if people do not have thirst now, it can become a troublesome symptom and therefore clinicians need to assess and evaluate thirst intensity regularly in patients with HF.
- Patients with fluid restriction were 6.2 times more likely to have high thirst intensity compared to those without fluid restriction. Interventions to relieve thirst in patients with HF should be approached individually and are dependent on the underlying factors. In addition to temporary solutions, such as sucking an ice cube, we propose preventive interventions against increased thirst. Current guidelines do not advise strict fluid restriction in all HF patients and this should be implemented in practice.

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Figures

Figure 1 The up-titration program at the outpatient heart failure clinic.

Figure 2 Flowchart of patient inclusion from identification to exit. HF indicates heart failure; LVEF, left ventricular ejection fraction.

Table 1 Demographic and clinical characteristics of the study patients with heart failure in group low thirst intensity and group high thirst intensity, comparisons between the groups at baseline and at exit, and differences between baseline and exit within the groups.

Variable	Low thirst intensity at exit		High thirst intensity at exit	
	(n=33)		(n=33)	
	Baseline		Baseline	
Demographic				
Age, years	72± 8		74± 7	
Gender, male n (%)	27 (82)		28 (85)	
Cohabiting, n (%)	16 (49)		21 (64)	
Clinical characteristic				
LVEF, %	33± 9		32± 10	
Length of up-titration, days	45 (29-81)		42 (27-64)	
	Baseline	Exit	Baseline	Exit
Questionnaires				
Thirst intensity, VAS 100 mm	10 (5-45)	9 (5-14)	18 (7-33)	39 (30-61)**

Thirst distress, scale 9-45	13 (10-21)	12 (10-18)	21 (12-23)	21 (14-25)**
HF self-care behaviour, scale 0-100	57±24	64±26	59±20	58±14
Feeling anxious, n (%)	8 (24)	8 (24)	6 (18)	14 (42)
Feeling depressed, n (%)	7 (21)	8 (24)	8 (24)	13 (39)

Clinical assessment

NYHA class III-IV, %	12 (36)	7 (21)	17 (52)	16 (49)*
Weight, kilogram	84±17	83±16	83±18	83±18
Heart rate, beat/minute	73±21	66±11	67±10	69±11

Physiological assessment

P/NT-proBNP, ng/L	1580 (477-2790)	1260 (349-2860)	2230 (1175-5015)*	2300 (787-4310)*
P/Aldosterone, pmol/L	162 (69-285)	164 (75-304)	229 (101-361)	258 (107-402)
P/Urea, mmol/L	7 (5-8)	7 (5-8)	8 (6-11)*	9 (7-11)**
P/Creatinine, µmol/L	97±27	96±29	109±30	111±27*
S/Osmolality, mosmol/kg	299±7	298±5	301±6	301±6
P/Sodium, mmol/L	139±3	139±2	140±3	139±2
Saliva cortisol, nmol/L	25 (19-34)	23 (17-32)	20 (12-26)	26 (19-37) ^{† †}

Treatment

Fluid restriction, n (%)	14 (42)	7 (21) [†]	18 (55)	21 (64)**
ACE, n (%)	25 (76)	26 (79)	23 (70)	22 (67)
ARB, n (%)	4 (12)	7 (21)	7 (21)	9 (27)
Beta-blocker, n (%)	31 (94)	32 (97)	32 (97)	31 (94)
MRA, n (%)	3 (9)	6 (18)	5 (15)	7 (21)
Diuretic, n (%)	22 (67)	19 (58)	24 (73)	23 (70)
Diuretic ≥40 mg, n (%)	14 (42)	10 (30)	21 (64)	18 (55)*

Values are mean ± SD, median (25th and 75th percentiles) and number of patients (%).

LVEF= left ventricular ejection fraction; HF= heart failure; NYHA= New York Heart Association; P= plasma;

S= serum; NT-proBNP= N-terminal of the prohormone brain natriuretic peptide; ACE= angiotensin-

converting enzyme; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

P value between groups *= ≤ 0.05; **= ≤ 0.01, tested with the Chi –square test, Mann-Whitney U test, or the unpaired t test.

P value within group [†]= ≤ 0.05; ^{† ‡}= ≤ 0.01, tested with the McNemar's test, Wilcoxon test or the paired t test.

Table 2 Thirst intensity at study exit for patients with heart failure (n=66) who reached the target doses after up-titration with heart failure medication compared with patients who did not reach the target doses.

HF medication*	At target dose		Not at target dose	
	N (%)	Thirst intensity (VAS)	N (%)	Thirst intensity (VAS)
ACE	35 (73)	18 (8-35)	13 (27)	27 (5-68)
ARB	7 (44)	18 (9-47)	9 (56)	21 (15-47)
Beta-blocker	26 (41)	19 (6-49)	37 (59)	21 (10-39)
MRA	13 (100)	22 (9-49)	-	-

HF= heart failure; N=number of patients; VAS= visual analogue scale 0-100 mm.

ACE= angiotensin-converting enzyme; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

*Not all patients were prescribed all of the heart failure medication.

Significant values: there were no significant differences in thirst intensity between the groups.

Table 3 Logistic regression with variables associated with high thirst intensity for patients with heart failure (n=66).

Variable	Odds Ratio	Confidence Interval 95%
Fluid restriction (no/yes)	6.25	1.90-20.5 **
P/Urea, mmol/L	1.33	1.07-1.65 *
NYHA class III-IV (no/yes)	1.99	0.56-7.00
Thirst intensity at baseline (100 mm)	0.99	0.96-1.02
Diuretic $\geq$ 40 mg/day (no/yes)	1.85	0.46-7.36
P/Creatinine, micromole/L	0.98	0.95-1.02
NT-proBNP, ng/L	1.34	0.35-5.17

Model: $R^2=0.42$ (Nagelkerke); NYHA, New York Heart Association; P, plasma; S, serum.

Theoretically relevant variables that were related by $P < .05$ in the univariate analyses at exit were entered into the backward logistic regression ($P < .10$ retention). Thirst intensity at baseline was included in the regression to test the association between thirst intensity at baseline and the variables related to thirst intensity at exit. Thirst distress was excluded from the regression because it was considered to be the outcome of thirst intensity and could bias the results.

Significant values presented as $* = \leq 0.05$; $** = \leq 0.01$.

Optimization of heart failure medical therapy at the outpatient heart failure clinic

The Up-titration Program

Up-titration of heart failure medical therapy: beta-adrenergic blockers; *and/or* angiotensin-converting enzyme inhibitor; *and/or* angiotensin receptor blocker; *and/or* mineralocorticoid receptor antagonist.

Information about heart failure self-care behavior: weighing every day; limiting the amount of fluids (1.5-2.0 L/day); exercising regularly; contact nurse/doctor: if shortness of breath increases, *or* if legs are more swollen, *or* if gaining weight more than 2 kg in 3 days, *or* experiencing fatigue; eating low-salt diet; and taking medication as prescribed.

Information about heart failure and medical therapy in heart failure.