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

Grand Rounds Rethinking Clinical Trials

May 2nd 2025

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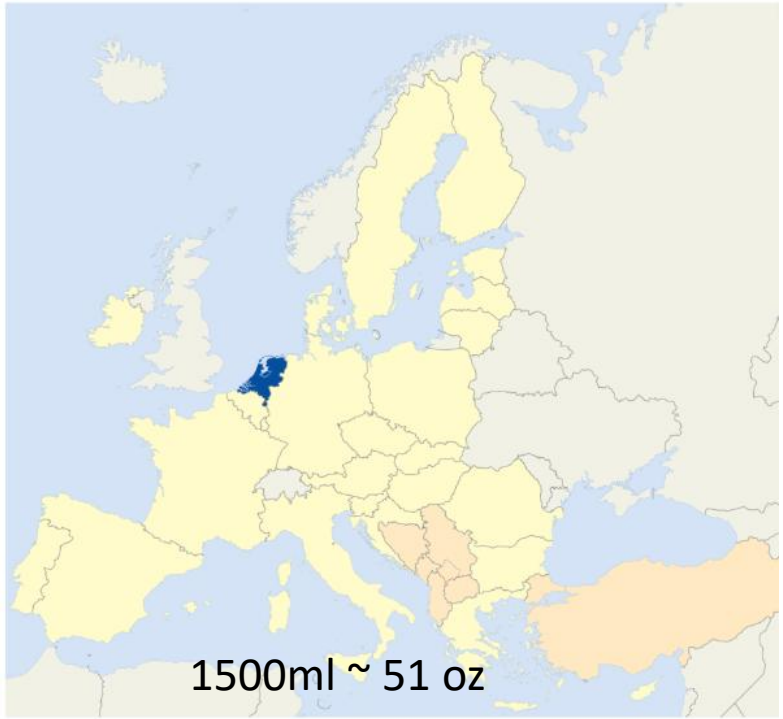
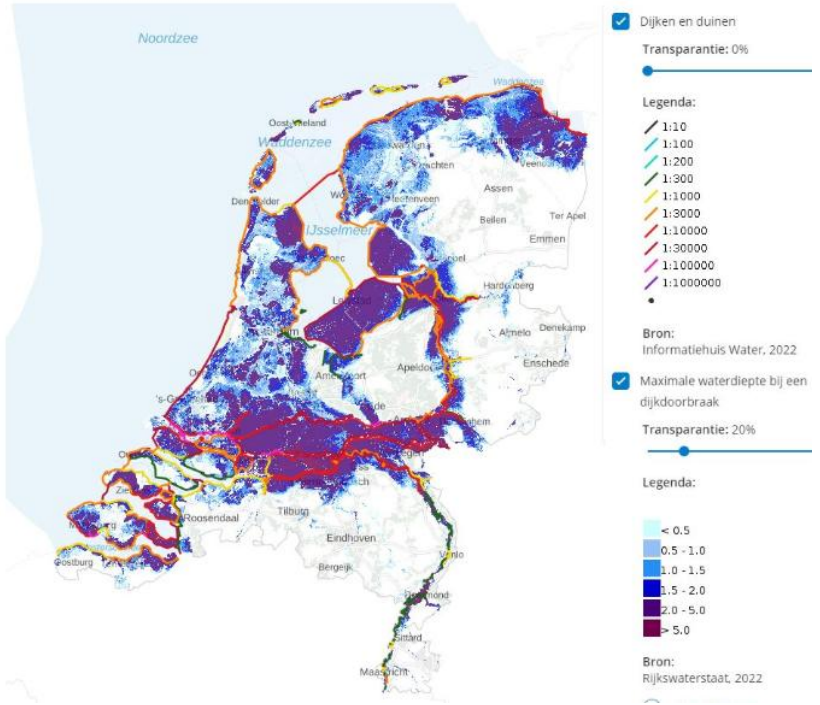
Disclosures

Consulting fees:
NovoNordisk, Roche Diagnostics

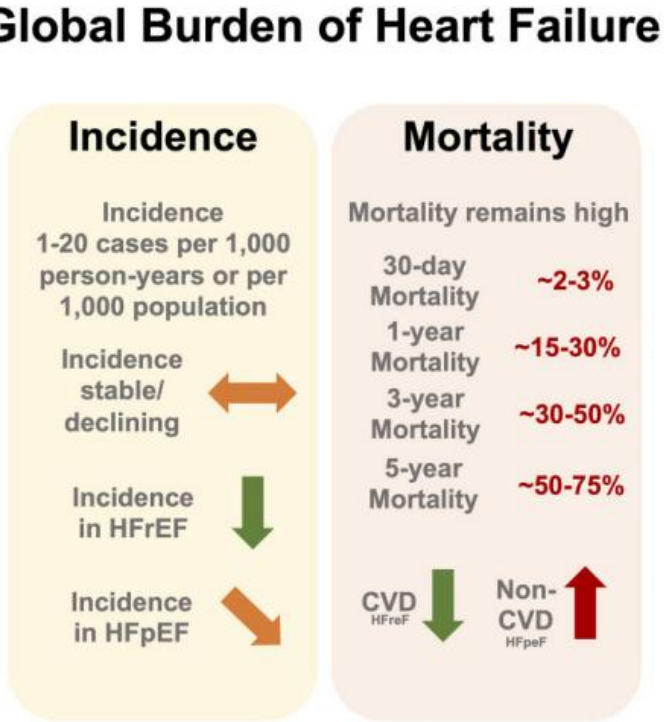
Speaker fee:
Hippocrates Academy/W.L.Gore & Associates

Background


1500ml ~ 51 oz


Noordzee
Waddenzee
IJsselmeer
Dijken en duinen
Transparantie: 0%
Legenda:
1:10
1:100
1:200
1:300
1:1000
1:3000
1:10000
1:30000
1:100000
1:1000000
Bron:
Informatiehuis Water, 2022
Maximale waterdiepte bij een dijkdoorbraak
Transparantie: 20%
Legenda:
< 0.5
0.5 - 1.0
1.0 - 1.5
1.5 - 2.0
2.0 - 5.0
> 5.0
Bron:
Rijkswaterstaat, 2022

Heart Failure

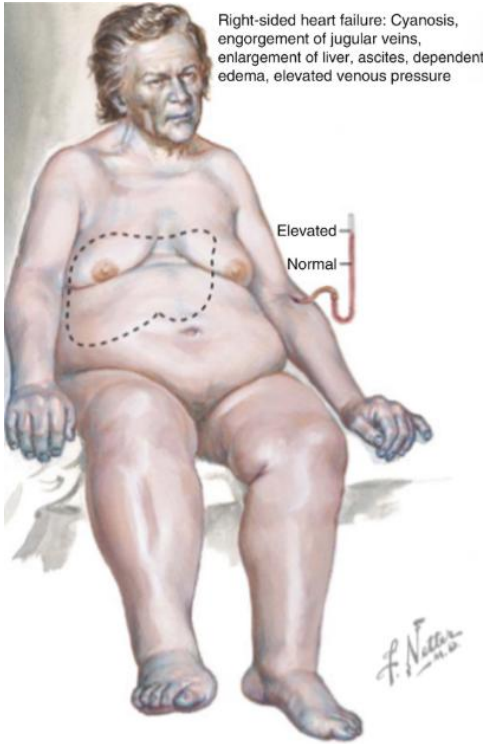


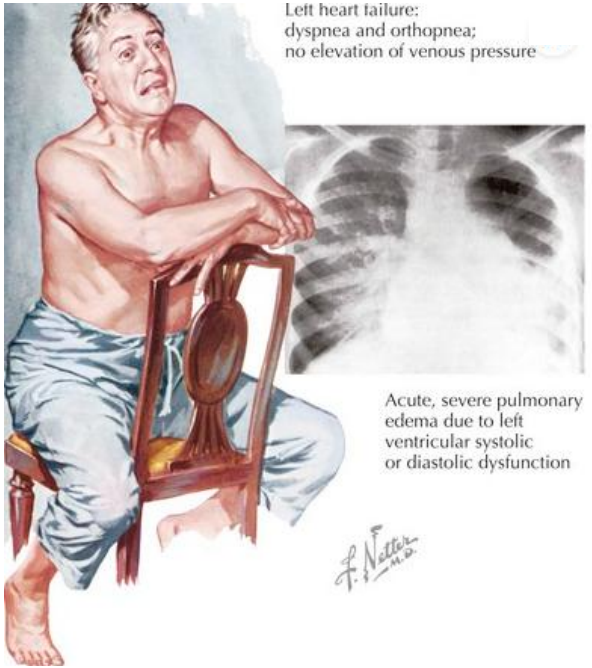
Savarese et al. *Cardiovascular Research* 2022

Heart Failure

- Orthopnea
- Edema

→ Congestion: ‘fluid retention’





Patients educational advices……

What if I am thirsty?

- To relieve dry mouth and thirst, try these tips:
  - Chew gum
  - Suck on sugar free candies
  - Suck on a lemon wedge – freezing it makes it more refreshing
  - Suck on frozen grapes or blueberries
  - Have small amounts of ice
  - Rinse you mouth with cold water or mouthwash, but don't swallow
  - Brush your teeth

From bedside to bench……..

Studies

Author, year	Type	N	Patients	Intervention	Control	Follow-up
Albert, 2013	RCT, parallel	52	ADHF, hyponatremia	1 L	Usual care	60 days
Holst, 2008	RCT, cross-over	74	CHF	1.5 L	30-35 ml/kg/day	32 weeks
Reilly, 2017	RCT, parallel, abstract	87	HF	1.5 / 2.5 L	Liberal	3 months
Travers, 2007	RCT, parallel	67	Inpatient, NYHA IV	1 L	Liberal	Until clinical stability

No differences in mortality or hospitalization…

…….while physiology underscores the lack of harm….!

ESC GUIDELINES

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Fluids	To avoid large volumes of fluid intake. A fluid restriction of 1.5–2 L/day may be considered in patients with severe HF/hyponatraemia to relieve symptoms and congestion.	Provide information and discuss the advantages and disadvantages of fluid restriction. Advise to adapt fluid intake to weight, and in times of high heat and humidity, nausea/vomiting.

Gaps in evidence

More evidence on the effects of fluid restriction, dietary salt restriction, and nutrition

Mc Donagh et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Although restricting fluid is a common recommendation for patients with HF, evidence in this area is of low quality

Table 33. Evidence Gaps and Future Research Directions

Efficacy and safety of specific dietary interventions, sodium restriction, and fluid restriction to prevent and treat HF.

Heidenreich et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *J Am Coll Cardiol* 2022

Crowdfunding

Crowdfunding

€ 60.554 opgehaald

Mirjam

Weinig mogen drinken is echt heel heftig en heeft een grote impact op je leven. Ik hoef er gelukkig niet meer op te letten. Fijn dat er onderzoek naar wordt gedaan.

Willie

Weet zelf heel goed wat het is om net vochtperperking om te gaan ivm hartfalen steun dit van harte Willie

Anoniem

Ik heb chronisch hartfalen. Ook ik heb moeite met de voorgeschreven 1,5 ltr vocht inname per dag. Ik ben dan ook zeer benieuwd naar de resultaten van een onderzoek hier naar.

Fluid RESTriction in Heart failure vs Liberal Fluid UPtake Study the FRESH-UP Study

Randomized Open-label Multicenter Clinical Trial

Inclusion criteria

- Diagnosis of chronic HF according to the ESC guidelines
  - > 6 months prior to randomization
  - NYHA class II/III

- Age ≥ 18 years

Exclusion criteria

- Changes in HF medical therapy < 14 days prior to randomization
- HF hospital admission < 3 months of randomization
- PCI/CABG or PM/CRT/ICD implantation < 3 months prior to randomization

- Hyponatremia at baseline (sodium < 130 mmol/L)
- eGFR of < 30mL/min/1.73m^2 at baseline

Primary Outcome

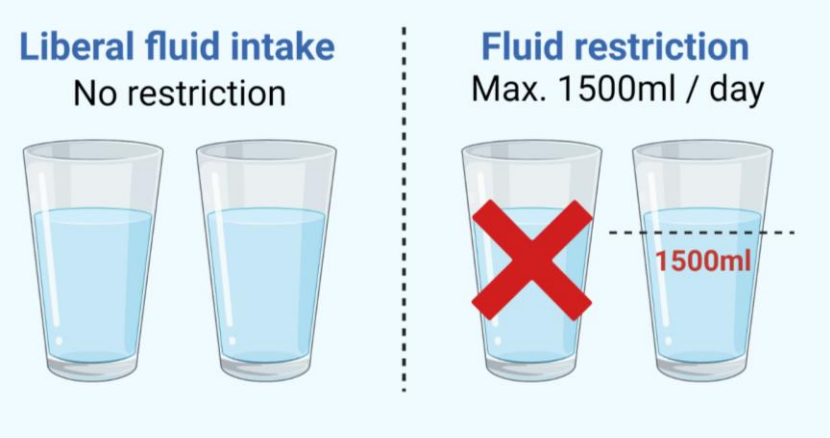
- Health status at 3 months as assessed by KCCQ-OSS
  - With adjustment for baseline values with ANCOVA

Key Secondary Outcome

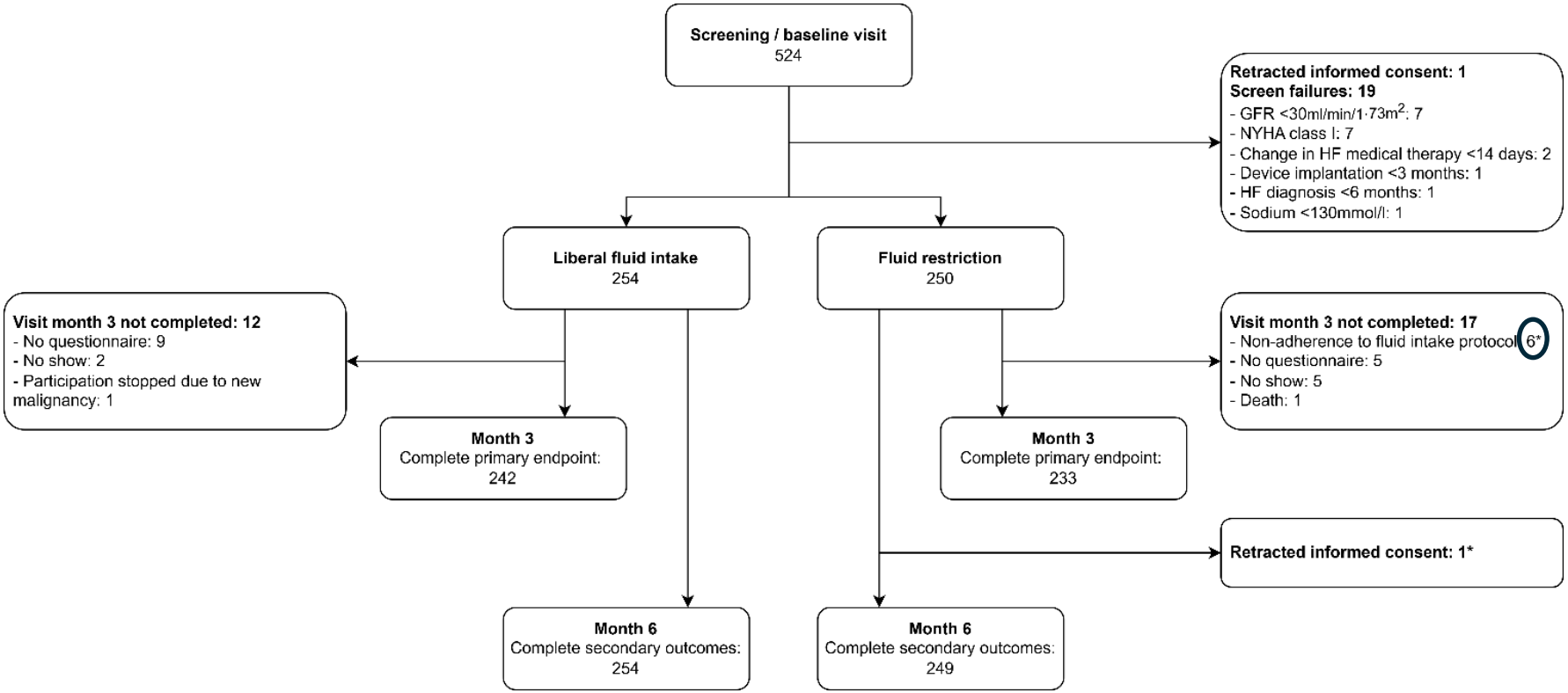
- Thirst distress at 3 months
  - assessed by the Thirst Distress Scale for patients with HF (TDS-HF)

Study Protocol

Recruitment : Between May 17 2021, and June 13, 2024



Flowchart


Screening / baseline visit
524
Retracted informed consent: 1
Screen failures: 19
- GFR <30ml/min/1·73m2: 7
- NYHA class I: 7
- Change in HF medical therapy <14 days: 2
- Device implantation <3 months: 1
- HF diagnosis <6 months: 1
- Sodium <130mmol/l: 1
Liberal fluid intake
254
Fluid restriction
250
Visit month 3 not completed: 12
- No questionnaire: 9
- No show: 2
- Participation stopped due to new malignancy: 1
Visit month 3 not completed: 17
- Non-adherence to fluid intake protocol: 6*
- No questionnaire: 5
- No show: 5
- Death: 1
Month 3
Complete primary endpoint:
242
Month 3
Complete primary endpoint:
233
Retracted informed consent: 1*
Month 6
Complete secondary outcomes:
254
Month 6
Complete secondary outcomes:
249

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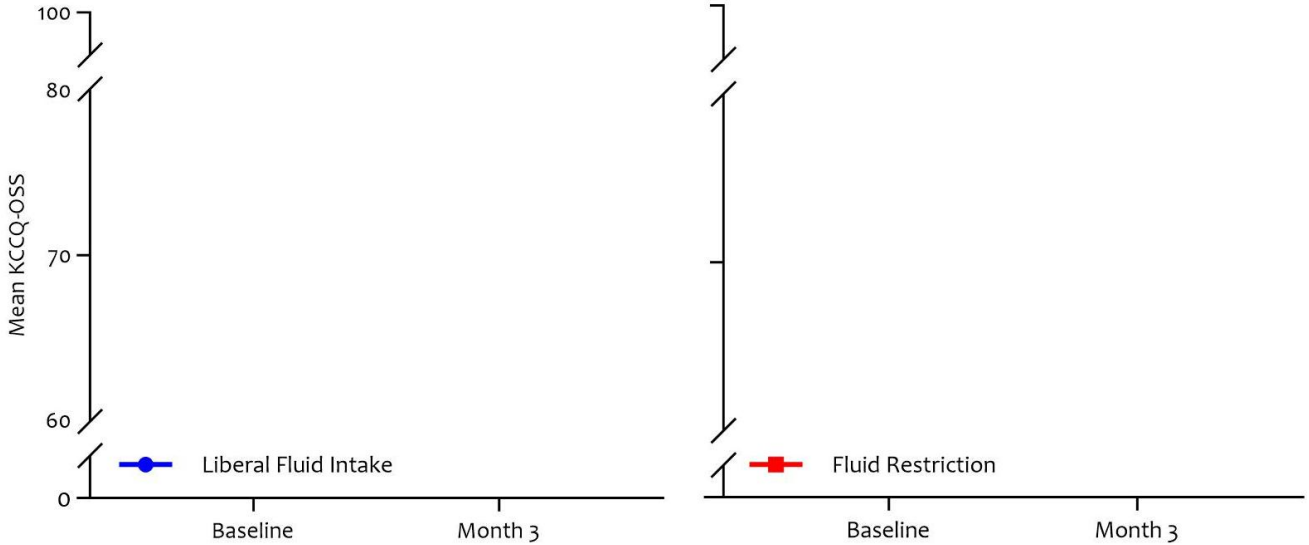
Patient Characteristics

	Liberal fluid intake (N = 254)	Fluid restriction (N = 250)
Age, years	69.4 ± 10.6	69.0 ± 10.8
Male	170 (66.9%)	169 (67.6%)
White	247 (97.2%)	245 (98.0%)
NYHA II	218 (85.8%)	221 (88.4%)
NYHA III	36 (14.2%)	29 (11.6%)
LVEF %	40.3 ± 10.9	40.2 ± 10.8
HFrEF	136 (53.5%)	124 (49.6%)
HFmrEF	60 (23.6%)	70 (28.0%)
HFpEF	58 (22.8%)	56 (22.4%)
Ischemic heart failure	108 (42.5%)	113 (45.2%)
Liberal fluid intake pre study	124 (48.8%)	111 (44.4%)

Patient Characteristics

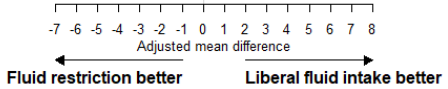
	Liberal fluid intake (N = 254)	Fluid restriction (N = 250)
RAASi	231 (90.9%)	241 (96.4%)
ARNI	149 (58.7%)	170 (68.0%)
β-blocker	228 (89.8%)	222 (88.8%)
MRA	199 (78.3%)	204 (81.6%)
SGLT2i	144 (56.7%)	162 (64.8%)
Loop diuretics	133 (52.4%)	125 (50.0%)
Furosemide equivalent per day, mg	40 [20 – 60]	40 [20 – 60]
Diabetes Mellitus	57 (22.4%)	54 (21.6%)
Sodium, mmol/l	139.6 ± 2.4	139.7 ± 2.5
BUN, mmol/l	8.0 ± 3.1	8.0 ± 3.6
eGFR, ml/min/1.73m^2	62.0 ± 17.2	62.6 ± 17.4
NT-proBNP, ng/l	430.0 [194.9 – 1100.0]	507.4 [193.5 – 1300.0]

Primary Outcome



Subgroup analysis

Subgroup	Liberal fluid intake (254)	Fluid restriction (250)	Adjusted mean difference	P-value (Interaction)
Sex at birth				**0.16**
Male	66%	67%	1.06 (-1.67-3.79)	
Female	34%	33%	4.47 (0.58-8.36)	
Median age				**0.62**
< 71 years	46%	48%	2.83 (-0.21-5.87)	
>= 71 years	54%	52%	1.71 (-1.52-4.95)	
HF type				**0.42**
HFrEF	53%	48%	0.77 (-2.37-3.91)	
HFmrEF	23%	29%	4.33 (-0.30-8.96)	
HFpEF	24%	23%	2.87 (-1.58-7.32)	
NYHA class				**0.18**
II	85%	89%	1.75 (-0.52-4.02)	
III	15%	11%	5.40 (-2.57-13.38)	
Median NT-proBNP				**0.66**
< 452 ng/L	54%	48%	2.50 (-0.39-5.38)	
>= 452 ng/L	46%	52%	1.54 (-1.86-4.94)	
Median BMI				**0.94**
< 27.7 kg/m2	49%	51%	1.99 (-1.16-5.13)	
>= 27.7 kg/m2	51%	49%	2.14 (-1.06-5.34)	
Diabetes Mellitus				**0.07**
Yes	22%	22%	-1.68 (-6.93-3.56)	
No	78%	78%	3.25 (0.81-5.70)	
Median sodium				**0.15**
< 140 mmol/L	46%	47%	0.44 (-2.68-3.56)	
>= 140 mmol/L	54%	53%	3.68 (0.53-6.84)	
Median BUN				**0.006**
< 7.4 mmol/L	50%	47%	5.37 (2.40-8.34)	
>= 7.4 mmol/L	50%	53%	-0.82 (-4.08-2.45)	
Median creatinine				**0.82**
< 97 mmol/L	43%	49%	1.91 (-1.25-5.06)	
>= 97 mmol/L	57%	51%	2.43 (-0.73-5.59)	
Loop diuretics usage				**0.53**
Yes	53%	50%	1.54 (-1.62-4.70)	
No	47%	50%	2.97 (-0.19-6.13)	
Overall	**100%**	**100%**	**2.17 (-0.06-4.39)**	



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Secondary Outcomes

	Liberal fluid intake (N = 242)	Fluid restriction (N = 233)	P value
Key secondary outcome			
Thirst Distress Scale in HF (TDS-HF)	**16.9 (15.8 – 18.0)**	**18.6 (17.5 – 19.6)**	**<0.001**
Secondary outcomes			
Reported fluid intake (ml)	**1764 [1488 – 2156]**	**1480 [1357 – 1561]**	**<0.001**
KCCQ-Clinical Summary Score	**75.9 (73.4 – 78.4)**	**74.5 (71.9 – 77.1)**	**0.032**
KCCQ-Total Summary Score	**78.5 (75.9 – 81.1)**	**77.2 (74.5 – 79.9)**	**0.020**
KCCQ-OSS (-5 to +5)	101 (41.7%)	96 (41.2%)	0.19
KCCQ-OSS (-5 or less)	65 (26.9%)	78 (33.5%)	
KCCQ-OSS (+5 or more)	76 (31.4%)	59 (25.3%)	

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Secondary Outcomes

	Liberal fluid intake (N = 242)	Fluid restriction (N = 233)	P value
Death	1 (0.4%)	2 (0.8%)	0.62
All-cause hospitalization	20 (7.9%)	15 (6.0%)	0.42
Hospitalization for HF	4 (1.6%)	4 (1.6%)	1.00
IV loop diuretics usage	5 (2.0%)	7 (2.8%)	0.54
Acute kidney injury	3 (1.2%)	4 (1.6%)	0.72
Δ NT-proBNP (ng/L) Baseline – 3M	-7.0 [-90.0 – 100.0]	-1.5 [-98.3 – 133.8]	0.52
Δ Weight (kg) Baseline – 3M	0.0 [-1.0 – 1.2]	0.0 [-1.1 – 1.0]	0.39
Loop diuretics dose increase/ initiation	10 (3.9%)	14 (5.6%)	0.38
Loop diuretics dose decrease/ termination	11 (4.3%)	9 (3.6%)	0.68
Any HF medication changes	48 (18.9%)	49 (19.7%)	0.82

Conclusion

- Difference in KCCQ-OSS after adjustment for baseline scores after three months was 2.17 (95%CI -0.06–4.39; P=0.06)
  - in favour of liberal fluid intake, but the primary outcome was not met

- Thirst distress was higher in the fluid restriction group
- No differences were observed for safety events between groups

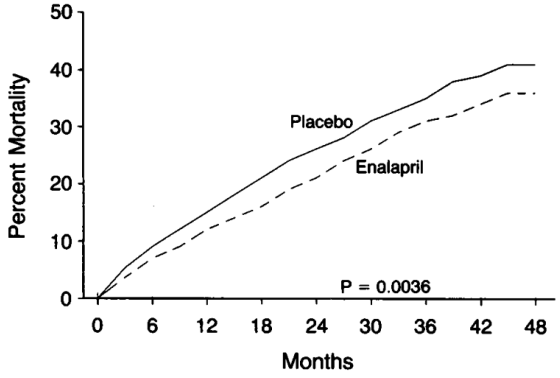
- The FRESH-UP study questions the benefit of fluid restriction in chronic heart failure

Points to discuss

- Primary endpoint
- Physiology
- Background fluid management

Primary Endpoint

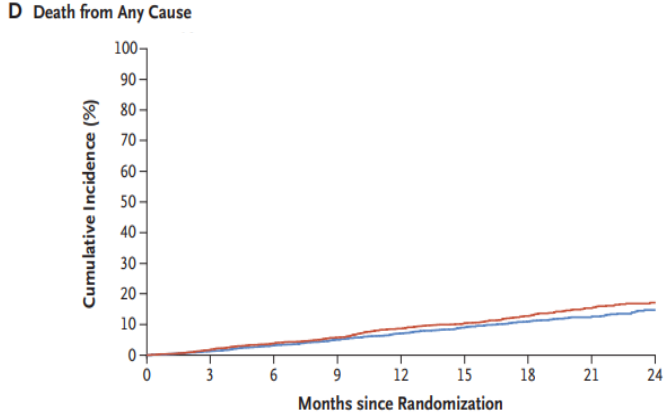
SOLVD (1991)



Placebo	1284	1159	1085	1005	939	819	669	487	299
Enalapril	1285	1195	1127	1069	1010	891	697	526	333

Figure 1. Mortality Curves in the Placebo and Enalapril Groups.

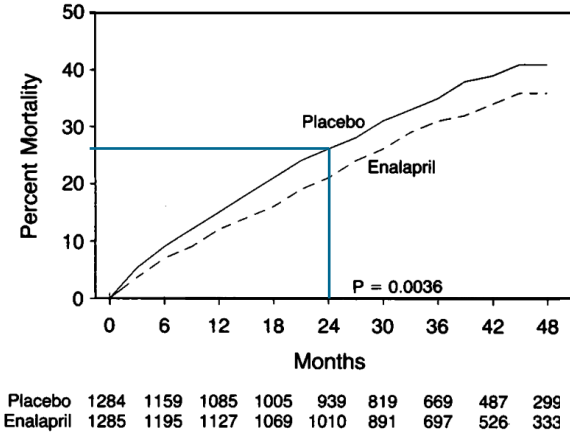
DAPA-HF (2019)



No. at Risk									
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233

The SOLVD investigators. *N Engl J Med* 1991
Mc Murray et al. *N Engl J Med* 2019

SOLVD (1991)



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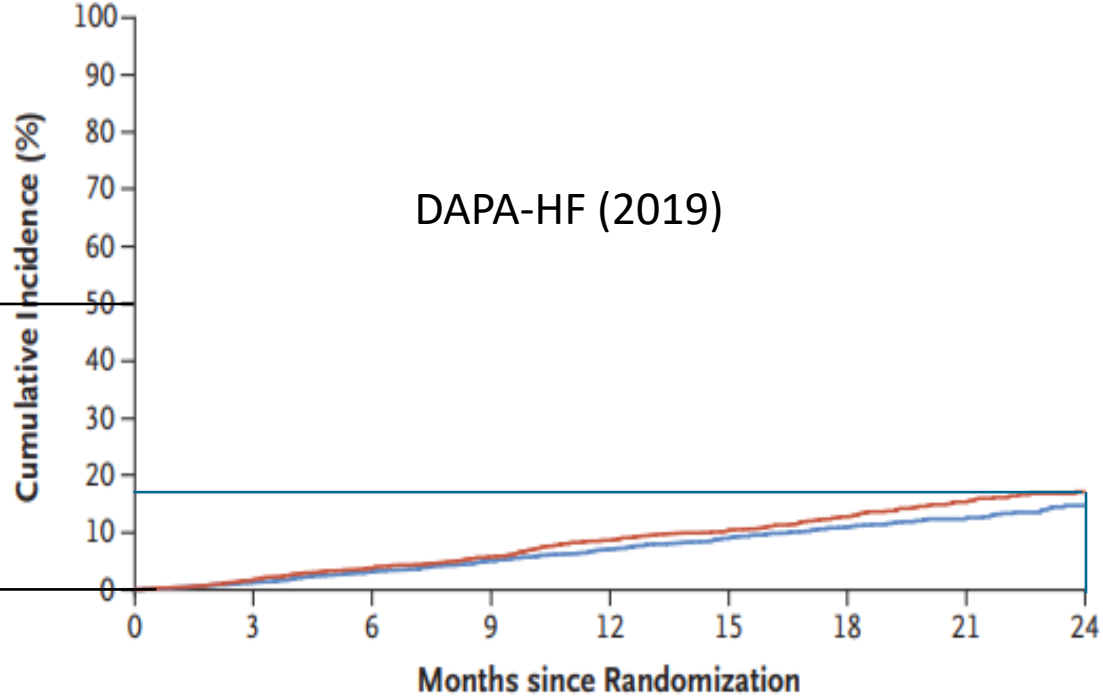

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The SOLVD investigators. *N Engl J Med* 1991
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Primary Endpoint

There are three major goals of treatment for patients with HFrEF: (i) reduction in mortality, (ii) prevention of recurrent hospitalizations due to worsening HF, and (iii) improvement in clinical status, functional capacity, and QOL.[100–102]

Mc Donagh et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021

Preferences of heart failure patients in daily clinical practice: quality of life or longevity?

Patient preferences of 100 patients with HF were assessed in interviews using the time trade-off (TTO) approach. Health-related quality of life (HR-QoL) was assessed with the EQ-5D and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Patients' own estimation of life expectancy was assessed with a visual analogue scale (VAS). Of the 100 patients (mean age 70 ± 9 years; 71% male), 61% attach more weight to quality of life over longevity; while 9% and 14% were willing to trade 6 and 12 months, respectively, for perfect health and attach more weight to quality of life. Patients willing to trade time had a significantly higher level of NT-proBNP and reported significantly more dyspnoea during exertion. Predictors of willingness to trade time were higher NT-proBNP and lower EQ VAS.

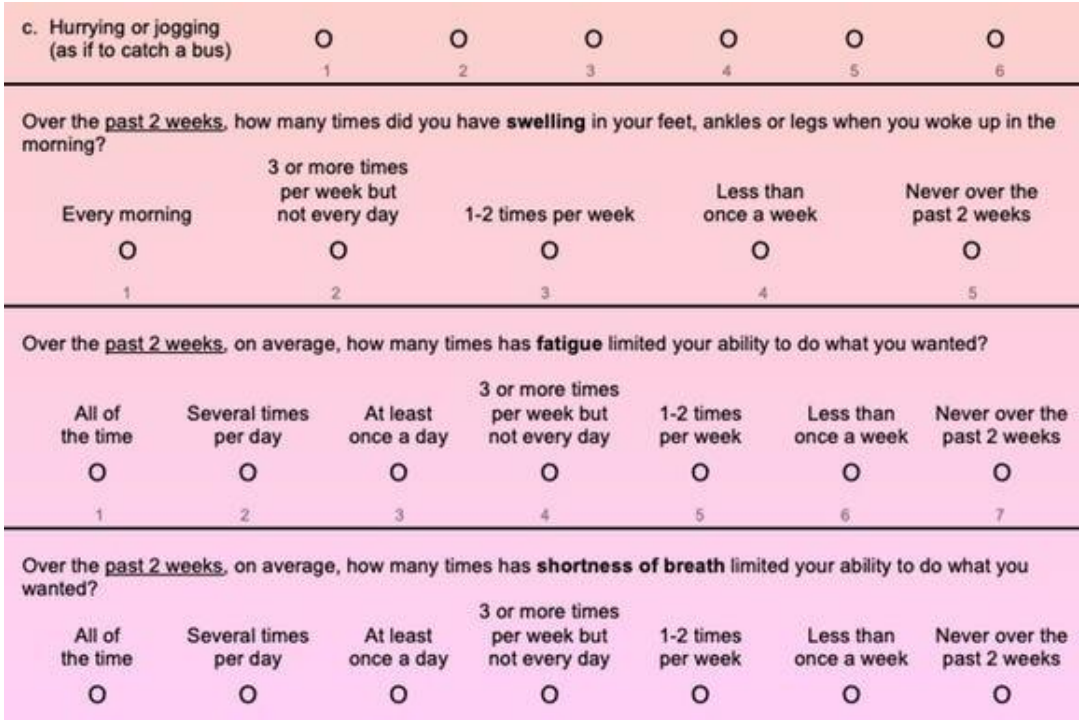
The majority of HF patients attach more weight to quality of life over longevity. There was no difference between both groups with respect to life expectancy described by the patients. These insights enable open and personalized discussions of patients' preferences in treatment and care decisions, and could guide the future development of more patient-centred care.

Kraai et al. Eur J Heart Fail. 2013 (15):1113-1121

Kansas City Cardiomyopathy Questionnaire

- Developed in 2000
- 23 questions

- Several domains
  - Seven subscores
  - Three summary scores
  - Maximum 100 points



c. Hurrying or jogging (as if to catch a bus)

O	O	O	O	O	O
1	2	3	4	5	6

Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O

Green et al. J Am Coll Cardiol 2000

JAMA Cardiology | Original Investigation

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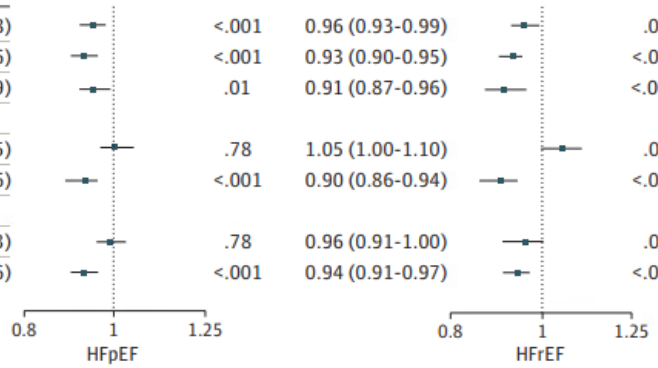
Association of Serial Kansas City Cardiomyopathy Questionnaire Assessments With Death and Hospitalization in Patients With Heart Failure With Preserved and Reduced Ejection Fraction

A Secondary Analysis of 2 Randomized Clinical Trials

Figure 4. Association of Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-os) With All-Cause Death in Patients With Heart Failure With Preserved Ejection Fraction (HFpEF) and Heart Failure With Reduced Ejection Fraction (HFrEF) in Unadjusted Analysis

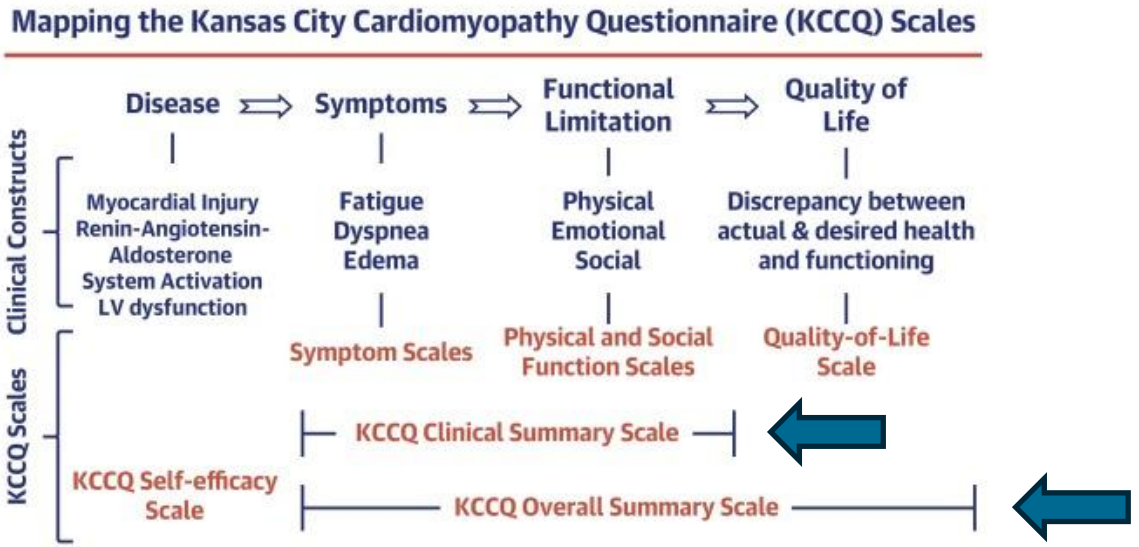
KCCQ-os Unadjusted Models	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Prior	0.95 (0.92-0.98)	<.001	0.96 (0.93-0.99)	.004
Current	0.93 (0.90-0.96)	<.001	0.93 (0.90-0.95)	<.001
Change	0.95 (0.92-0.99)	.01	0.91 (0.87-0.96)	<.001
Prior and current				
Prior	1.00 (0.97-1.05)	.78	1.05 (1.00-1.10)	.07
Current	0.93 (0.89-0.96)	<.001	0.90 (0.86-0.94)	<.001
Change and current				
Change	0.99 (0.96-1.03)	.78	0.96 (0.91-1.00)	.07
Current	0.93 (0.90-0.96)	<.001	0.94 (0.91-0.97)	<.001



Hazard ratios (HRs) for current and prior KCCQ-os are scaled per 5 points. Hazard ratios for change in KCCQ-os are per 5-point change from prior to current visit. Hazard ratios less than 1 suggested lower all-cause death and HR greater than 1 suggested higher all-cause death.

Kansas City Cardiomyopathy Questionnaire

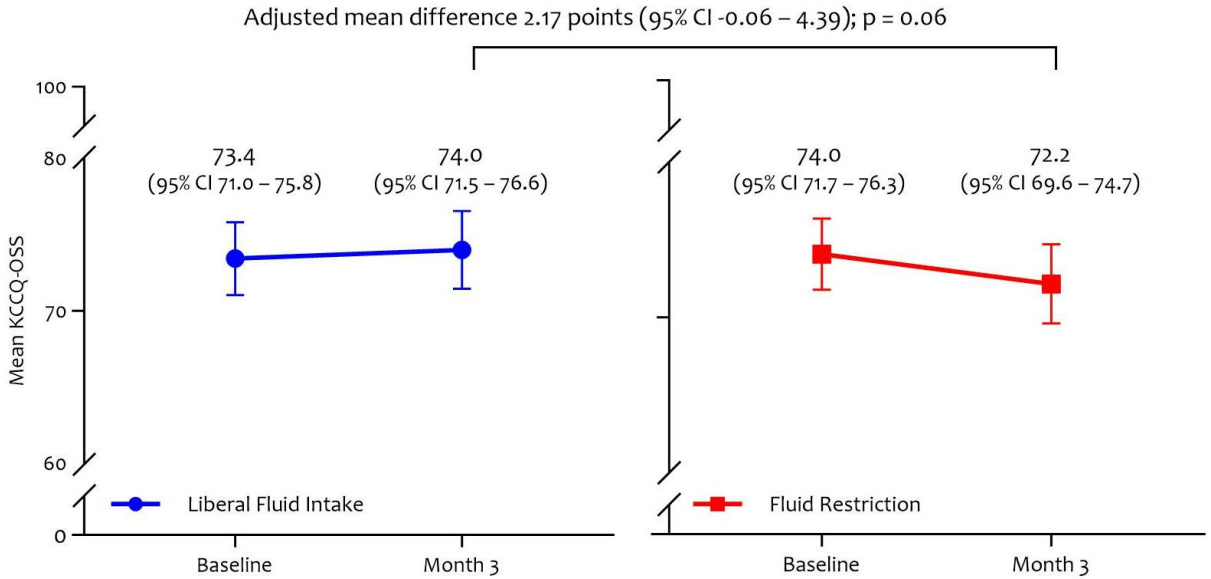
CENTRAL ILLUSTRATION: Conceptual Mapping of the Kansas City Cardiomyopathy Questionnaire to Different Manifestations of Heart Failure



Spertus, J.A. et al. J Am Coll Cardiol. 2020;76(20):2379-90.

Change in KCCQ: population level

- DAPA-HF:
  2.3 points difference
- EMPEROR-Reduced:
  1.5 points difference
- PARADIGM-HF:
  1.3 points difference



FDA and KCCQ

This qualification statement supports the KCCQ-23 Total Symptom Score, Physical Limitations Score and Clinical Summary Score as measures of their respective concepts in drug development.

www.FDA.gov

Would *fluid restriction* get FDA approval…?

This qualification statement supports the KCCQ-23 Total Symptom Score, Physical Limitations Score and Clinical Summary Score as measures of their respective concepts in drug development.

	Liberal fluid intake (N = 242)	Fluid restriction (N = 233)	P value
KCCQ-Clinical Summary Score	75.9 (73.4 – 78.4)	74.5 (71.9 – 77.1)	0.032
KCCQ-Total Summary Score	78.5 (75.9 – 81.1)	77.2 (74.5 – 79.9)	0.020

www.FDA.gov

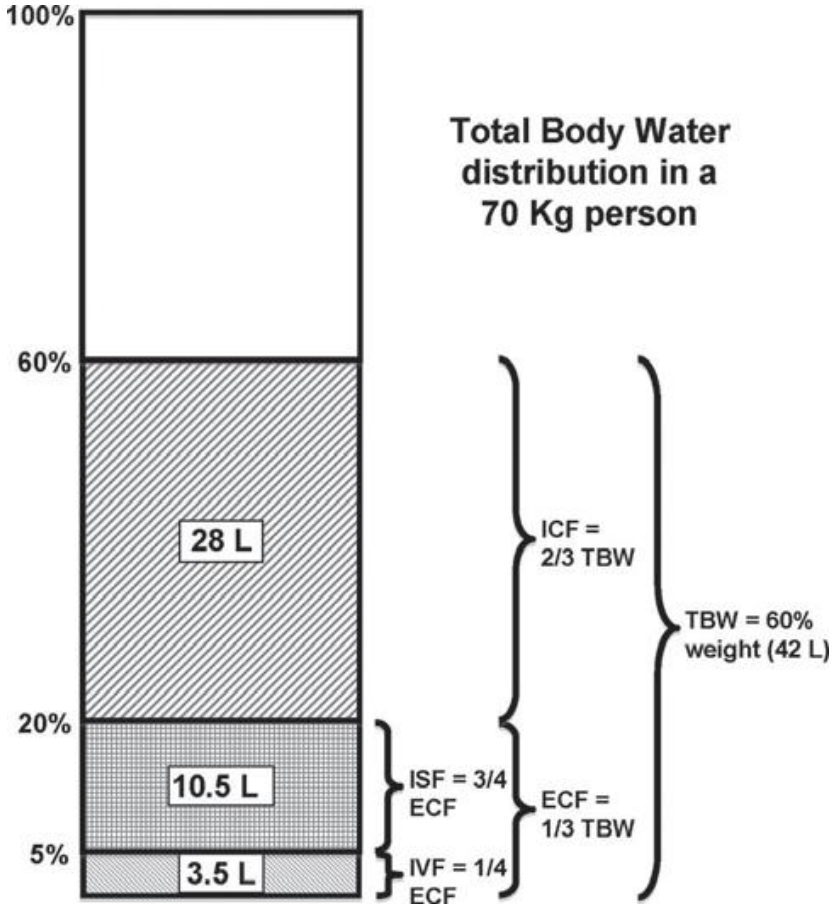
Fluid distribution

- 2000ml free water
  - 667ml extracellular
    - **167** ml intravascular

- 70% in venous pool

→ **<u>50 ml</u>** in effective circulating volume

TBW= total body water
ICF=intracellular fluid
ECF=extracellular fluid
ISF= interstitual fluid
IVF=intravascular fluid



Fallick et al. Circ Heart Fail. 2011;4:669-675c

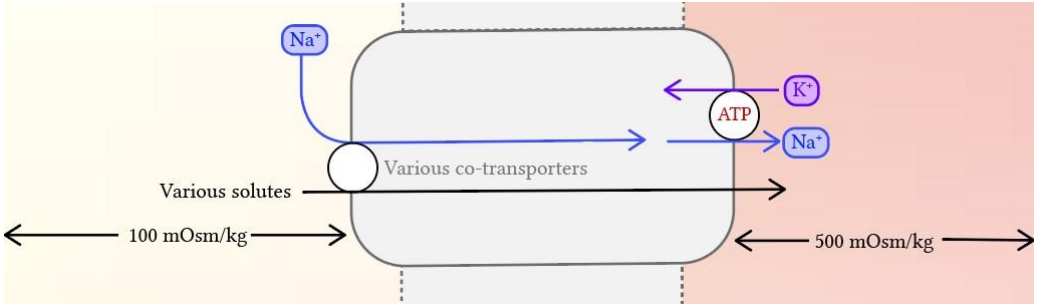
Venous (splanchic) reservoir

- More compliant
- 70% total blood volume
- Rapid fluid shifts up till **800ml** within minutes

Kraai et al. Eur J Heart Fail. 2013 (15):1113-1121

Sodium and free water

- Volumeregulation = sodium regulation
- Water regulation = osmol regulation



→ water follows sodium

Background Fluid Management

- where patients ‘drilled’ to a fluid restriction regime ?

- Is 1764 ml [1488 – 2156] really liberal intake?

Background Fluid Management

FRESH-UP
Total study population

N = 504

European Food Safety Authority

EFSA Journal 2010; 8(3):1459

SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for water[1]

EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

This Opinion of the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA) deals with the setting of dietary reference values for water for specific age groups. Adequate Intakes (AI) have been defined derived from a combination of observed intakes in population groups with desirable osmolarity values of urine and desirable water volumes per energy unit consumed. The reference values for total water intake include water from drinking water, beverages of all kind, and from food moisture and only apply to conditions of moderate environmental temperature and moderate physical activity levels (PAL 1.6). AIs for infants in the first half of the first year of life are estimated to be 100-190 mL/kg per day. For infants 6-12 months of age a total water intake of 800-1000 mL/day is considered adequate. For the second year of life an adequate total water intake of 1100-1200 mL/day is defined by interpolation, as intake data are not available. AIs of water for children are estimated to be 1300 mL/day for boys and girls 2-3 years of age; 1600 mL/day for boys and girls 4-8 years of age; 2100 mL/day for boys 9-13 years of age; 1900 mL/day for girls 9-13 years of age. Adolescents of 14 years and older are considered as adults with respect to adequate water intake. Available data for adults permit the definition of AIs as 2.0 L/day (P 95 3.1 L) for females and 2.5 L/day (P95 4.0 L) for males. The same AIs as for adults are defined for the elderly. For pregnant women the same water intake as in non-pregnant women plus an increase in proportion to the increase in energy intake (300 mL/day) is proposed. For lactating women adequate water intakes of about 700 mL/day above the AIs of non-lactating women of the same age are derived.

Total fluid intake and its determinants: cross-sectional surveys among adults in 13 countries worldwide

C. Ferreira-Pêgo[1,2] · I. Guelinckx[3] · L. A. Moreno[4] · S. A. Kavouras[5] · J. Gandy[6,7] · H. Martinez[8,9] · S. Bardosono[10] · M. Abdollahi[11] · E. Nasseri[11] · A. Jarosz[12] · N. Babio[1,2] · J. Salas-Salvadó[1,2]

Table 3 Percentage of the population by adequacy percentage categories, achieving EFSA adequate intake of water from fluids

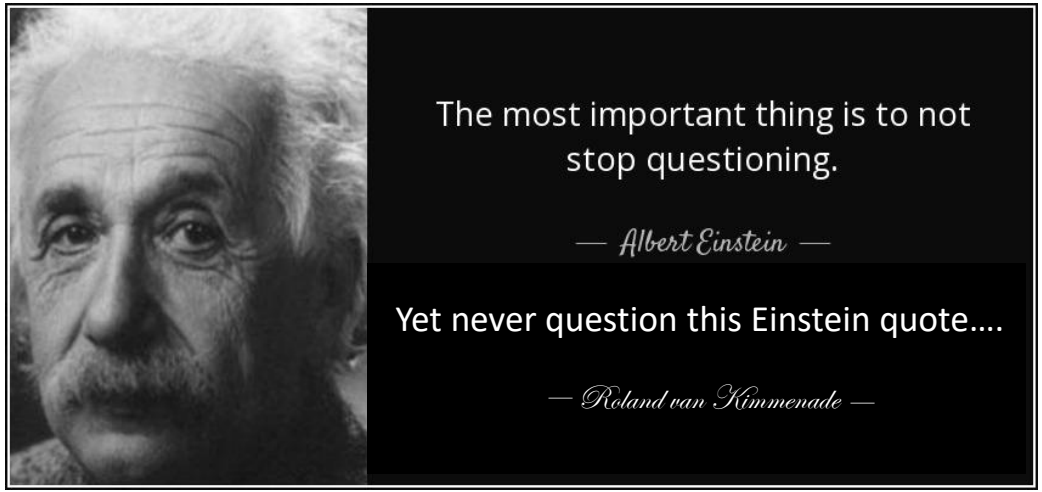
	≤50 %	50–75 %	75–100 %	>100 %
Mexico ($n = 1498$)	13.5	22.4	20.8	43.3
Brazil ($n = 1924$)	7.5	16.6	17.7	58.2
Argentina ($n = 507$)	2.8	13.2	19.9	64.1
Spain ($n = 1240$)	7.4	17.1	26.2	49.3
France ($n = 1534$)	15.9	28.2	25.0	30.9
UK ($n = 897$)	1.2	10	17.8	70.9
Germany ($n = 1868$)	4.1	7.9	14.2	73.8
Poland ($n = 1062$)	6.1	26.5	32.8	34.7
Turkey ($n = 961$)	5.8	16.8	19.5	58.4
Iran ($n = 572$)	5.3	21.2	23.1	50.5
China ($n = 1466$)	14.1	23.6	23.7	38.7
Indonesia ($n = 1366$)	2.7	15.5	15.6	66.2
Japan ($n = 1381$)	17.1	29.8	24.2	28.8
Total population ($n = 16{,}276$)	9.0	19.3	21.2	50.5

Conclusion

- The FRESH-UP study questions the benefit of fluid restriction in chronic heart failure

- Patient centered research is key in pragmatic trials

Conclusion


The most important thing is to not stop questioning.
— Albert Einstein —
Yet never question this Einstein quote....
— Roland van Kimmenade —

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Herrmann et al. Liberal Fluid Intake versus Fluid Restriction in Chronic Heart Failure: a randomized clinical trial. *Nat. Med 2025 in press*

nature medicine

DOI : 10.1038/s41591-025-03628-4

Radboudumc

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

Grand Rounds Rethinking Clinical Trials

May 2nd 2025

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