Supplementary Appendix

1. Weekly BCM measurement schedule

Throughout the three month study, 55 whole-body bioimpedance measurements had to be performed every week before the dialysis treatments, giving a total of 55x13=715 measurements. Performance of such a large number of measurements, calculations and prescriptions required proper scheduling, as displayed in Figure S1. Measurements were performed on four days of the week (Monday to Thursday), in morning and afternoon shifts. New fluid management plans were then calculated and transferred to the clinician on Friday, and new prescriptions were prepared for the following week. New targets were to be reached at the end of the week after the measurements were performed. How to reach these weekly targets on a day-to-day basis was solely controlled by the clinician, no proposals were given for the first and second dialysis day of the week.

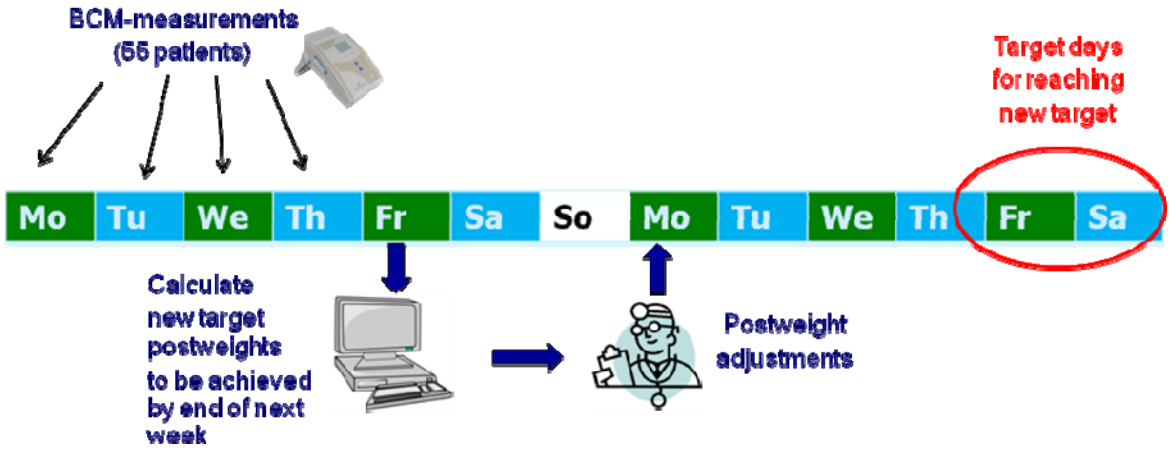


Figure S1: Schedule of weekly BCM measurements and postweight adjustments.

2. TAFO in Nephrocare Centers

Prior to the study start, the bioimpedance device used in this study (BCM) had been introduced into Fresenius Nephrocare centers, measuring fluid status on a regular basis in more than 17.000 patients. Figure S2 shows the distribution of TAFO in these centers. TAFO in the Nephrocare centers ranged from -1.4L to 2.8L (10^{th} and 90^{th} percentile) with a median of 0.5L. For comparison, TAFO in this study ranged from -1.1L to 3.4L at baseline, and from -0.7L to 2.1L at study end. The improvement achieved in this center compared to the Nephrocare reference suggests that centers may benefit from introducing a strategy such as that investigated in the current study.

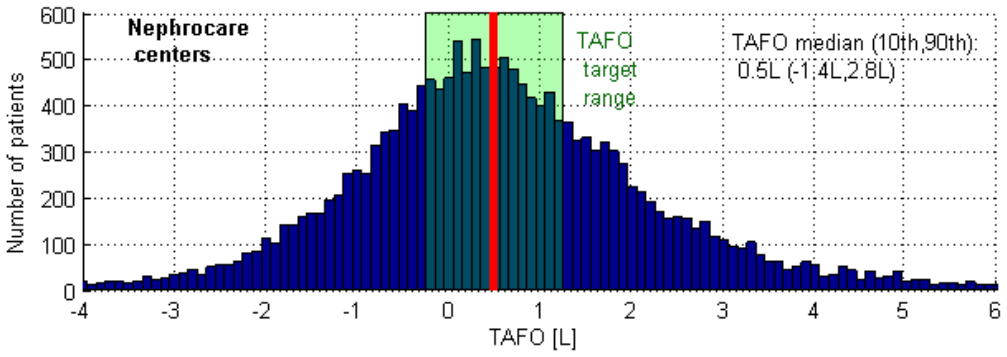


Figure S2. Distribution of TAFO in >17.000 patients in Fresenius Nephrocare Centers.

3. *Postweight prescription rules*

Postweight adjustment was mandatory (if clinically possible) in all patients who were outside the TAFO target range (-0.25 to 1.25L) after a BCM measurement. Further lowering was recommended (but not mandatory) in patients who were in the upper half of the target range (from +0.51 to 1.25L), while no change was recommended for patients in the lower part of the target range (i.e. from -0.25 to +0.49L). The rationale behind this was that as long as patients tolerated mild dehydration there was no clinical reason to increase their postweight. Extreme dehydration however, even if tolerated, was not acceptable due to risks such as myocardial stunning, access failure or decline in residual renal function.

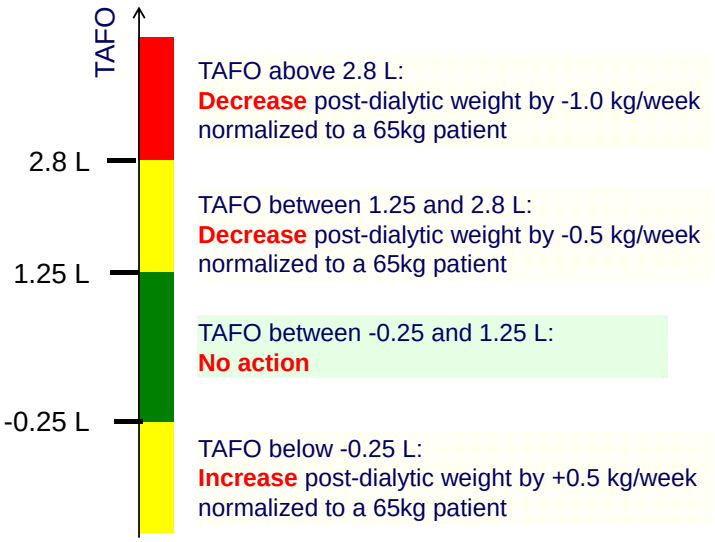


Figure S3. Postweight prescription steps according to a patient's time averaged fluid overload and weight (TAFO).

4. Weekly fluid status center overview

In order to concentrate the available time on most critical patients with regard to fluid status, a weekly graphical center overview of fluid status was generated depicting pre- and post-dialysis FO, TAFO, and a TAFO target range (Figure S4). It was the aim of the study to bring all the TAFO marks into the magenta colored TAFO target range. The x-axis denotes the patient ID, and each bar in the diagram represents one patient; only the last available BCM measurements were used for this diagram.

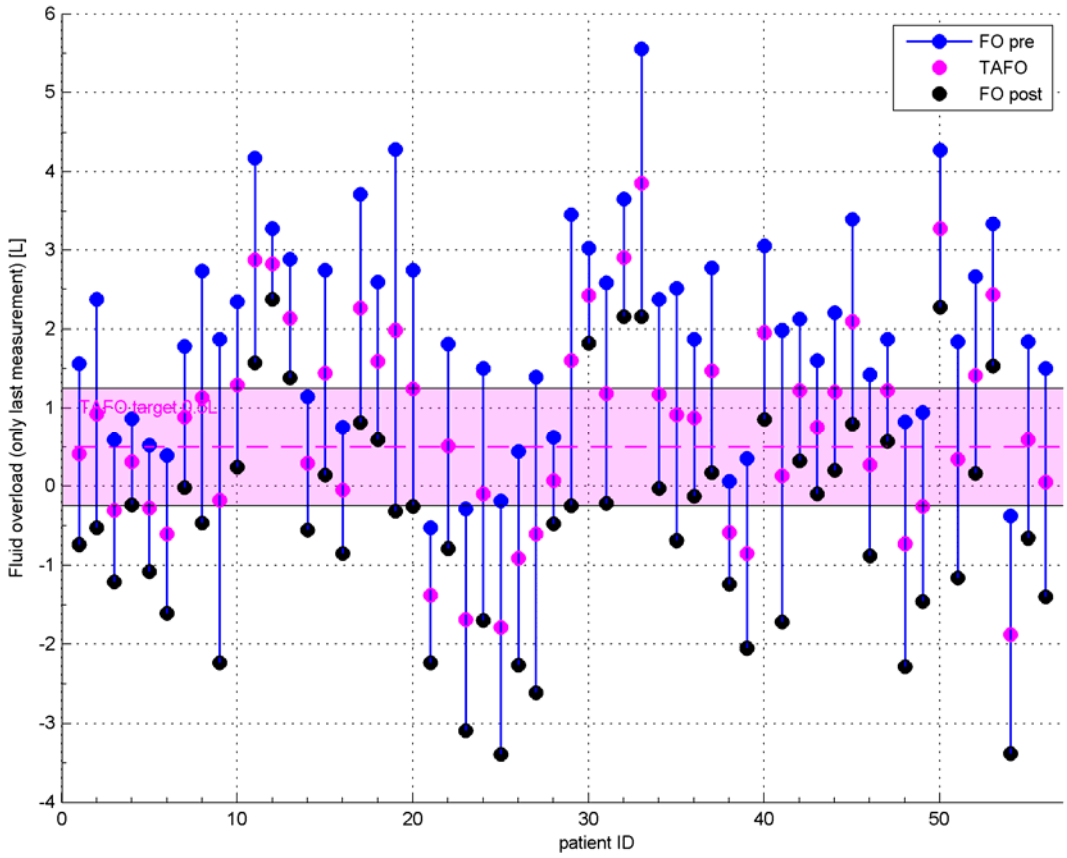


Figure S4. Center overview of fluid status. This graph was conveyed every week to allow quick identification of patients with extreme over- and dehydration.

5. Fluid management plan

Figure S5 gives an example of the weekly fluid management plans. To produce these plots, data was extracted from a clinical database and further processed in a Matlab R2011b script to calculate targets according to the predefined rules, and to plot the diagrams. The first diagram at the upper left displays pre- and post-dialysis fluid overload together with TAFO. Real measurements were indicated by a box while all remaining FO values were calculated from preweight differences and UF volumes as described earlier in the methods section. As an example for this calculation, assume a patient presented a FO measurement of 3L on a Monday having a preweight of 70 kg. If the same patient had a preweight of 69 kg on the following Wednesday, $FO_{Wedesday}$ would have been estimated as 3L + (69-70) = 2L. The second upper diagram displays pre-dialysis systolic and diastolic blood pressures measured on the dialysis machine by the Fresenius blood pressure monitor (BPM), and the third diagram depicts hemoglobin measured by the Fresenius blood volume monitor (BVM) during the first and the last 2 minutes of the treatment.

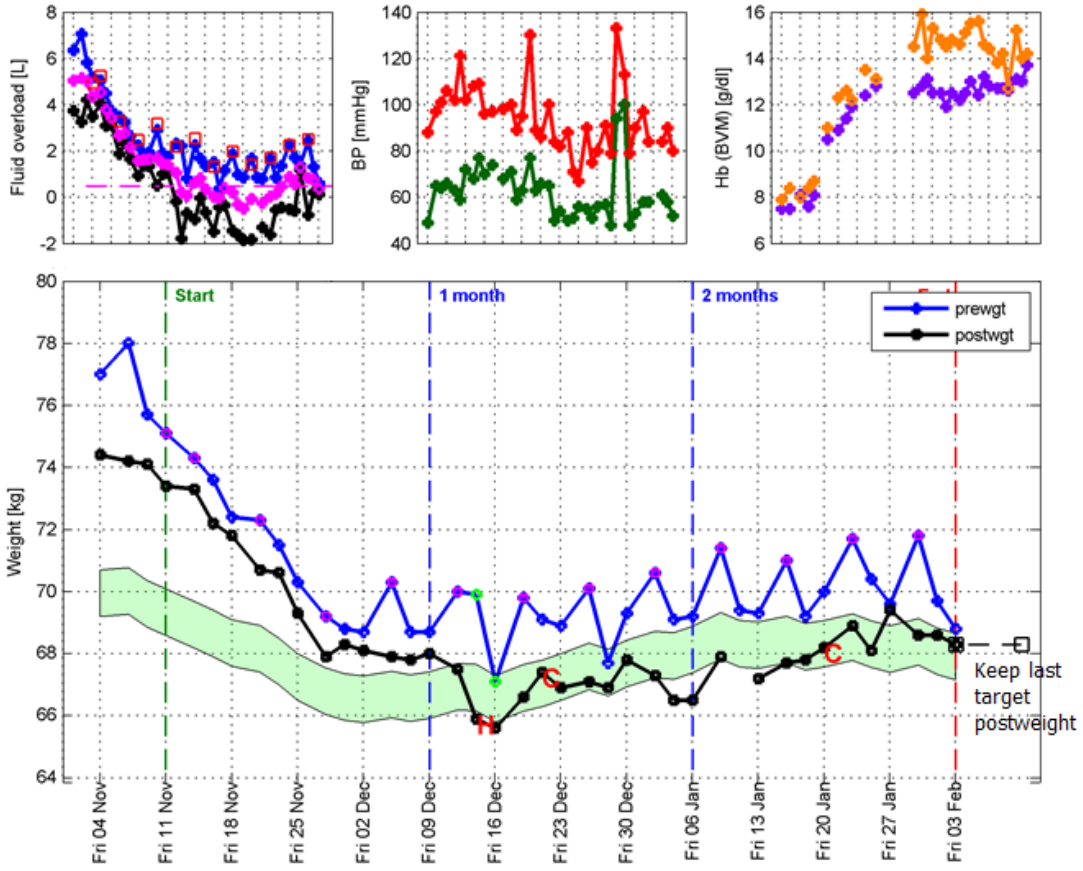


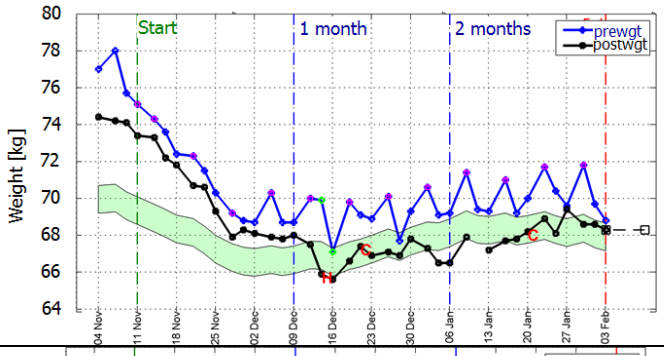
Figure S5. Example of a fluid management plan at study end.

The lower diagram is the most important one and displays pre- and postweight together with a green target range for the postweight. In addition, a line originating at the last postweight value indicated the target for the following week, together with a small annotation specifying the target postweight in kilograms. The occurrence of intradialytic symptoms was indicated in the same diagram by the small red letters “C” for cramps, “H” for hypotension” and “O” for other symptoms. While the three upper diagrams serve as “watchdog” to detect detrimental trends in blood pressure or hemodilution/-concentration, the lower diagram was used for adjusting postweights and deciding whether the onset of symptoms may not allow further modification of dry weight. Thus, the principal idea was to display all relevant clinical information for a fluid management decision on a single diagram.

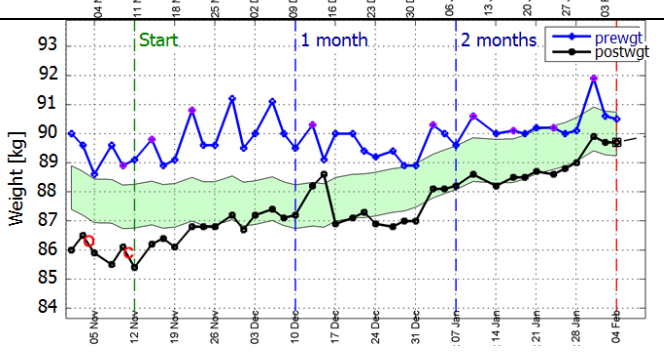
The example in Figure S5 shows a patient who was overhydrated by more than 6L before dialysis, and whose fluid status was gradually normalized over the first month and maintained there until study end. The hemoglobin increased dramatically in the reduction phase even though EPO and iron prescription were not changed. This is most likely an effect of hemoconcentration caused by the fact that part of the excess fluid had accumulated in the blood compartment and diluted hemoglobin. Therefore, anemia was corrected in this patient simply by normalizing fluid status.

6. *Individual examples*

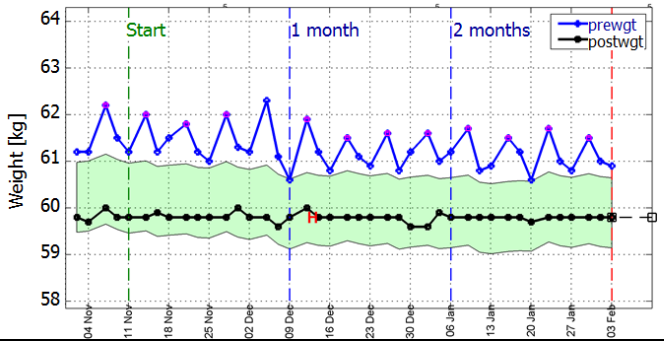
Figure S6. Four examples of fluid status optimization. The two lines indicate pre- and postweight over the complete study period. The green range represents a target range for the postweight. If the postweight is in the middle of the green range, then time averaged fluid overload (TAFO) is automatically on target.



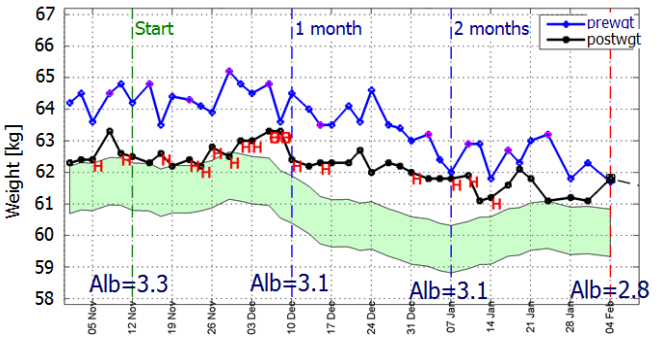
a) Successful fluid reduction
Age: 60 years, male; 5 years on dialysis; Catheter; Metabolic, gastrointestinal and psychiatric disease. No EPO, iron=100mg/week. BCM was very useful in reducing the patient's fluid status. Pre-dialysis hemoglobin improved from 8 to 12 mg/dl after fluid status correction.



b) Improvement of residual function
Age: 86 years, male. Patient had only 500ml of residual function at study start and was dehydrated after dialysis. After increasing his fluid status into the target range, residual function recovered gradually to 1600ml. Postweight maintained on lower edge of target range even though bodycomposition increased in second half of study.



c) No change necessary
Age 81 years, female. This patient had a very stable body composition, and was on target throughout the whole study. No postweight adjustments were necessary.



d) Difficult to reduce (low albumin)
Age: 77 years, female; 1.5 years on dialysis, no co-morbidities. This patient's fluid overload was very difficult to reduce (hypotension occurred when trying to reach the target range). Albumin was only 3.3 g/dl at study start, and declined further to 2.8 g/dl after three months. Difficulties may have been linked to impaired vascular refilling due to low albumin.

7. *Weekly development of fluid status*

The development of average weekly TAFO over the complete study is shown in Figure S7. Each dot in the diagram represents the measurement of a patient; the respective week is indicated by the x-axis ranging from week 1 to week 13. The green bar represents the TAFO target range. Only minor changes in the mean TAFO of each week can be observed, since both overhydrated and dehydrated patients moved closer to the target range. Therefore the success of the treatment strategy can be better expressed in terms of scatter or SD, as shown in Figure S8. Overall scatter improved in the first 7 weeks, and then became slightly worse again for the following 2-3 weeks which may have been caused by three consecutive holidays in Spain (Christmas, New Year and the 6th of January, Epiphany).

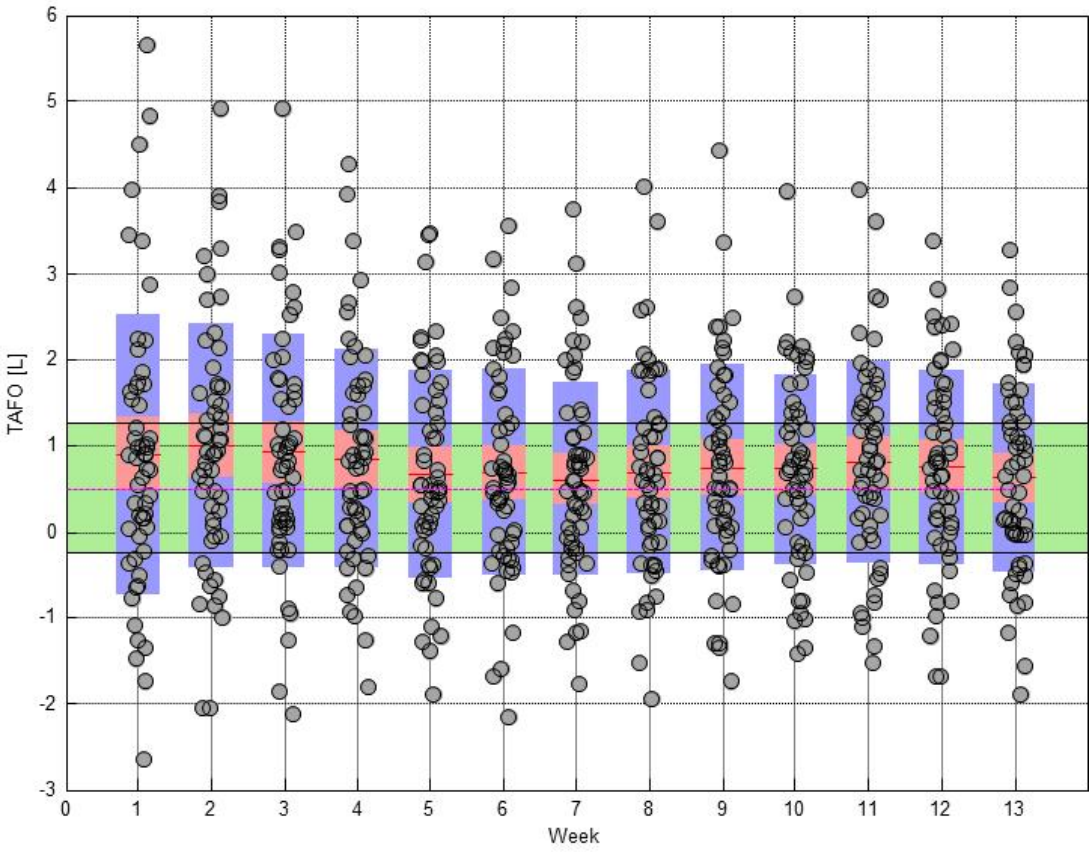


Figure S7. Development of time averaged fluid overload (TAFO) over the three month study period.

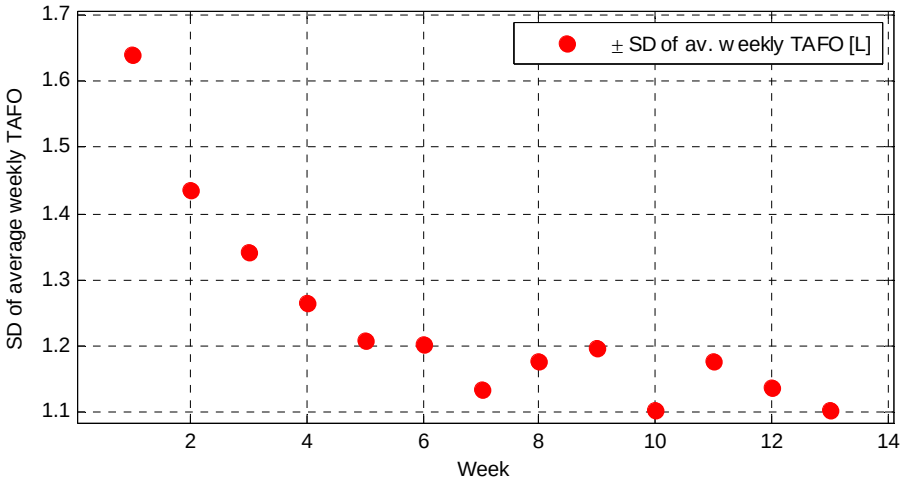


Figure S8. Reduction of SD in average weekly TAFO. Scatter decreases significantly during the first weeks, and increases again in weeks 8 and 9 due to three holidays in Spain (Christmas, New Year and Epiphany).

8. Intradialytic symptoms and adverse events

Intradialytic symptoms which occurred during the course of the study were recorded and classified into three different types: cramps, hypotension and other symptoms. Table S1 gives an overview of how many treatments were accompanied by symptoms in each of the study weeks. Note, that patients may have had more than one symptom in one treatment, which explains the discrepancy to the number of patients with symptoms reported in the main manuscript.

An overview of all non-fatal (N=10) and fatal (N=1) adverse events is provided in Table S2.

Table S1. Number of treatments with intradialytic symptoms, grouped by fluid status at baseline (dehydrated, on target, overloaded). H=hypotensive episode, C=cramps, O=other symptoms.

Study week	**Dehydrated**				**On target**				**Overloaded**				**All patients**			
	H	**C**	**O**	**Σ**	**H**	**C**	**O**	**Σ**	**H**	**C**	**O**	**Σ**	**H**	**C**	**O**	**Σ**
1	8	1	2	**11**	2	0	6	**8**	2	0	1	**3**	12	1	9	**22**
2	3	0	0	**3**	4	0	0	**4**	3	1	6	**10**	10	1	6	**17**
3	5	2	0	**7**	5	1	4	**10**	5	1	2	**8**	15	4	6	**25**
4	5	4	2	**11**	2	0	3	**5**	6	2	5	**13**	13	6	10	**29**
5	3	0	1	**4**	0	0	2	**2**	7	1	9	**17**	10	1	12	**23**
6	11	0	4	**15**	6	1	6	**13**	5	6	2	**13**	22	7	12	**41**
7	5	0	3	**8**	8	1	8	**17**	5	2	6	**13**	18	3	17	**38**
8	2	1	3	**6**	2	2	3	**7**	2	2	0	**4**	6	5	6	**17**
9	4	1	1	**6**	3	0	7	**10**	3	0	0	**3**	10	1	8	**19**
10	2	0	0	**2**	2	0	6	**8**	3	2	6	**11**	7	2	12	**21**
11	4	2	1	**7**	5	0	13	**18**	4	1	5	**10**	13	3	19	**35**
12	5	1	1	**7**	2	0	4	**6**	4	0	3	**7**	11	1	8	**20**
13	5	1	0	**6**	1	0	5	**6**	3	1	4	**8**	9	2	9	**20**

Table S2. Overview of adverse events which occurred during the study.

Number	Adverse event	Fatal?	Related to study procedures?
1	Post-dialysis hypotension that needs volume replacement	No	*Yes*
2	After week-end presents dyspnea and edemas	No	*Yes*
3	Post-dialysis hypotension that needs volume replacement	No	*Yes*
4	Subdural Hematoma and arm fracture secondary to accidental fall	No	No
5	Hospitalization for hematuria.	No	No
6	Hospitalization for amputation of necrotic toe	No	No
7	Hospitalization for a vascular access complication	No	No
8	Hospitalization for removing left renal upper polar cap (tumor)	No	No
9	Hospitalization for surgery of ischemic ulcers in inferior extremities	No	No
10	Cellulitis associated with hemodialysis vascular access	No	No
11	Sudden death at home	*Yes*	No