Fluid REStriction in Heart failure versus liberal fluid UPtake: the FRESH-UP study

Statistical Analysis Plan

Version 2.0

14-04-2024

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Study identifiers

NL75112.091.20

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List of Abbreviations

ACEi		Angiotensin Converting Enzyme inhibitor
ARB		Angiotensin Receptor Blocker
ARNI		Angiotensin Receptor/Neprilysin Inhibitor
BB		Beta blocker
CABG		Coronary Artery Bypass Grafting
CRT		Cardiac Resynchronization Therapy
	-D	Defibrillator
	-P	Pacemaker
DM		Diabetes mellitus
DSMB		Data Safety Monitoring Board
EAC		Event Adjudication Committee
EF		Ejection Fraction
eGFR		Estimated Glomerular Filtration Rate
EQ-5D-5L		European Quality of Life Five Dimensions Five Levels questionnaire
HF		Heart Failure
	rEF	with reduced ejection fraction
	mrEF	with mildly reduced ejection fraction
	pEF	with preserved ejection fraction
IC		Informed Consent
ICD		Implantable Cardioverter Defibrillator
KCCQ		Kansas City Cardiomyopathy Questionnaire
	-OSS	Overall Summary Score
	-CSS	Clinical Summary Score
GDMT		Guideline directed medical therapy
MRA		Mineralocorticoid Receptor Antagonists
NYHA		New York Heart Association
NT-proBNP		N-terminal pro–B-type natriuretic peptide
PCI		Percutaneous Coronary Intervention.
QoL		Quality of life
SGLT2i		Sodium-glucose Cotransporter-2 inhibitor
TDS-HF		Thirst Distress Scale for patients with HF

1. Administrative Information

1.1. Study identifiers

- Protocol: NL75112.091.20, version 4.2, 02-12-2022
- ClinicalTrials.gov register Identifier: NCT04551729

1.2. Revision history

Version	Date	Changes made to document	Authors
1.0	01-09-2023	Drafted version 1.0	J.J. Herrmann L. Rodwell D.H.F. Gommans R.R.J. van Kimmenade
2.0	17-04-2024	Subanalyses added EQ-5D-5L missing value handling	J.J. Herrmann L. Rodwell D.H.F. Gommans R.R.J. van Kimmenade

1.3. Contributors to the statistical analysis plan

1.3.1. Roles and responsibilities

Names	Affiliation	Role on study	SAP contribution
J.J. Herrmann	Radboud University Medical Center, department of Cardiology	Coordinating investigator	Drafting the statistical analysis plan
L. Rodwell	Radboud University Medical Center, department for Health Evidence	Study statistician	Revisions
D.H.F. Gommans	Radboud University Medical Center, department of Cardiology	Coordinating investigator	Revisions
R.R.J. van Kimmenade	Radboud University Medical Center, department of Cardiology	Principal investigator	Revisions

1.3.2.Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention(s) being assessed).

J.J. Herrmann

[redacted] 18-04-2024

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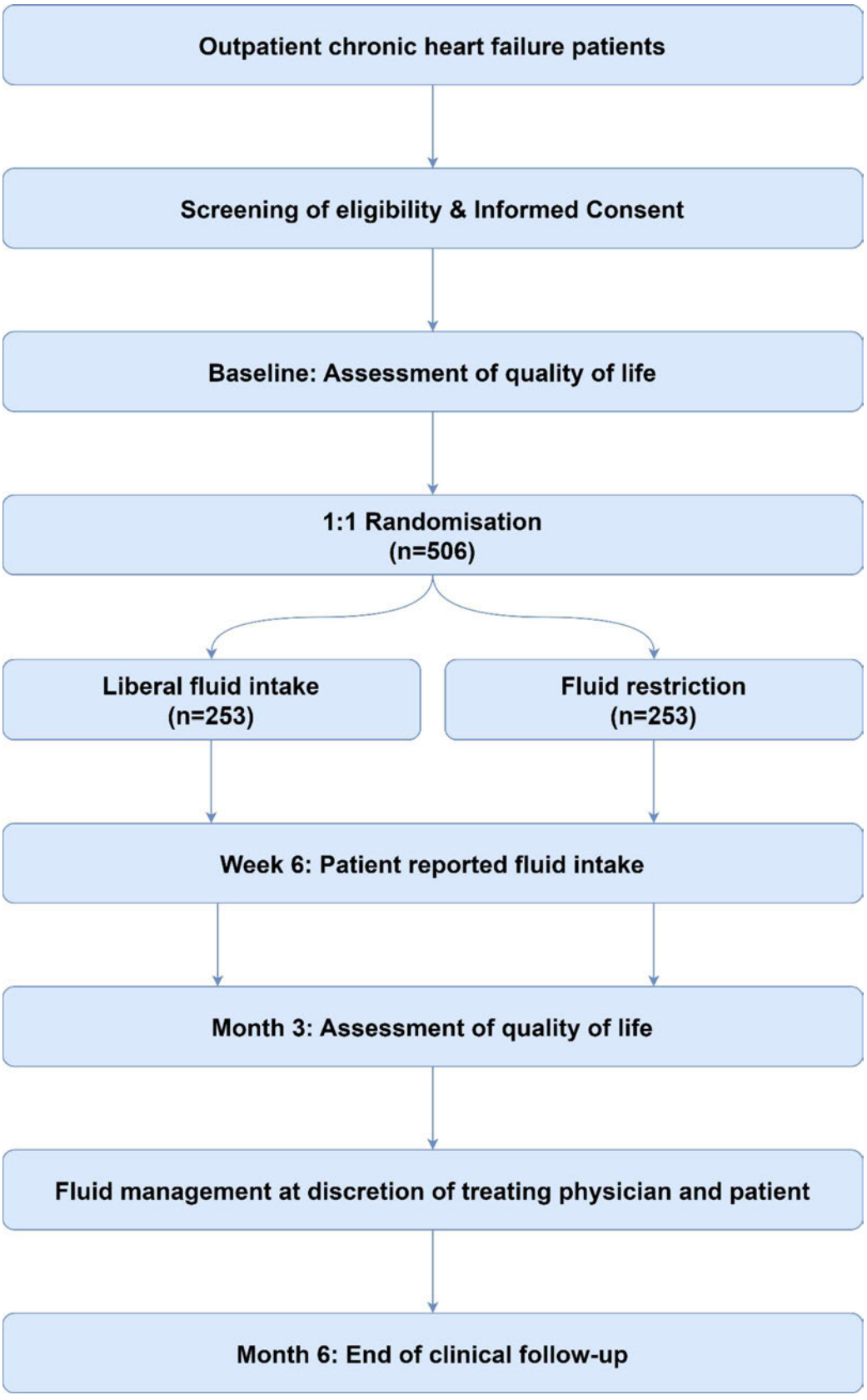
2. Study synopsis

The FRESH-UP study is a randomised, controlled, open-label, multicentre trial to investigate the effects of a 3-month period of liberal fluid intake vs fluid restriction (1500 ml/day) on quality of life (QoL) in outpatients with chronic heart failure (HF).



2.1. Study objectives

2.1.1. Primary objective

To investigate the effect of liberal fluid intake versus standard fluid restriction (1500 ml/day) on QoL in outpatient chronic HF patients at 3 months after randomisation, as assessed by the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS).

2.1.2. Secondary objectives

To investigate the effect of liberal fluid intake versus standard fluid restriction (1500 ml/day) on:

- Thirst distress at 3 months after randomisation, as assessed with TDS-HF
- QoL at 3 months after randomisation, 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, and the European Quality of Life Five Dimensions Five Levels questionnaire (EQ-5D-5L)
- Patient reported fluid intake at week 6
- Safety, as assessed by the composite of: death, all-cause hospitalisation and the requirement to apply iv-loop diuretics during the 6-month clinical follow-up duration.

2.1.3. Exploratory objectives

To investigate the effect of liberal fluid intake versus standard fluid restriction (1500 ml/day) on:

- Safety as assessed by (time to the first) occurrence of: death, all-cause or unplanned HF hospitalisation or the requirement of iv-loop diuretics during the 6-month clinical follow-up duration
- The (time to the first) occurrence of acute kidney injury defined as a 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 during the 6-month clinical follow-up duration
- Serum biomarkers (NT-proBNP, sodium, osmolality, haemoglobin, haematocrit) and weight at 3 months after randomisation
- The use of concomitant medication (diuretics in particular)

2.2. Patient population

2.2.1. Inclusion criteria

- Diagnosis of chronic HF with New York Heart Association (NYHA) class II/III according to the prevailing guidelines > 6 months prior to randomisation
- Adult (age ≥ 18 years)

2.2.2. Exclusion criteria

- Reversible cause of HF (thyroid disorders, severe anaemia, vitamin deficiencies)
- Hospital admission for HF within 3 months of randomisation
- Chronic HF with NYHA class I/IV
- Hyponatremia at baseline (sodium <130 mmol/l)
- Estimated Glomerular Filtration Rate (eGFR) of <30 ml/min/1.73 m2 at baseline
- Changes in HF medical therapy in last 14 days prior to randomisation
- Scheduled cardiac surgery within 3 months of randomisation
- 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 (e.g. nephrologist)
- Life expectancy of less 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 IC

2.3. Outcomes

2.3.1. Primary outcome

- QoL as assessed by KCCQ-OSS[1] at 3 months after randomisation

2.3.2. Secondary outcome

Key secondary outcome:

- Thirst distress as assessed by the TDS-HF[1]

Other secondary outcomes:

- QoL at 3 months as assessed by KCCQ-CSS
- QoL at 3 months as assessed by each of the KCCQ domains and the proportion of patients with clinically meaningful changes in these scores
- QoL at 3 months as assessed by EQ-5D-5L[1]
- Patient-reported fluid intake in week 6
- Safety: The composite clinical endpoint: death, all-cause hospitalisation and the requirement of iv-loop diuretics during the 6-month clinical follow-up duration

2.3.3. Exploratory outcomes

- Safety: The number of occurrences of: death, all-cause or unplanned HF hospitalisation or the requirement of iv-loop diuretics during the 6-month clinical follow-up duration
- Safety: The time to the first occurrence of: death, all-cause or unplanned HF hospitalisations or the requirement of iv-loop diuretics during the 6-month clinical follow-up duration
- Safety: The number of occurrences of acute kidney injury (defined as a 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 during the 6-month clinical follow-up duration)
- Safety: The time to the first occurrence of acute kidney injury (defined as a 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 during the 6-month clinical follow-up duration)
- Serum biomarkers (NT-proBNP, sodium, osmolality, haemoglobin, haematocrit) at 3 months after randomisation
- Weight at 3 months after randomisation
- Use of concomitant medication (diuretics in particular)

[1] The KCCQ, TDS-HF and EQ-5D-5L are scored according to 'Appendix 2: Scoring of the Questionnaires'.

2.4. Intervention

Patients will be randomised to standardized lifestyle advice by the treating physician and/or nurse practitioner of either liberal fluid intake (no restrictions, fluid intake as desired) or fluid restriction of 1500 ml/day for a period of 3 months. Other lifestyle interventions (e.g., sodium restriction or activity) remain unadjusted. The latter is emphasized during the standardized lifestyle advice.

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

2.5. Randomisation and blinding

Randomisation 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 randomised 1:1 to either liberal fluid intake or standard fluid restriction using Castor EDC with a random block randomisation algorithm and stratified randomisation per each including centre. A patient cannot be randomised more than once in the study.

Members of the steering committee and Event Adjudication Committee (EAC) members are blinded to randomisation.
The coordinating investigator (JH) and DSMB members are not blinded. The coordinating investigator (JH) prepares the data overview for the statistician of the DSMB who performs the interim analysis. The data overview is not shared with the members of the steering committee or EAC members.

2.6. Sample size

Sample size calculation was performed with the software package G*Power 3.1.7 and performed as previously described methods for repeated measures ANCOVA analysis, using baseline QoL as a covariate (1).

For our sample size calculation, a correlation of 0.88 between baseline and follow-up KCCQ-OSS was assumed (2). Furthermore, a follow-up KCCQ-OSS of 66.25 with a standard deviation of 20 was assumed for liberal fluid intake group (3-7). Next, we assume a 2.5-point difference in KCCQ-OSS follow-up scores at 3 months between both randomisation groups (3-7). To test this difference at a p-value of 0.05 and power of 80%, we need a total of 454 evaluable patients. Anticipating a drop-out rate of 10% we aim to enrol 506 patients.

To interpret the clinical relevance of a mean difference of 2.5 points in KCCQ score, it is important to differentiate between differences in scores on a patient level or group level. Based on previous validation studies on a patient level, a change of 5, 10 and 20 points in KCCQ-OSS follow-up scores are considered small, moderate-to-large and large-to-very large clinical important changes respectively (8, 9). Moreover, even smaller changes are possibly associated with clinically important improvements or deteriorations (10). However, a mean difference on randomisation group level is not directly comparable with the clinically important changes on a patient level. Randomisation group means reflect many different outcomes amongst patients, as in each randomisation group patient's clinical status will improve, deteriorate or remain stable.

In view of the above, it is illustrative to look at the results of previous landmark trials which demonstrated positive effects on clinical outcome for the studied interventions, which are now part of guideline-directed medical therapy.

For example, in the PARADIGM-HF (sacubitril/valsartan versus enalapril), the KCCQ-OSS mean difference was 1.27 points , while the proportion of clinically important improvements was greater and the proportion of deterioration was lower for sacubitril/valsartan group compared to the enalapril group (35% versus 33% and 27% versus 31%, respectively) (7).
The same applies for the DELIVER trial (dapagliflozin versus placebo) where the mean KCCQ-OSS was 2.1 points higher at follow-up in the dapagliflozin group (P<0.001) while on a patient level less patients experienced deterioration (>5 points worse) (21% versus 25%) and more patients had 10+ and 15+ points improvement (40% versus 36% and 28% versus 25%, respectively) (11).
Also in the SHIFT-HF (ivabradine versus placebo), the proportions of clinically important changes on patient level were in favour of ivabradine, although not significant, the KCCQ-OSS mean difference was 2.4 points higher in the ivabradine group (P<0.001) (4).

In light of these trials, we consider a statistically significant 2.5-point mean difference in KCCQ-OSS follow-up scores between study groups as clinically relevant, which is very likely to represent clinically relevant differences on a patient level.

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

3. Statistical analysis

3.1. General principles

Unless stated otherwise, analyses will be performed using SPSS statistics V27 (IBM, Armonk, New York) or higher.

Prior to performing a hard database lock, all variables will be checked including any outliers. Any missing or outlying values with be checked with the investigator at the corresponding site.

3.2. Interim analyses

The DSMB will perform two interim analyses, when data are available, of 33% and 66% of the patients for safety concerning the occurrence of death, HF hospitalisations and acute kidney injury.

The objective of the interim analysis will be to assess the following:

- Safety: is there any difference in the safety profile between treatment groups?
- Are there any other observations in the accumulated data that should be communicated to the sponsor?

The following will be the main parameters of interest for the DSMB:

- The occurrence of HF hospitalisations
- The occurrence of death
- The occurrence of acute kidney injury

All appropriate safety measures will be summarized for the safety population by treatment for the treatment period. Safety measures will be reported per treatment group, the number (n) and percentage (%) of patients experiencing at least one event. The denominator for computation of percentages is the safety population within each treatment group.

There are no interim analyses for efficacy.

3.3. Multiplicity adjustment

The primary and key secondary endpoints will be tested hierarchically. Other secondary endpoints will be considered supportive only and there will no corrections for multiple testing.

3.4. Blind review

An independent EAC will adjudicate the cause of death and any hospitalisations as either HF-related or not, and will be blinded to treatment allocation. The events of interest will be adjudicated according to a predefined scheme based on the consensus of two committee members; in case of no consensus, the third committee member will provide final adjudication.

The members of the steering committee and the principal investigator of the sponsor site, Radboudumc, are blinded to the randomisation group. After database lock, the analysis will be performed with knowledge of randomisation.

3.5. Data sets to be analysed

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, as described in '3.8 Compliance to study intervention'. Patients who were non-compliant according to '3.8 Compliance to study intervention', will be excluded from the per-protocol analysis. Non-adherence is considered not possible for the liberal fluid intake arm, therefore all liberal fluid intake patients will be included in the per-protocol analysis.

3.6. Subject disposition

The study disposition figure will include:

- Number of patients screened
- Number of screen failures and retracted IC before randomisation
- Number of patients enrolled
- Number of patients randomised per intervention group
- Number of patients lost to follow-up

3.7. Patient characteristics and baseline comparisons

Baseline descriptive statistics will be presented both in text (for certain characteristics) and in table. Categorical variables will be presented with numbers (percentages) and compared using a Chi-squared test or Fisher exact test, whichever is appropriate. Continuous variables will be assessed for normal distribution and reported as means (standard deviation) or medians (interquartile range), whichever is appropriate. Baseline characteristics will be presented by randomisation group and for the overall population.

The following characteristics will be presented:

- Age
- Sex at birth
- Race
- Baseline KCCQ-OSS
- Baseline TDS-HF
- NYHA Class
- Ejection fraction (percentage, HFrEF, HFpEF)
- Pathogenesis of heart failure (ischemic, dilating, hypertension, valvular, drug-induced, other, unknown)
- Heart failure duration
- Medical history (current fluid management, atrial fibrillation/flutter, BMI, COPD, DM, hypertension, currently smoking)
- Laboratory values (haemoglobin, sodium, potassium, urea, eGFR, NT-proBNP, osmolality)
- Concomitant therapies (see below)

3.8. Compliance to study intervention

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. Patients are considered as compliant in case daily fluid intake did not exceed 1500 ml in at least 5 of 7 days according to the patient-reported fluid intake in week 6. Besides that, adherence is questioned during the month 3 visit. However, the latter will only be reported descriptively and will not formally be used for the assessment of therapy adherence. Non-adherence is considered not possible for the liberal fluid intake arm.

3.9. Concomitant therapies

Concomitant medication will be focused on HF therapy and will be presented as numbers and percentages and in accordance with '3.7 Patient characteristics and baseline comparisons'.

The following concomitant therapies will be presented at least:

- ACEi
- ARB
- ARNI
- BB
- Digoxin
- MRA
- Loop diuretics
- Thiazides
- SGLT2i
- ICD
- CRT
- GDMT score

The GDMT score was primarily developed by the Scientific Expert Panel From the Heart Failure Collaboratory and Academic Research Consortium, and later updated with the latest HF guidelines, to improve comparability between HF trials for HFrEF patients (12, 13).

GDMT score is calculated by adding scores of each drug class. RAAS Inhibition is assigned 0 (no treatment), 1 (ACEi/ARB, <50% max daily dose), 2 (ACEi/ARB, ≥50% max daily dose) or 3 (ARNI, any dose) points. For BB, 0 (no treatment), 1 (<50% max daily dose) or 2 (≥50% max daily dose) points are assigned. MRA and SGLT2i are assigned 0 (no treatment) or 2 (any dose) points.
Ivabradine, vericiguat and hydralazine and isosorbide dinitrate are assigned 0 (no treatment) or 1 (any dose) points.

The total GDMT scores will be assessed for normal distribution and reported as means (standard deviation) or medians (interquartile range), whichever is appropriate.

3.10. Analysis of the primary outcome

3.10.1. Main analysis

The difference between the two 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. The difference will be presented as the average treatment effect for liberal fluid – restricted fluid arm. The estimated difference will be presented with a point estimate and 95% confidence interval. A p-value of <0.05 will be considered significant.

For the primary analysis, the intention-to-treat principle will be applied.

3.10.2. Adjusted analyses

Not applicable.

3.10.3. Subgroup analyses

The following prespecified subgroups will be analysed in relation to the primary endpoint: Sex at birth (male/female), including centre, HF type based on last known EF (HFrEF ≤40%/HFmrEF 41-49%/HFpEF ≥50%), NYHA class (II/III), age (above/below median), BMI (above/below median), baseline diuretic dosage (above/below median), DM (yes/no), and baseline sodium, urea, creatinine, and NT-proBNP concentrations (above/below median).

3.10.4. Treatment of missing data

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, a multiple 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. For the imputation procedure, m = 50 imputed datasets and the missing 3-month KCCQ scores will be imputed using predictive mean matching, type 1 and with k = 5 nearest neighbours specified (14). In the case of any missing data on the selected auxiliary variables, a fully conditional specification imputation approach will be specified with the imputation model for each variable defined according to the variable type.

3.10.5. Other sensitivity analyses

The main analysis for the primary outcome will be performed also according to the per-protocol principle. The per-protocol population is defined as described in '3.5. Data sets to be analysed'.

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 procedure (15).

3.11. Analysis of the secondary outcomes

For the secondary parameters thirst distress, as assessed with the TDS-HF, and QoL at 3 months after randomisation, as assessed with the KCCQ-CSS, each of the KCCQ domains and the EQ-5D-5L, a similar approach as for the primary study parameters will be adopted.

The difference between groups in proportion of patients with clinically meaningful changes (defined as a difference of 5 points compared to baseline) in KCCQ-OSS and KCCQ-CSS (8, 10) and the percentage of events (death, all-cause hospitalisations, the need for iv-loop diuretics and acute kidney injury) will be tested with Chi-square or Fisher exact test, whichever appropriate. The

difference in between groups patient reported fluid intake will be analysed with a Students' t test or Mann-Whitney U test, whichever appropriate.

3.12. Analysis of other outcomes

Time-to-event outcomes will be analysed using a Cox proportional hazards model, with, if necessary, baseline covariate adjustment in case of unexpected differences in baseline descriptive statistics. The estimated treatment effect will be presented in the form of hazard ratios with 95% confidence intervals. Kaplan-Meier plots will be used to present the pattern of events per treatment group over the follow-up period. The assumption of proportional hazards will be checked using statistical tests and graphical diagnostics based on the Schoenfeld residuals.

The exploratory safety endpoint will be assessed using a unmatched win ratio approach (16). Patients from the liberal fluid intake arm will be paired with every single patient from the standard fluid restriction arm. For each pair the better clinical outcome will be determined in the following sequential criteria and will stop after either patient has shown profit.

A 'win' is defined as the patient in the liberal fluid intake arm has the better outcome compared to the patient in the standard fluid restriction group. A 'loss' is defined in the opposite manner.

1. Death within 6 months follow-up
    a. Death is worse than no death
    b. Tied, if not possible to determine
2. HF hospitalisations within 6 months follow-up
    a. More HF hospitalisations is worse
    b. Tied, if not possible to determine
3. Requirement of iv-loop diuretics within 6 months follow-up
    a. More events is worse
    b. Tied, if not possible to determine
4. All-cause hospitalisation within 6 months follow-up
    a. More all-cause hospitalisations is worse
    b. Tied, if not possible to determine

The win ratio is: total number of wins / total number of losses.
The win difference is: percentage of wins minus percentage of loses.

4. Prespecified subanalyses

All patient characteristics of the prespecified subanalyses listed below will be presented in accordance with '3.7 Patient characteristics and baseline comparisons' of this document, unless stated otherwise.

Change of fluid management analysis

Aim:

1. To investigate the effect of liberal fluid intake versus fluid restriction in the subgroup of patients who were prescribed a fluid restriction prior to randomisation on the primary, (key) secondary and explorative endpoints
2. To investigate the effect of increased fluid intake in the subgroup of patients who were prescribed a fluid restriction at baseline on the primary, (key) secondary and explorative endpoints

Analysis:

1. Population: Patients who were prescribed any form of fluid restriction prior to randomisation will be included.

2. Population: Patients who were prescribed any form of fluid restriction prior to randomisation and who were randomised to liberal fluid intake. Patients will be divided into two groups for analysis based on their average fluid intake at week 6 (less or more than 2L).

3. Population: Patients who were prescribed any form of fluid restriction prior to randomisation. Patients will be divided into three groups:
    a. Randomised to fluid restriction.
    b. Randomised to liberal fluid intake and a fluid intake of less than 2L based on their average fluid intake at week 6.
    c. Randomised to liberal fluid intake and a fluid intake of more than 2L based on their average fluid intake at week 6.

The analysis on the primary, (key) secondary and exploratory endpoints will be performed as described in '3.10 Analysis of the primary outcome', '3.11. Analysis of the secondary outcomes' and '3.12 Analysis of other outcomes'.

Thirst and QoL analysis

Aim:

1. To investigate the relationship between thirst and QoL.
2. To investigate the effect of thirst status on the effect of liberal fluid intake versus fluid restriction.

Analyses:

1. Population: All patients with completed KCCQ and TDS-HF
    a. At baseline;
    - Correlation between baseline KCCQ-OSS (and subdomains) and TDS-HF
    - A multiple regression analysis between baseline KCCQ-OSS (and subdomains) and TDS-HF.
    b. Follow-up;
    - Correlation between the change in KCCQ-OSS and subdomains and TDS-HF per randomisation arm.

2. Population: Patients will be categorized into based on the TDS-HF:
    a. No thirst (score = 8).
    b. Minimal to moderate thirsty (score = 9 to 24).
    c. Moderate to very thirsty (score = 25 to 40).

The analysis on the primary and secondary endpoints will be performed as described in '3.10 Analysis of the primary outcome' and '3.11. Analysis of the secondary outcomes'. Baseline characteristics will include all subdomains of the KCCQ.

In depth analysis

If the subgroup analyses suggest that there is a signal of effect modification for the pre-specified subgroups, then this specific subgroup will be explored further to understand the potential reasons for the observed differences.

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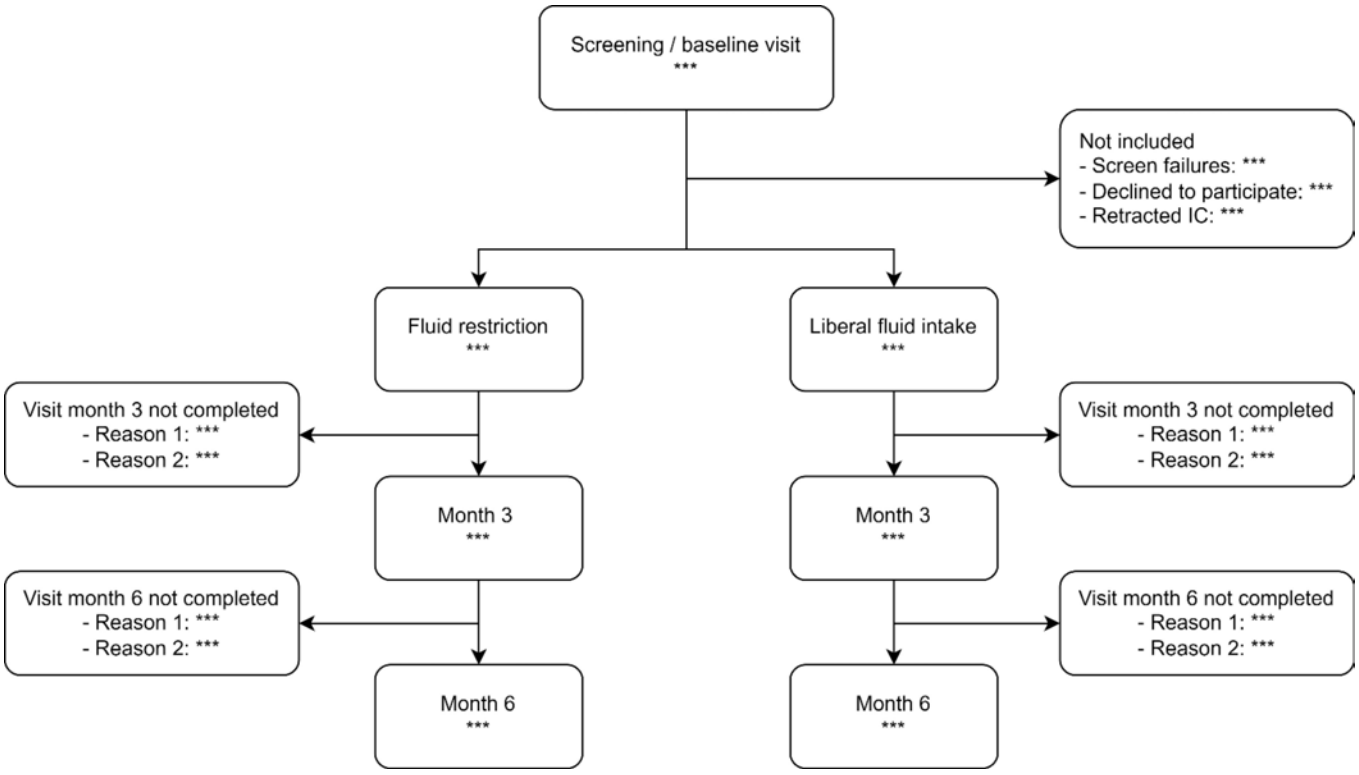
20. EuroQol. EQ-5D-5L Netherlands Value Set 2021 [Available from: https://euroqol.org/wp-content/uploads/2024/01/Netherlands_valueset_SPSS.txt.

Appendix 1: Proposed tables and figures

All tables and figures are drafts and will not necessarily be included in the final papers in this form.

1. Study disposition figure



2. Baseline characteristics table

	Total (N = ***)	Fluid restriction (N = ***)	Liberal fluid intake (N = ***)
Age, years			
Male			
White†			
Quality of life			
KCCQ-OSS			
TDS-HF			
EQ-5D-5L			
NYHA functional class			
II			
III			
LVEF			
%			
HFrEF			
HFmrEF			
HFpEF			
Pathogenesis HF			
Ischemic			
Dilating			
Hypertension			
Valvular			
Drug-induced			
Other			
Unknown			
HF duration, years			
Fluid management			
Fluid restriction of 1L			
Fluid restriction of 1.5L			
Fluid restriction of 1.5 to 2L			
Fluid restriction of 2L			
Liberal fluid intake			
Other			
HF treatment			
ACEi or ARB			
ARNI			
β-blocker			
Digoxin			
MRA			
SGLT2i			
Loop diuretics			
Thiazides			
GDMT score‡			
ICD			
CRT			

Medical history
Atrial fibrillation or flutter
BMI, kg/m^2
COPD
DM
Hypertension
Currently smoking
Laboratory results
Haemoglobin, mmol/l
Sodium, mmol/l
Potassium, mmol/l
Urea, mmol/l
eGFR, $ml/min/1.73m^2$
Nt-proBNP, pg/ml
Osmolality, mosm/kg

3. Outcomes

Table: 'Primary and secondary outcomes.'

	Fluid restriction (N = ***)	Liberal fluid intake (N = ***)	P value
Primary outcome			
KCCQ-OSS			
Key secondary outcome			
TDS-HF			
Other secondary outcome			
KCCQ-CSS			
KCCQ-TSS			
KCCQ-PLS			
KCCQ-QoL			
KCCQ-SBS			
KCCQ-SES			
KCCQ-SFS			
KCCQ-SLS			
KCCQ-SSS			
KCCQ-OSS (-5 to +5)			
KCCQ-OSS (-5 or less)			
KCCQ-OSS (+5 or more)			
EQ-5D-5L			
Reported fluid intake			
Safety			
Death			
All-cause hospitalisation			
IV-loop diuretics usage			
Composite of the above			
Acute kidney injury†			

Values are mean ± SD or median (interquartile range)
† Acute kidney injury is defined as a 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.
EQ-5D-5L = European Quality of Life Five Dimensions Five Levels questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; -CSS = Clinical Summary Score; -TSS = Total Symptom Score; -OSS = Overall Summary Score; -PLS = Physical Limitation Score; -QoL = Quality of Life; -SBS = Symptom Burden Score; -SES = Self-Efficacy Score; -SFS = Symptom Frequency Score; -SLS = Social Limitation Score; -SSS = Symptom Stability Score; IV = intravenous; TDS-HF = Thirst Distress Scale for patients with HF;

Figure: primary outcome: 'Mean KCCQ-OSS score at baseline and month 3 visit.'
For illustration purposes only. Hypothetical data.

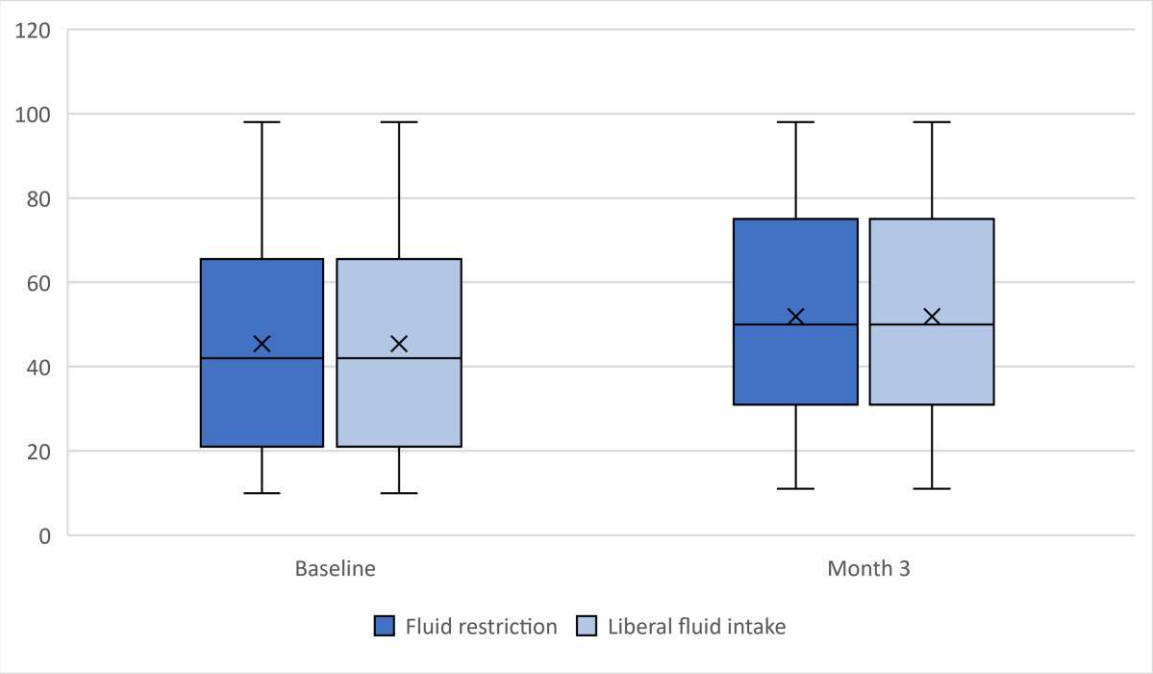


Figure secondary outcome: 'Mean quality of life questionnaires scores at month 3 visit.'
For illustration purposes only. Hypothetical data.

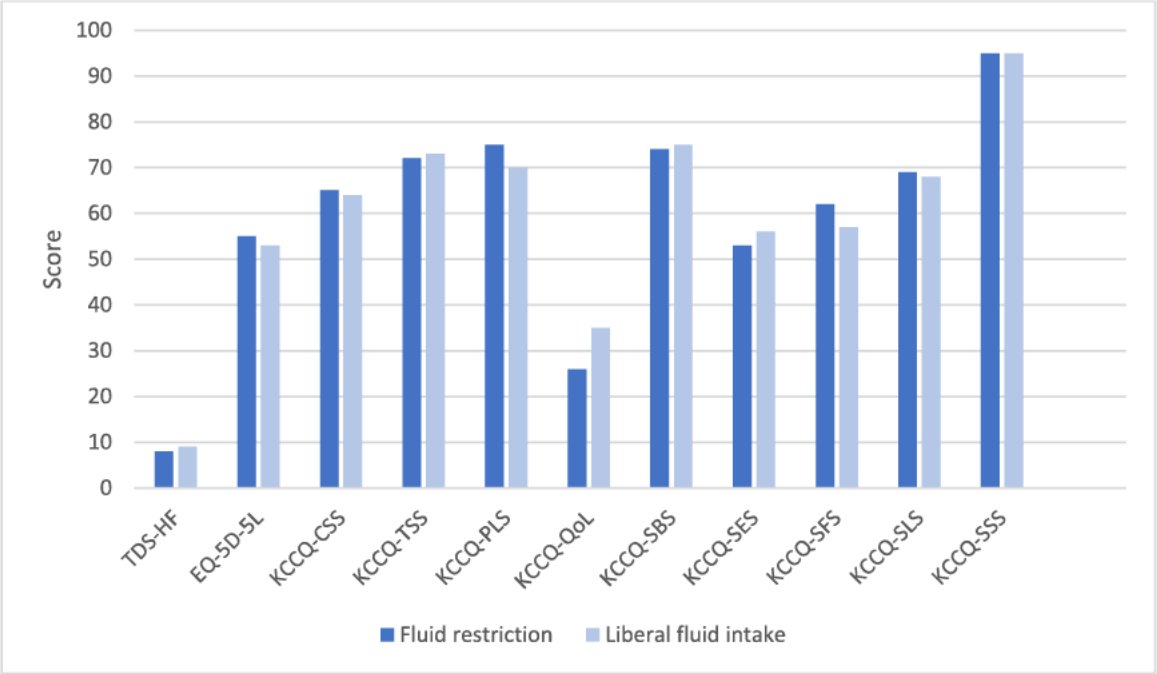
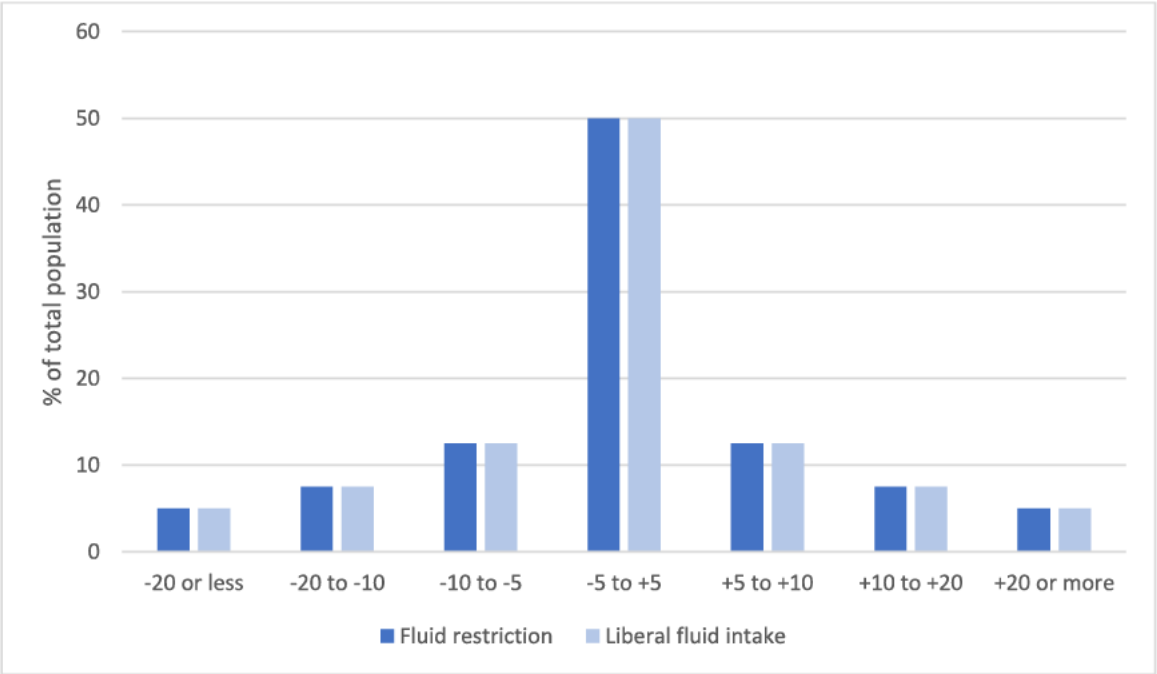


Figure secondary outcome: 'KCCQ-OSS at month 3 improvement and deterioration compared to baseline.' *For illustration purposes only. Hypothetical data.*



Appendix 2: Scoring of the questionnaires

1. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is scored according to 'The Kansas City Cardiomyopathy Questionnaire Scoring Instructions'. In brief, each answer option is assigned an ordinal value starting with 1 (indicating the lowest level of performance). Within each domain, all scores are summed up and converted to a 0 to 100 scale by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. As described in the scoring instructions, at least one or two questions, depending on the domain, need to be answered before any score can be assigned. Missing values of each domain will be assigned the average of the answered items within that same domain (17).

The Overall Summary Score is calculated as the mean of the following available summary scores: Physical Limitation Score, Total Symptom Score, Quality of Life Score and Social Limitation Score.

The handling of missing KCCQ questionnaires is described in '3.10.4. Treatment of missing data'.

2. Thirst Distress Scale for Heart Failure

The eight items, on thirst dimensions, are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). The total score ranges from 8 (no thirst) till 40 (very thirsty) (18).

In case of at least two missing items on the questionnaire, the questionnaire is excluded from the analyses. If only one item is missing, this item will be scored as the mean of the other items on the questionnaire.

3. European Quality of Life Five Dimensions Five Levels questionnaire (EQ-5D-5L)

The EQ-5D-5L consist of two parts. The first part assess five domains of health (mobility, self-care, usual activities, pain and discomfort, anxiety and depression) which all has five levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to). This generates a health state which can be summarised in an index score generally range from less than 0 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility. The health state is region specific (19). The second part consists of a visual analogue scale raging form 0 (worst imaginable health) to 100 (best imaginable heath).

In case of at least one missing item the questionnaire will be excluded from the analyses (20).