

Fluid REstriction in Heart Failure vs Liberal Fluid UPtake: Rationale and Design of the Randomized FRESH-UP Study

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ABSTRACT

Aims: It is common practice for clinicians to advise fluid restriction in patients with heart failure (HF), but data from clinical trials are lacking. Moreover, fluid restriction is associated with thirst distress and may adversely impact quality of life (QoL). To address this gap in evidence, the Fluid REstriction in Heart failure vs liberal fluid UPtake (FRESH-UP) study was initiated.

Methods: The FRESH-UP study is a randomized, controlled, open-label, multicenter trial to investigate the effects of a 3-month period of liberal fluid intake vs fluid restriction (1500 mL/day) on QoL in outpatients with chronic HF (New York Heart Association Classes II–III). The primary aim is to assess the effect on QoL after 3 months using the Overall Summary Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ). Thirst distress, as assessed by the Thirst Distress Scale for patients with HF, KCCQ Clinical Summary Score, each of the KCCQ domains and clinically meaningful changes in these scores, the EQ-5D-5L, patient-reported fluid intake and safety (ie, death, HF hospitalizations) are secondary outcomes. The FRESH-UP study is registered at ClinicalTrials.gov (NCT04551729).

Conclusion: The results of the FRESH-UP study will add substantially to the level of evidence concerning fluid management in chronic HF and may impact the QoL of these patients. (*J Cardiac Fail* 2022;28:1522–1530)

Key Words: Chronic heart failure, Fluid restriction, Liberal fluid intake, Quality of life.

Heart failure (HF) is a growing global health problem affecting approximately 1 in 5 people and

leading to high morbidity and mortality rates and reduced quality of life (QoL).^{1–3}

Congestion can cause signs and symptoms, such as dyspnoea, orthopnoea and peripheral oedema, and may result in hospitalization, so it has been common clinical practice for many decades to advise patients with chronic HF to limit their fluid intake to, eg, 1500 mL/day. Strikingly, this advice is based on mere intuition rather than clinical evidence. In fact, the limited data available suggest that fluid restriction may not be favorable compared to liberal fluid intake.^{4–7}

Although the beneficial effect of fluid restriction in chronic HF is uncertain, it has been suggested that it may even adversely impact these patients.^{4,8–10} Fluid restriction as a part of daily chronic HF care is, from patients' perspectives, challenging and cumbersome, because (1) patients have to monitor fluid intake; (2) fluid restriction leads to thirst distress; and (3) it constantly confronts patients with their chronic disease.⁸ Consequently, nonadherence is common, which may detrimentally impact doctor/nurse-patient relationship and/or patients' self-

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esteem.⁸ All these factors of fluid restriction may contribute to a reduced QoL for patients with HF.

In the absence of supportive evidence, the recent ESC guidelines for the diagnosis and treatment of acute and chronic HF provide only a general recommendation supporting fluid restriction for selected patients with symptomatic HF, without providing a level of evidence, similar to the American College of Cardiology/American Heart Association (ACC/AHA) guideline of 2022.^{1,2} There is a demand for randomized trials, which is supported by the recent ESC and ACC/AHA guidelines that state explicitly that more evidence is needed about the effects of fluid restriction.^{1,2,11}

To address this gap in evidence, the effect of liberal fluid intake vs fluid restriction on QoL of outpatient patients with chronic HF will be investigated in a randomized clinical trial.

Study Design

Standard Protocol Items

Recommendations for Interventional Trials (SPIRIT) guidelines were followed during the design of the study's protocol.¹²

Aim of the Study

The primary aim of the FRESH-UP study is to investigate the effect of liberal fluid intake vs fluid restriction of 1500 mL/day on QoL in outpatients with chronic HF at 3 months after randomization, as assessed by the Overall Summary Score (OSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ).¹³

Design Overview

The FRESH-UP study is a pragmatic, 1:1 randomized, open-label, controlled, multicenter clinical trial of the effect on QoL of a lifestyle advice of either liberal fluid intake or fluid restriction of 1500 mL/day for 3 months in outpatients with chronic HF (Visual Take-Home Graphic). The hypothesis of the study is that liberal fluid intake leads to greater QoL compared to fluid restriction.

Patients will be recruited and followed according to standard clinical practice with a 3-month interval, including standard clinical assessment (eg, anamnesis, physical examination and laboratory analyses). At baseline and after 3 months, patients are asked to fill in the QoL questionnaires. In addition, at week 6, patients are asked to report their daily fluid intake for 1 week. After the intervention period, further fluid management is up to the discretion of the treating physician and the patient.

For additional clinical follow-up to assess clinical events, the patient is contacted after 6 months. The study flowchart is depicted in [Fig. 1](#).

Patients

The source population comprises all adult outpatients with chronic HF at the participating centers (currently 4; $n \approx 500$ –1500 per site). All study patients are 18 years or older, have been diagnosed with chronic HF (according to the prevailing [ESC] guidelines) at least 6 months before randomization, have mild to moderate symptoms (New York Heart Association [NYHA] class II or III) and had no hospital admission for HF, invasive procedures in the past 3 months or recent changes in HF therapy. Stable optimal guideline-directed therapy (GDMT) is assumed, because patients have been diagnosed with HF for at least 6 months and have had no recent changes in HF therapy. The GDMT score will be used to grade the level of GDMT.¹⁴ Full inclusion and exclusion criteria are detailed in [Table 1](#).

Randomization and Data Management

Randomization takes place after the patient is eligible according to the inclusion and exclusion criteria and has provided informed consent and completed the QoL questionnaires. Patients are 1:1 randomized using Castor Electronic Data Capture (EDC) with a random block randomization algorithm and stratified randomization per each including center. Castor EDC is also used as electronic case record form.

Intervention

On a background of standard GDMT, patients are randomized to standardized lifestyle advice by the treating physician and/or nurse practitioner of either liberal fluid intake or fluid restriction of 1500 mL/day for a period of 3 months. Other lifestyle interventions (eg, sodium restriction or activity) remain unadjusted.

Fluid restriction of 1500 mL/day is considered standard clinical practice, and liberal fluid intake is considered the investigational treatment.

Outcome

The primary outcome is QoL at 3 months as assessed by KCCQ-OSS.¹³ The key secondary outcome is thirst distress as assessed by the Thirst Distress Scale for patients with HF (TDS-HF).¹⁵ Other secondary outcomes are QoL at 3 months as assessed by KCCQ Clinical Summary Score (CSS), each of the KCCQ domains and the proportion of patients with clinically meaningful changes in these scores, a visual analogue scale (EQ-5D-5L), patient-reported fluid intake in week 6, and safety.¹³

Apart from the KCCQ score, which also contains important safety information,¹⁶ safety will be assessed by the number of occurrences (and the

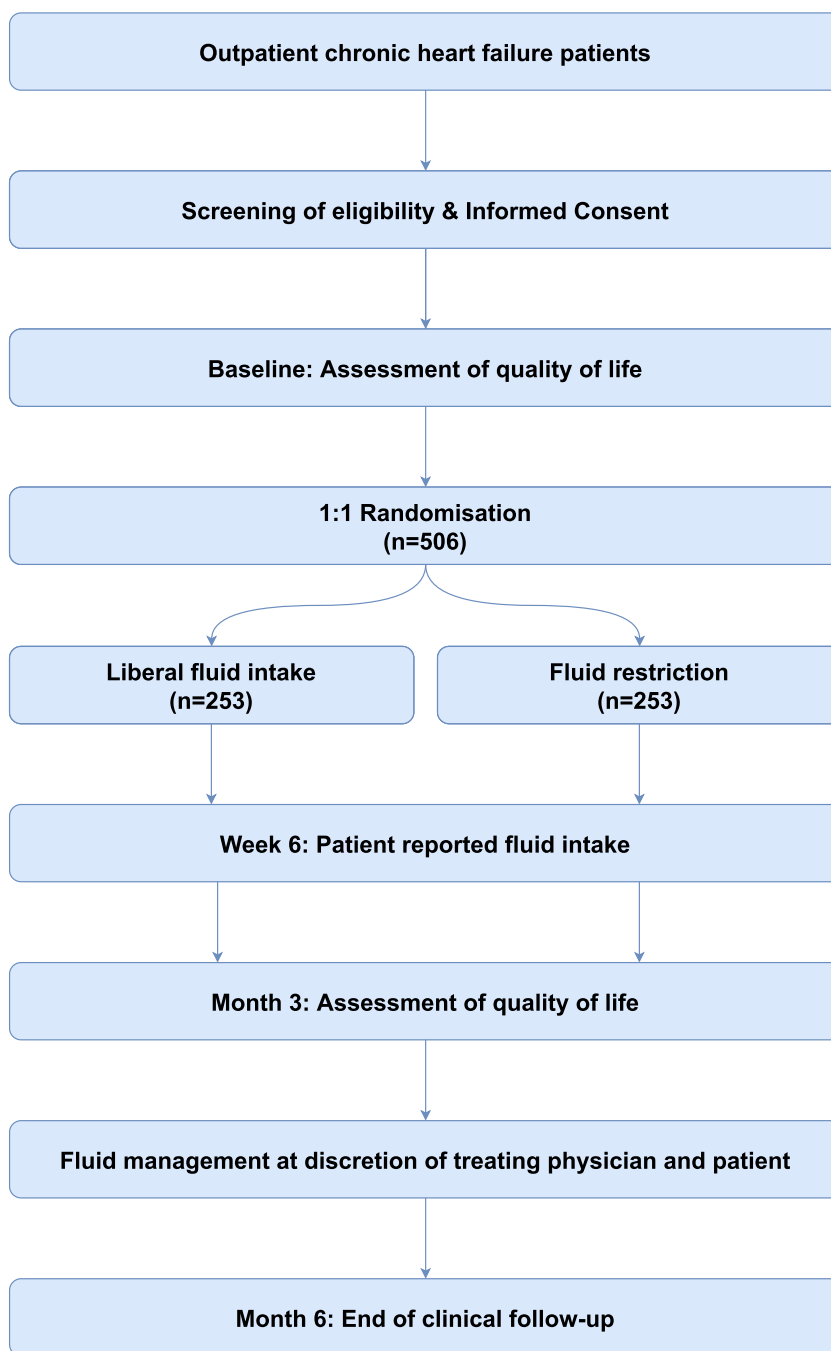


Fig. 1. Study flowchart.

time to the first occurrence) of the composite clinical endpoint: death, all-cause or unplanned HF hospitalization, and the requirement to apply intravenous loop diuretics, which will be evaluated at the 3- and 6-month clinical follow-up. Furthermore, the occurrence of acute kidney injury ($\geq 50\%$ decline in estimated glomerular filtration rate relative to baseline or decrease of > 30 mL/min/1.73m² and to a value below 60 mL/min/1.73m²) will be evaluated.

In addition, exploratory subgroup analyses of the respective outcome measures: sex at birth, including center, HF type, NYHA class, age, diuretic dosage at

start, and baseline biomarker concentrations (sodium, urea, creatinine, and NT-proBNP) will be performed.

Other Study Parameters

Data on age, sex, comorbidities, and concomitant medication are collected according to standard clinical practice. At baseline and after 3 and 6 months, data on weight, vital parameters, serum biomarkers (NT-proBNP, sodium, creatinine, hemoglobin,

Table 1. FRESH-UP Study Inclusion and Exclusion Criteria

| | |
|--------------------|--|
| Inclusion criteria | <ul style="list-style-type: none"> • Diagnosis of chronic HF with NYHA class II/III according to the prevailing (ESC) guidelines > 6 months prior to randomization • Adult (age \geq 18 years) |
| Exclusion criteria | <ul style="list-style-type: none"> • Reversible cause of HF (thyroid disorders, severe anemia, vitamin deficiencies, etc.) • Hospital admission for HF within 3 months of randomization • Chronic HF with NYHA class I or IV • Hyponatremia at baseline (sodium < 130 mmol/L) • eGFR of < 30mL/min/1.73m² at baseline • Changes in HF medical therapy in past 14 days prior to randomization • Scheduled cardiac surgery within 3 months of randomization • Recent (within 3 months) coronary intervention (PCI or CABG) or implantation of pacemaker device • Comorbidity for which fluid restriction is advised by a different treating physician (eg, nephrologist) • Life expectancy of fewer than 6 months • The treating clinician believes that participation in the study would not be in the best interests of the patient • Inability to provide informed consent |

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

hematocrit), and medication changes (diuretics, in particular) is assessed.

Follow-up Assessment

Patients visit the outpatient clinic every 3 months and undergo standard clinical assessment (eg, anamnesis, physical examination and laboratory analysis).

All patients are asked to fill in 3 validated questionnaires concerning QoL (the KCCQ, the TDS-HF and the EQ-5D-5L) at baseline and at 3 months for the primary and secondary endpoints.^{13,15} In addition, an investigator notifies the patients prior to week 6 by telephone to report their fluid intake for 1 week in a fluid-intake diary or via Castor EDC. Study participation ends after clinical follow-up at 6 months.

Hereafter, patients can participate in a long-term follow-up registry with telephone contact every 6 months about current fluid management and the occurrence of all-cause hospitalization and mortality.

Discontinuation of Study Treatment

There are multiple scenarios (eg, dehydration, fever or any other scenario that may lead to a decreased circulatory volume with consequent end-organ injury, prerenal acute kidney injury, severe hyponatremia [$<$ 125mmol/L], or progression of HF to NYHA class IV), for which the treating physician

at his/her discretion can judge that the advice according to randomization is no longer appropriate, and fluid management should be adjusted accordingly. Patients will be instructed to contact their treating physician and/or specialized HF nurse in case of doubt about whether to adhere to the randomized treatment regimen.

Statistical Considerations

Baseline descriptive statistics will be presented by treatment arm. Continuous variables will be assessed for normal distribution and reported as means (standard deviation) or medians (interquartile range), whichever is appropriate. Continuous data will be compared using a Student *t* test or a Mann-Whitney U test, whichever is appropriate. Categorical variables will be presented with numbers (percentages) and compared using a χ^2 or Fisher exact test, whichever is appropriate. A *P* value of $<$ 0.05 will be considered significant.

Primary Endpoint Analysis

The difference between the 2 treatment arms in QoL after 3 months, as assessed with KCCQ-OSS, will be tested with the use of an ANCOVA analysis, using baseline QoL as a covariate. A *P* value of $<$ 0.05 will be considered significant.

For the primary analysis, the intention-to-treat principle will be applied. In the unlikely case that

any baseline scores on the KCCQ-OSS are missing, they will first be multiply imputed using imputations drawn from the distribution of the full study population. Following this, the imputation model will be specified separately by treatment arm and will include baseline and 3-month KCCQ-OSS as well as any auxiliary variables that are considered to be associated with the outcome or with the probability of missing the 3-month KCCQ scores.

A sensitivity analysis will be performed to examine the sensitivity of the results to missing data assumptions. For this sensitivity analysis, a delta-adjustment approach will be applied, with a fixed constant (to be elicited from a panel of experts) added to the values imputed under the standard missing at random (MAR) procedure.¹⁷

Secondary Endpoint Analysis

The difference in thirst distress between the 2 treatment arms after 3 months, as assessed by TDS-HF, will be tested applying the same methods as those described for the analysis of the primary endpoint. The difference between groups in proportion of patients with clinically meaningful changes (defined as a difference of 5 points) in KCCQ-OSS and KCCQ-CSS and the percentage of events (death, all-cause hospitalizations, the need for intravenous loop diuretics, and acute kidney injury) will be tested with a χ^2 or Fisher exact test, whichever is appropriate. The difference between groups in patient-reported fluid intake will be analyzed by a Student *t* test or a Mann-Whitney U test, whichever is appropriate.

The primary and key secondary endpoints will be tested hierarchically. Other secondary endpoints will be considered supportive only.

Analysis Populations

The intention-to-treat principle will be used for the primary analysis. In addition, an analysis according to the per-protocol principle will be performed. The patient-reported fluid intake in week 6 will be used to assess whether the patients in the fluid restriction arm did adhere to the fluid restriction of 1500 mL/day.

Sample Size Calculation

Sample-size calculation was performed with the software package G*Power 3.1.7 (Dusseldorf, Germany) and was performed as previously described in methods for ANCOVA analysis, using baseline QoL as a covariate.¹⁸

A correlation of 0.88 between baseline and follow-up KCCQ-OSS was assumed.^{13,16} Furthermore, a follow-up KCCQ-OSS of 66.25 with a standard

deviation of 20 for liberal-fluid-intake group was assumed.¹⁹⁻²¹ Next, a 2.5-point difference in KCCQ-OSS follow-up at 3 months between both randomization groups was assumed, based on corresponding results of recent randomized HF trials.¹⁹⁻²¹ To test this difference at a *P* value of 0.05 and a power of 80%, a total of 454 evaluable patients is needed. Anticipating a drop-out rate of 10%, a total of 506 patients will be enrolled.

This sample size also allows adequate power to assess a 1.5-point difference in thirst distress at 3 months between both randomization groups (mean score of 16 with a standard deviation of 8 and an intraclass correlation of 0.88; *P* value: 0.05 and power: 80%).

Study Organization

The study was conceived and designed by the Trial Steering Committee and sponsored by the Radboud University Medical Centre in Nijmegen. The study protocol, written informed consent form and patient-recruitment procedures have been approved by the institutional review board. Monitoring will be done according to a predefined monitoring plan, in accordance with the prevailing guidelines. The review and adjudication of all secondary clinical endpoints will be conducted by an independent event-adjudication committee.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) is established to perform analyses according to the DSMB charter (Appendix 1). The composition of the DSMB comprises a chair who is a clinical expert, a second clinical expert and an experienced statistician, who are independent of the steering committee.

The DSMB has 2 mandates. First, to perform 2 interim analyses, when data are available, of 33% and 66% of the patients for safety concerning the occurrence of the clinical endpoints and, second, to monitor the overall conduct of the trial, eg, to monitor the enrolment rate.

Moreover, the DSMB is entitled to advise stopping the study prematurely based on the above mandates.

The advice and reports of the analyses of the DSMB will be sent to the steering committee of the study and to the accredited medical research ethics committee (MREC). Should the steering committee decide not to fully implement the advice of the DSMB, the steering committee will send the advice to the reviewing MREC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Independent Event Adjudication Committee

An independent Event Adjudication Committee comprises 3 clinical HF experts, who will adjudicate the cause of death and any hospitalizations as either HF-related or not. The events of interest will be adjudicated according to a predefined scheme based on the consensus of 2 committee members; in case of nonconsensus, the third committee member will provide final adjudication. The event-adjudication committee members are independent of the steering committee and the DSMB.

Ethical Considerations

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. The MREC of the Radboud University Medical Centre in Nijmegen has passed a positive judgment on the study. All patients will provide written informed consent before participating in the trial. The FRESH-UP study is registered at ClinicalTrials.gov (NCT04551729).

Discussion

The FRESH-UP study is the first randomized, multicenter trial to investigate the effects of liberal fluid intake vs fluid restriction on QoL in patients with chronic HF. The results of this study will lead to more evidence-based guidelines on fluid management and may have a major impact on the QoL of patients with chronic HF. Due to its pragmatic design, the FRESH-UP study approximates daily clinical practice.

Currently, only 2 small comparative, randomized studies have been published on the effect of fluid restriction solely, both in fewer than 75 patients.^{4,5} In these 2 studies, fluid restriction showed no clinical benefit compared to unrestricted fluid intake, whereas liberal uptake resulted in an improved patient-reported outcomes, ie, less thirst. This has made clinicians and investigators begin to question the value of fluid restriction in patients with HF.

Apart from the potentially detrimental effect on QoL, several authors have previously disputed the rationale of fluid restriction in HF management.^{4,6,7,22}

Several arguments suggest that fluid intake is most likely not the key factor in the development of (acute) decompensation.

First, normal fluid intake is considered to be 2000–2500 mL, depending on sex, which differs little compared to fluid restriction.²³ The effective circulating volume (ECV) composes only 12% of the total body water. As water is distributed via the oncotic pressure among various components of the body (eg, intra- and extracellular fluid), a relatively large expansion of the total body water will lead to just a small increase in ECV.^{24,25} For example, an intake of 2500 mL (ie, an extra intake of 1000 mL) will, therefore, add only 120 mL to the ECV, which is not expected to result in congestion complaints.

Second, this amount of fluid pales in comparison to the large fluid shifts caused by sympathetic stimulation of the venous reservoir.²⁴ The venous system contains approximately 70% of the total blood volume and has a much higher compliance compared to the arterial system. Due to plenty adrenergic receptors of the venous system, a sympathetic stimulus results in a large response, which causes rapid fluid shifts from the venous reservoir to the ECV, up to 800 mL of blood in a matter of seconds.²⁴

Third, water clearance is sodium-mediated and is conducted mainly by the kidney through a passive process in which water moves according to the osmotic pressure gradient between the tubule lumen and its surrounding interstitium. As long as renal perfusion is maintained, the kidneys can produce urine with a range of osmolalities, and in the absence of hyponatremia, excessive fluid should be surmountable.²⁵

However, it should be acknowledged that a specific subgroup of patients with HF may potentially benefit from strict fluid restriction. In a highly vulnerable population with limited diuresis and with recent discharge after acute HF, it was suggested that fluid restriction to < 1000 mL/day may lead to a reduction in HF readmissions.²⁶ Also, in the presence of hyponatremia, fluid restriction may be indicated.^{1,2} Therefore, the selected study population, the more stable outpatients with HF, may benefit less from fluid restriction compared to the decompensated inpatients.^{4,6,7}

Rationale for Intervention

Normal fluid intake is considered to be 2000–2500 mL, depending on sex.²³ Although there are various fluid-restriction strategies, fluid intake in the FRESH-UP study is limited at 1500 mL/day because this strategy is most frequently reported in studies and probably resembles current clinical practice in most hospitals.²⁷

The treating physician and/or HF nurse provides lifestyle advice according to a standardized script to avoid possible bias of the open-label design. Previously given lifestyle advice, other than the fluid

advice, will remain unadjusted. Hereby, the additional value of the fluid restriction or liberal fluid intake will be investigated.

There is no strict oversight of actual fluid intake, aside from the self-reported intake; therefore, therapy compliance is expected to be acceptable and comparable to the real-world situation.²⁸

Rationale for the Outcome Measures

The KCCQ is a well-validated questionnaire specific to HF and is sensitive to changes in clinical status. An improvement in general well-being in terms of mental health is expected to affect the score positively, whereas any deterioration of HF is expected to affect the score negatively. Moreover, a change in KCCQ is predictive of future adverse disease progression and mortality and has even been demonstrated to be more predictive than the NYHA classification.^{16,29,30} Therefore, effects on QoL (assessed by OSS), symptoms and functional limitations (assessed by CSS and other KCCQ domains), and self-efficacy, as well as signals of potential safety issues, are tested with this questionnaire.¹⁶ This is endorsed by the U.S. Food and Drug Administration, which qualified the KCCQ as Clinical Outcome Assessment.³¹

As a key secondary outcome measure, the TDS-HF, will be used. Thirst-distress measurement is relevant, as thirst decreases QoL in HF patients.⁸ The 8-item TDS-HF is the only validated questionnaire available in 22 languages, which evaluates thirst distress in patients with HF. It was developed from the original TDS for patients with renal failure. The TDS-HF combines 8 items about the patient's mouth feeling (ie, "My mouth feels dry when I am thirsty") and general claims about thirst (ie, "My thirst feels difficult to overcome"), which are scored from 1 (strongly disagree) to 5 (strongly agree).¹⁵ The total score ranges from 8–40.

To reduce open-label bias, randomization will take place after all baseline QoL questionnaires have been completed.

Limitations

Although the lifestyle advice is standardized for optimal adherence, there is only limited insight into the actual fluid intake of the patients. Patient-reported fluid intake at week 6 may not be fully reliable. However, this strategy may best reflect clinical reality. Second, the outpatient population with HF in the participating centers is made up primarily of white patients, which possibly limits the generalizability of our results to all patients with HF. Last, a period of 3 months may not reflect the effect of years of liberal (or restricted) fluid intake.

Current Status

Currently, at the end of May 2022, there are 4 participating centers, Radboud University Medical Centre, Maastricht University Medical Centre, Rijnstate hospital and Zuyderland Medical Centre, which included 156 patients. Ultimately, the study will expand to 5 actively recruiting centers.

Recruitment started in May 2021 and is expected to continue until 2023. The outpatient population of patients with HF of the participating centers comprises > 1500 patients; the excellent logistics of the participating centers and the high percentage of eligible potential patients mean that the required number of inclusions is expected to be feasible.

Conclusion

The FRESH-UP study is the first randomized, controlled, multicenter trial to investigate the effects of liberal fluid intake vs fluid restriction on the QoL of patients with chronic HF. The results of this study may provoke a paradigm shift and lead to a more evidence-based guideline, and they could have a major impact on the QoL of millions of patients with chronic HF.

Lay Summary

Patients with HF are often advised to reduce fluid intake to a maximum of 1500 mL per day to prevent or reduce symptoms of HF. However, clinical evidence to support this advice is lacking. Moreover, many patients are thirsty, and this daily confrontation with HF has a significantly negative impact on quality of life. In this light, we initiated the FRESH-UP study, the first multicenter randomized clinical trial to investigate the effect of liberal fluid intake vs fluid restriction of 1500 mL/day for 3 months on the QoL of outpatients with chronic HF.

- Fluid restriction of 1500 mL per day is common clinical practice to prevent or reduce symptoms of HF. However, data from clinical trials are lacking.
- Many patients are thirsty, and this daily confrontation with HF has a negative impact on quality of life.
- The FRESH-UP study is the first randomized clinical trial to investigate the effect of liberal fluid intake vs fluid restriction of 1500 mL/day on the quality of life in outpatient patients with chronic HF.

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University Medical Centre in Nijmegen and Maastricht University Medical Centre [R0005106].

Conflicts of Interest

None declared.

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Visual Take Home Graphic was created with BioRender.com.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.05.015.

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