Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients

Boon K. Tan[1,2,6], Zanzhe Yu[1,3,6], Wei Fang[3], Aiwu Lin[3], Zhaohui Ni[3], Jiaqi Qian[3], Graham Woodrow[4], Sarah B. Jenkins[5], Martin E. Wilkie[5] and Simon J. Davies[1,2]

[1]Institute for Science and Technology in Medicine, Keele University, Keele, UK; [2]Department of Nephrology, University Hospitals of North Midlands, Stoke-on-Trent, UK; [3]Department of Nephrology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [4]Department of Nephrology, Leeds Teaching Hospitals, Leeds, UK; and [5]Department of Nephrology, Sheffield Northern General Hospital, Sheffield, UK

Bioimpedance (BI) has the potential to enable better management of fluid balance, which can worsen over time on peritoneal dialysis (PD) due to loss of residual kidney function and progressive muscle wasting. We undertook a prospective, randomized, open-label, blinded end-point controlled trial to determine whether availability of longitudinal BI measures as vector plots helped clinicians maintain stable fluid status over 12 months in 308 peritoneal dialysis patients from the United Kingdom and Shanghai, China. Patients were recruited into 4 groups nested within a single trial design according to country and residual kidney function. Nonanuric subjects from both countries demonstrated stable fluid volumes irrespective of randomization. Hydration worsened in control anuric patients in Shanghai with increased extracellular/total body water (ECW/TBW) ratio (0.04; 95% CI: 0.01, 0.06) and reduced TBW (−1.76 L 95% CI: −2.70, −0.82), but was stable in the BI intervention group whose dialysate glucose prescription was increased. However, multilevel analysis incorporating data from both countries showed worsening ECW/TBW in active and control anuric patients. Clinicians in the United Kingdom reduced target weight in the nonanuric BI intervention group causing a reduction in TBW without beneficial effects on ECW or blood pressure. Thus, routine use of longitudinal BI vector plots to improve clinical management of fluid status is not supported.

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Correspondence: *Simon Davies, Department of Nephrology, University Hospitals of North Midlands, Newcastle Rd, Stoke-on-Trent, Keele ST4 6QG, UK. E-mail: simondavies1@compuserve.com or simonj.davies@uhns.nhs.uk*

[6]These authors contributed equally to this work.

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Optimal fluid management is one of the primary objectives of dialysis treatment, and there is significant concern that peritoneal dialysis (PD) patients can become progressively fluid-loaded with time on treatment, especially as residual kidney function declines.[1,2] There is a growing body of evidence that bioimpedance (BI) analysis has a role to play in assisting the clinician in managing fluid status;[3] this is primarily based on observational studies showing that overhydration, as determined from BI, predicts worse survival[4,5] and the demonstration that BI can detect changes following interventions designed to improve fluid status.[6,7] BI data comprise the following two components: resistance to an electrical current, typically passed through the body from the wrist to the ankle, which is inversely proportional to total body water (TBW), and reactance, which is the impedance to this alternating current, also measured in Ohms, as it passes through tissues with cell membranes and thus it is proportional to cell mass. These two components can be plotted as a two-dimensional vector and used to track changes in fluid status that could support clinical decisions (Figure 1). However, few clinical trials have been conducted that clearly demonstrate a benefit of BI over and above good-quality standard clinical management.

Longitudinal studies of body composition indicate that progressive overhydration is usually associated with a decline in muscle mass and a potential failure to adjust the dialysis prescription so as to reduce the extracellular water (ECW) volume down in parallel with this.[8–11] We hypothesized that the longitudinal application of BI alongside clinical evaluation would help the clinician identify this problem and thus make appropriate adjustments to the prescription. To test this hypothesis, we undertook a randomized controlled trial to determine whether the additional information available from longitudinal BI over 12 months could assist in maintaining stable or improved fluid status. Using the same basic design, we included four independent randomization groups comprising nonanuric and anuric patients from three UK dialysis centers (Stoke-on-Trent, Leeds, and Sheffield) and one Chinese center (Shanghai), respectively. Our aim was to determine whether routine clinical management supported by the longitudinal plot of the BI vector, which shows the direction in which fluid status is changing, resulted in more

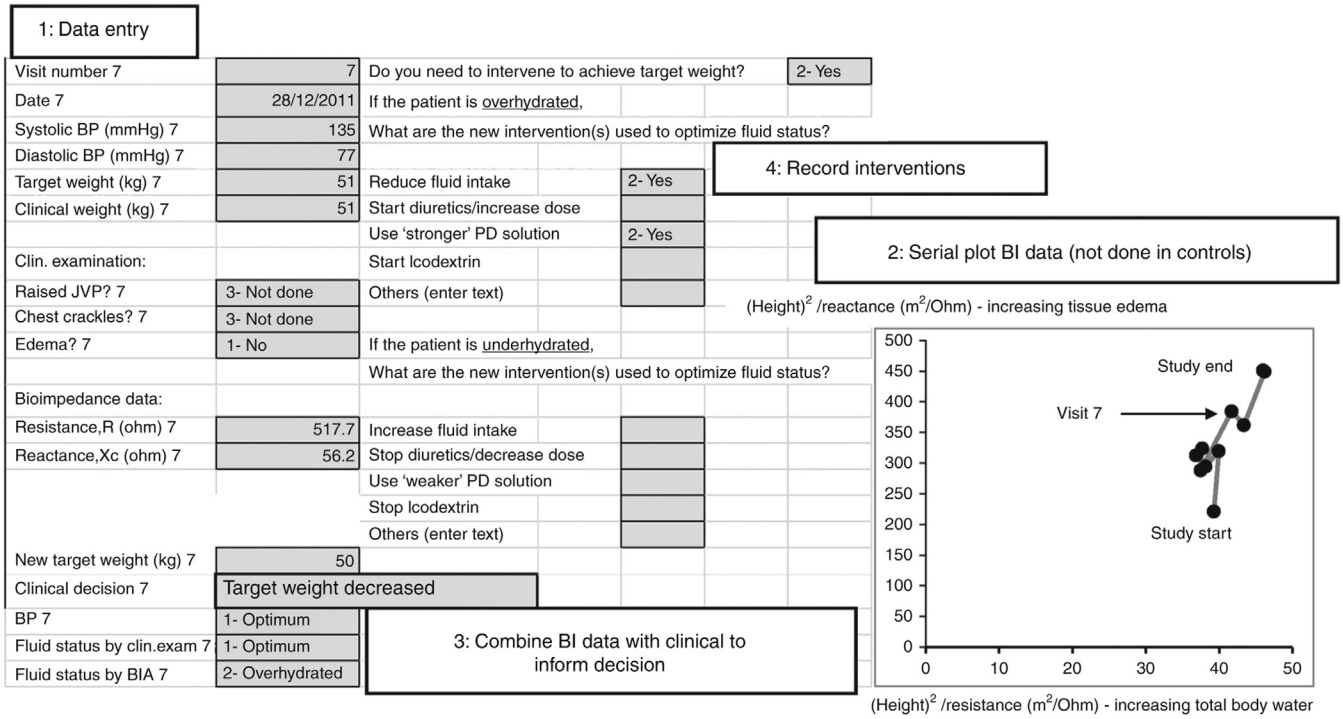

Figure 1 | The procedure for documenting clinical interventions is summarized. (Step 1) The clinical and bioimpedance (BI) data were entered onto an electronic clinical research record. For the intervention group, only BI data were automatically plotted (step 2) as the serial reciprocal height^2 (H^2) normalized data. In this format, increasing H^2/resistance implies increasing total body water and H^2/reactance reflects increasing extracellular fluid. (Step 3) This was then combined with clinical observations to inform the decision. In this example shown at assessment number 7, although the patient was clinically euvolemic, the BI indicated a progressive overhydration with lengthening and widening of the BI vector, and hence the target weight was reduced. Step 4 records the methods used to achieve this, in this case both advising reduced fluid intake and increased glucose prescription. This resulted in a temporary reduction in the phase angle, but this patient went on to become progressively overhydrated despite further reductions in target weight. This example shows that patients with unstable fluid status could have additional assessments (i.e., more than the five standard study visits; see also Supplementary Material online for further examples).

stable fluid status than control subjects. The outcome, to which the clinicians were blinded, was fluid volumes, ECW, TBW, and their ratio (ECW/TBW), as determined from the BI measurements after the trial was completed.

RESULTS

Patient characteristics

Recruitment, randomization, and dropout to and from the four study groups are summarized in the consort diagram (Figure 2). With the exception of the UK anuric group, recruitment was sufficient to test our primary outcome with 80% power to detect a 1-kg change (in ECW) in the Shanghai (nonanuric and anuric) patients and a 0.8-kg change in the UK nonanuric (UK nonanuric) patients. Failure to achieve power in the UK anuric group was because of a combination of lack of recruitment indicative of the low proportion of anuric patients in the three UK centers and a high dropout (66%). There was a nonsignificant increase in deaths in this patient group randomized to the BI intervention; careful analysis of these 4 deaths (cancer or sepsis) and adverse outcomes did not indicate any common factor or plausible relationship to the intervention, but this group was excluded from further analysis apart from the multivariate models. Dropout in the remaining groups was well balanced over the course of the study, as shown by Kaplan–Meier plots and log-rank tests (Supplementary Data, Supplementary Figure S1 online).

There were no significant differences between patients randomized to the BI intervention or control arm in any of the groups in terms of their baseline demography, dialysis prescription, residual kidney function, peritoneal membrane function, blood pressure, or body composition (Table 1). Shanghai patients tended to be younger (mean age 54.0 vs. 58.6 years), have less comorbidity (20 vs. 60% with at least one other diagnosis), and weigh significantly less than UK patients (58.9 vs. 76.8 kg), which was reflected in a lower dialysis prescription volume. The average blood pressure and peritoneal solute transport rates (PSTR) were lower in the Shanghai patients. On comparing the nonanuric patients, normalized residual renal clearances were higher in UK patients, as was the absolute residual urine volume, unless this was corrected for body weight when the difference was nonsignificant (16.7 vs. 17.4 ml/kg). As expected, anuric patients had been on PD for longer periods: Shanghai-anuric versus Shanghai-nonanuric, 58 (26–90) versus 19 (7–41) months; and UK anuric versus UK nonanuric, 57 (36–72) versus 22 (7–33) months.

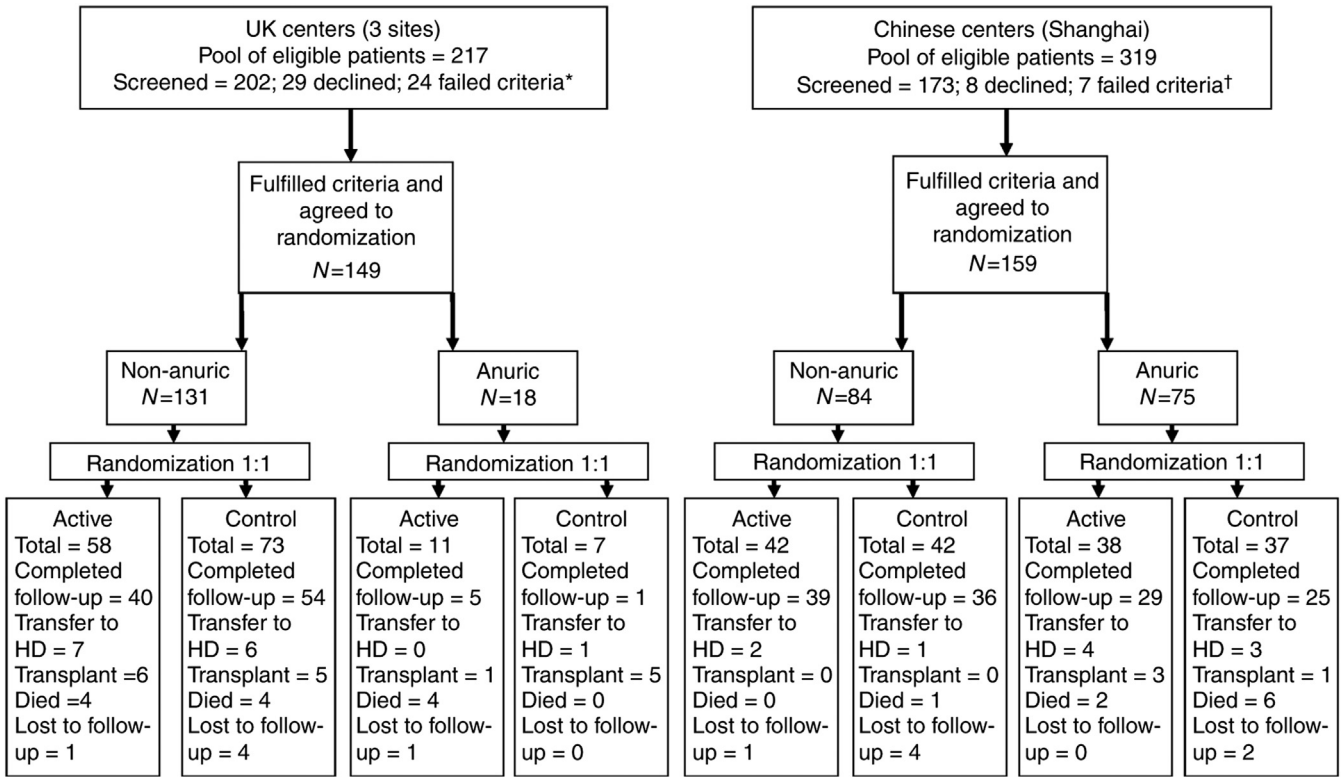

Figure 2 | Consort diagram (reasons for failing criteria for recruitment: *unlikely to remain on peritoneal dialysis [PD] for 6 months because of planned transplant or modality transfer, †unable to achieve clinical euvolemia during run-in).

Table 1 | Baseline characteristics of patient groups according to randomization

	UK nonanuric		UK anuric		SH nonanuric		SH anuric	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
N	58	73	11	7	42	42	38	37
PD duration (months, range)	18 (7–32)	22(8–34)	67(34–81)	45(36–60)	17(7–37)	24(11–41)	52(22–86)	65(31–105)
Age (year)	58.3 ± 15.3	56.9 ± 14.7	64 ± 14.7	56.4 ± 11	56.6 ± 11.2	52.5 ± 14.4	51.1 ± 13.1	55.5 ± 13.5
D/P creatinine	0.70 ± 0.12	0.68 ± 0.12	0.69 ± 0.1	0.79 ± 0.07	0.60 ± 0.09	0.58 ± 0.11	0.61 ± 0.09	0.65 ± 0.11
Albumin (g/l)	33.41 ± 4.47	33.48 ± 3.85	33.4 ± 1.9	34.3 ± 5.2	32.57 ± 2.90	32.54 ± 3.61	32.8 ± 4.3	33.4 ± 2.9
Gender F/M	20/38	29/44	7/4	4/3	26/16	31/11	19/19	14/23
Comorbidity (low/medium/high)	25/29/4	28/39/6	5/6/0	2/5/0	34/7/1	35/7/0	31/7/0	27/10/0
ECW (L)	18.3 ± 4.3	19.2 ± 4.0	16.4 ± 4.0	14.5 ± 3.0	16.7 ± 3.1	15.9 ± 2.6	16.3 ± 3.2	17.4 ± 3.5
TBW (L)	41.5 ± 8.2	42.3 ± 8.5	37.4 ± 5.6	36.1 ± 8.6	35.0 ± 5.2	33.9 ± 4.8	34.6 ± 6.6	35.8 ± 6.9
ECW/TBW	0.44 ± 0.07	0.46 ± 0.06	0.45 ± 0.1	0.42 ± 0.1	0.48 ± 0.06	0.47 ± 0.05	0.47 ± 0.06	0.49 ± 0.06
H^2/R (cm^2/Ω)	58.6 ± 13.6	59.6 ± 13.2	51.9 ± 9	47.6 ± 12	49.4 ± 11.8	48.8 ± 8.1	49.5 ± 12.3	51.9 ± 12.4
H^2/X (cm^2/Ω)	538.9 ± 172	570.1 ± 162	487.7 ± 164	384.2 ± 102	526.3 ± 132	497.5 ± 129	502.6 ± 135	560.9 ± 159
Target weight (kg)	76.2 ± 15.7	78.4 ± 18.5	72.4 ± 12.2	72.4 ± 20.6	59.9 ± 8.2	58.4 ± 8.9	58.0 ± 9.5	59.0 ± 11.0
Systolic BP (mm Hg)	136.8 ± 20.1	143.4 ± 22.5	131.8 ± 28	136.4 ± 16.6	130.2 ± 14.8	130.5 ± 17.7	128.3 ± 20.4	127.2 ± 23.0
Diastolic BP (mm Hg)	79.7 ± 11.4	81.3 ± 12.3	75.0 ± 10.3	73.9 ± 12.3	82.7 ± 11.2	83.5 ± 9.5	79.9 ± 12.1	79.5 ± 10.2
N	58	73	11	7	42	42	38	37
Diuretics (%)	54.3	54.8	9.1	0	29.3	28.6	0	2.6
Beta-blockers (%)	25.7	27.4	18.2	0	34.1	26.2	18.9	26.3
ACE inhibitors (%)	24.3	21	0	28.6	9.8	21.4	24.3	18.4
ARBs (%)	18.6	12.9	18.2	14.3	46.3	50	24.3	48.4
Calcium-channel blockers (%)	22.9	24.2	6.4	14.3	63.4	71.4	59.6	71.1
Alpha-blockers (%)	14.3	21	18.2	0	2.4	4.8	0	2.6

ACE, angiotensin-converting enzymes; ARB, angiotensin receptor blocker; BP, blood pressure; ECW, extracellular water; F, female; H^2/R, height^2/resistance; H^2/X, height^2/reactance; M, male; PD, peritoneal dialysis; SH, Shanghai; TBW, total body water.

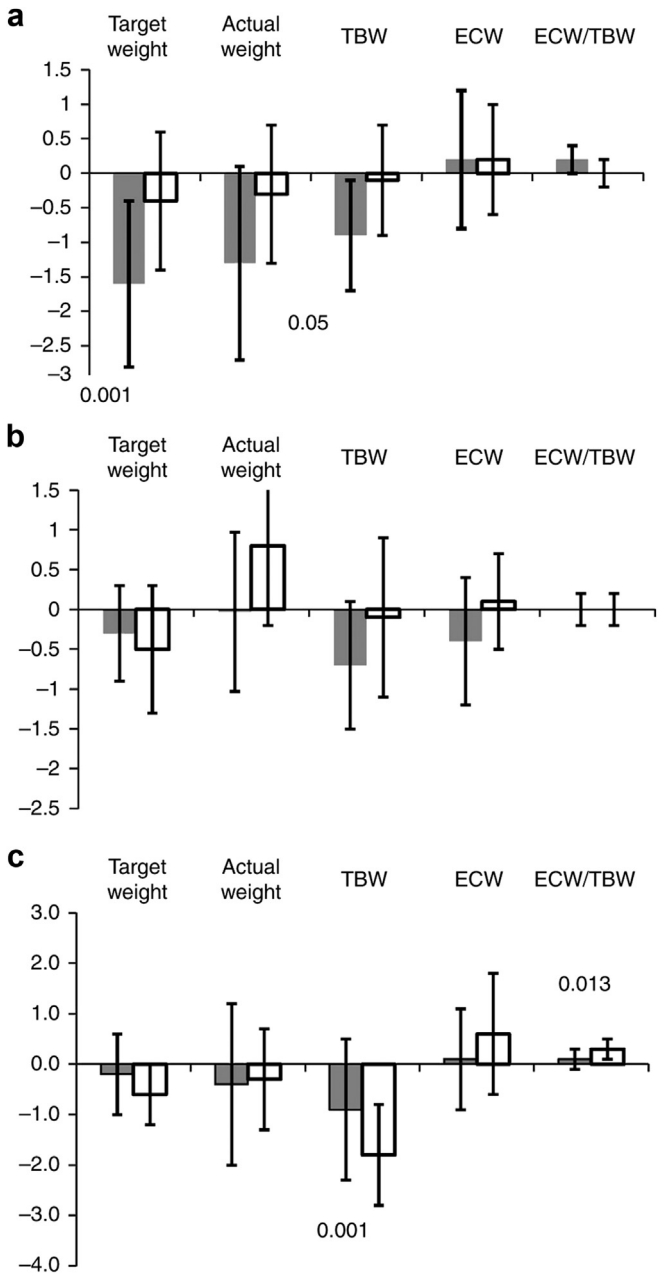

Figure 3 | Net changes in body composition (kg, liters or ratio) at 12 months for (a) UK-nonanuric, (b) Shanghai-nonanuric, and (c) Shanghai-anuric patients (active BI intervention group, solid bars; controls, open bars). Significant *P*-values shown, error bars, 95% confidence intervals. The values for ECW/TBW ratios have been multiplied by 10. BI, bioimpedance; ECW, extracellular water; TBW, total body water.

Primary outcome—longitudinal change in ECW and body composition

In both the UK and Shanghai nonanuric controls and the Shanghai BI intervention group, there were no significant changes in body composition over the 12-month study period (see Figure 3a and b and Table 2). In the UK-nonanuric BI intervention group, there was a reduction in TBW (−0.9 kg, 95% confidence interval (CI): 0 to −1.74) that was associated with a reduced target weight set by clinicians (−1.7 kg, 95% CI: −0.39 to −2.96) and actual weight (−1.3 kg 95% CI: −0.09 to −2.69). Despite this, there was no change in the ECW (+0.3 kg, 95% CI: −0.69 to 1.24) or the ECW/TBW (0.01 95% CI: −0.04 to 0.01 Figure 3a). In the Shanghai anuric patients, a significant deterioration in body composition occurred in the control patients because of a fall in TBW (−1.76 kg, 95% CI: −2.70 to −0.82), increase in ECW (+0.59 kg, 95% CI: −0.67 to 1.86), and thus worsening of the ECW/TBW ratio (0.04, 95% CI: 0.01–0.06), whereas body composition remained stable in the BI intervention group (Figure 3c). This was associated with stability of the BI vector plot used to aid clinical decision-making in the intervention group, whereas in the controls there was a reduction in Height^2/Resistance in keeping with reduced muscle mass and worsening in the phase angle (−0.58°, 95% CI: 0.08–1.07°), indicating a relative excess in tissue hydration (Figure 4). On multilevel analysis combining the data from both countries and all study visits, these differences remained significant and independent of baseline determinants of fluid volumes including gender, age, and grade of comorbidity (Table 3). By visit 5 (12 months), the ECW/TBW ratio worsened significantly in both the anuric control and intervention groups.

Secondary clinical outcomes—blood pressure, residual kidney function, membrane function, and dialysis dose

There were no significant longitudinal changes in blood pressure in any of intervention or control groups (Table 4). In all the nonanuric patient groups over 12 months, there was a significant fall in the residual Kt/V_{urea} associated with reductions in urine volume, with the exception of the UK intervention group in which residual urine volume was maintained. Although relative preservation of urine volume in the context of loss in solute clearance is in keeping with increased diuretic use, it was not possible to demonstrate this (Table 5). The reduction in residual function in the nonanuric groups was associated with increases in the prescribed dialysis dose (volume) in all patient groups. There were no changes in plasma albumin, ultrafiltration capacity, or PSTR in any of the groups with the exception of a significant increase in PSTR in the Shanghai anuric cohort, seen in both study arms, slightly greater in the intervention arm.

Analysis of interventions related to fluid management

A key aspect of the study design was to capture decisions at the point of fluid management assessments so as to better understand how clinicians were using the additional information from BI. Of a potential 1274 visits and 1394 assessments (additional assessments were allowed in the active BI group) of fluid status, data were captured and recorded for analysis at 1106 visits (89.6%): 568 for Shanghai with >95% data validity and 538 for the UK with 85% validity; the proportions are not significantly different by randomization group. Frequency of intervention type was highly variable by patient, usually multiple and often repeated (see Table 5), but not demonstrably different according to randomization, with

Table 2 | Longitudinal changes on body composition

	UK nonanuric						Shanghai nonanuric						Shanghai anuric					
	Control			BI intervention			Control			BI intervention			Control			BI intervention		
	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value
ECW (l)	19.5 ± 4.2	19.7 ± 4.6	0.70	18.2 ± 4.3	18.4 ± 4.0	0.57	16.0 ± 2.4	16.1 ± 2.6	0.84	17.2 ± 2.5	16.7 ± 3.2	0.25	17.7 ± 3.2	18.3 ± 4.6	0.342	16.3 ± 3.2	16.2 ± 2.6	0.787
TBW (l)	42.9 ± 8.6	42.8 ± 8.8	0.92	41.3 ± 8.4	40.4 ± 7.9	0.05	34.3 ± 6.6	34.2 ± 6.9	0.82	35.4 ± 5.2	34.7 ± 5.8	0.10	37.2 ± 6.0	35.5 ± 5.9	0.001	35.0 ± 6.5	34.0 ± 5.5	0.179
ECW/TBW	0.46 ± 0.06	0.46 ± 0.07	0.56	0.44 ± 0.08	0.46 ± 0.06	0.17	0.47 ± 0.06	0.47 ± 0.06	0.75	0.48 ± 0.08	0.48 ± 0.07	0.89	0.48 ± 0.06	0.51 ± 0.09	0.013	0.47 ± 0.06	0.48 ± 0.08	0.221
H^2/R (cm^2/Ω)	59.8 ± 14.0	59.9 ± 14.4	0.93	58.3 ± 14.5	56.9 ± 13.8	0.13	49.5 ± 17.4	48.9 ± 10	0.61	48.5 ± 10.4	49.3 ± 9.8	0.08	54.7 ± 10.5	50.4 ± 9.8	0.001	50.5 ± 12.3	48.5 ± 10.4	0.168
H^2/X (cm^2/Ω)	576 ± 171	595 ± 221	0.39	539 ± 175	543 ± 176	0.88	499 ± 127	498 ± 154	0.98	538 ± 146	529 ± 183	0.72	567 ± 147	621 ± 253	0.209	505 ± 139	511 ± 145	0.815
Phase angle (degrees)	6.14 ± 1.2	6.13 ± 1.55	0.91	6.59 ± 2.08	6.25 ± 1.35	0.25	6.14 ± 1.20	6.13 ± 1.55	0.82	5.50 ± 0.82	5.66 ± 1.49	0.42	5.72 ± 1.30	5.15 ± 1.72	0.03	5.90 ± 1.36	5.75 ± 1.68	0.50
Target weight (kg)	78.7 ± 19	78.3 ± 19	0.44	75.2 ± 15	73.6 ± 15	0.01	59.2 ± 9.0	58.7 ± 9.1	0.20	60.7 ± 8.6	60.3 ± 8.6	0.30	61.4 ± 10.2	60.8 ± 10.5	0.099	58.3 ± 9.8	58.1 ± 8.9	0.588
Clinical weight (kg)	79.3 ± 18	79.0 ± 19	0.72	75.8 ± 16	74.5 ± 15	0.07	59.2 ± 9.0	60 ±9.7	0.13	60.7 ± 8.6	60.6 ± 8.8	0.94	61.2 ± 10.4	60.9 ± 10.9	0.586	58.3 ± 9.8	57.9 ± 8.4	0.622

BI, bioimpedance; ECW, extracellular water; H^2/R, height^2/resistance, H^2/X, height^2/reactance; TBW, total body water. Phase angle is calculated as the arc tangent ($(H^2/R)/(H^2/X)$) expressed in degrees.

the exception of significantly higher glucose prescription in the Shanghai-anuric BI group (Table 4). By taking a change in target weight of ≥1 kg in either direction as a cutoff value for a clinically significant decision, it can be seen (Table 6) that the weight was more likely to be reduced in the intervention compared with the control groups in all three substudies, with the primary reason given as 'to improve control of high blood pressure', whereas hydration status on clinical examination was less likely to be a factor (although reduction of weight in the Shanghai-anuric BI group was borderline significant). Overall, this effect on decision-making was most marked in the UK-nonanuric BI patients, thus explaining the overall greater likelihood of weight reduction in this intervention group, as already discussed (Figure 3a).

DISCUSSION

The most important finding of this trial was the greater than anticipated stability over 12 months of Bl-derived fluid volumes, especially in nonanuric patients. In cases in which significant changes were seen, with or without adjustment for baseline factors associated with BI volumes (gender, age, comorbidity), these were reductions in the TBW with or without parallel change in the ECW. In anuric subjects, this was spontaneous and likely to reflect loss in lean tissue, as we originally hypothesized, leading to an increase in the ECW/TBW ratio. There was marginal evidence that this could be ameliorated in the Shanghai BI intervention group that achieved greater stability of the BI vector associated with higher dialysate glucose prescription, but no difference in blood pressure, which was well controlled in both groups. In the UK-nonanuric BI intervention group, the fall in TBW was because of the setting of a lower target weight but no change in the ECW/TBW ratio or improvement in blood pressure. Taken together, these findings suggest that longitudinal BI vector plotting adds little additional value to clinical fluid management.

The spontaneous fall in BI-derived TBW with an increase in ECW/TBW seen in the anuric patients is in keeping with our own study of longitudinal body composition in hemodialysis patients in whom increased ECW/TBW associated with comorbidity reflected overhydration supported by independent measures of TBW from deuterium dilution,[12] as well as longitudinal studies using various methods in PD patients.[9,13] It is important to emphasize that our study design was intended to address this problem by showing how BI may be used to detect longitudinal changes in body composition and to adjust for these rather than using it as a tool to drive patients to a specific target hydration status. This approach is in contrast to other current[14,15] or recently completed study protocols,[16,17] and it was chosen in order to minimize risk, especially premature loss of residual kidney function. Indeed, a recent study using the overhydration index to reduce dry weight was associated with a significant loss of urine output in nonanuric hemodialysis patients.[17] This problem was not reported in the only other trial completed in PD patients that did find that BI improved fluid status and

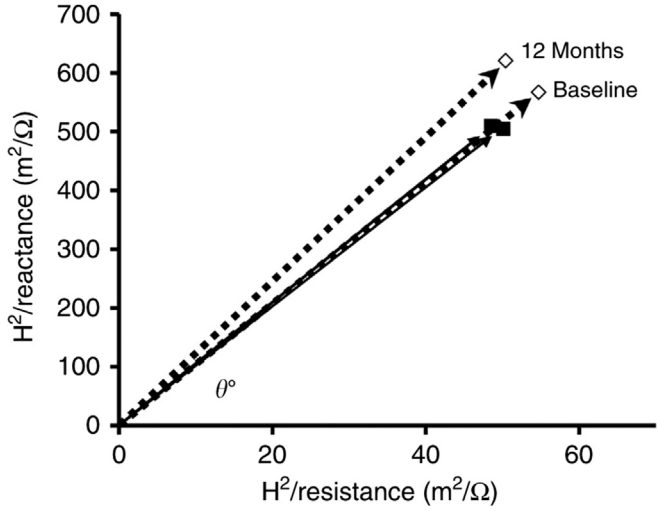

Figure 4 | Vector plot showing mean changes in bioimpedance and their associated vectors for the Shanghia-anuric patients (controls, ◇; active, ■). Increasing H^2/resistance reflects increasing body water, increasing H^2/reactance, and widening of the vector plot (inversely related to phase angle), indicating increasing tissue hydration. The control group demonstrates worsening tissue overhydration despite a reduction in body water, whereas the BI intervention group was kept stable. BI, bioimpedance; H^2, height^2.

blood pressure, but follow-up was limited to 3 months only.[18] Our decision to use vector plots of BI data rather than calculated volumes is also worthy of comment. This was driven by a number of considerations. First, given the lack of a known value for optimal ECW volume in the PD population in which overhydration is driven by many factors such as comorbidity and hypoalbuminemia, we were reluctant to set absolute targets. This was mainly for the reasons already given, and the vector plot approach discourages clinicians from making such judgements. Second, this made it very easy to blind clinicians from the BI data, which necessitates plotting before it can be interpreted and by delaying the calculations of interpolated volumes on which the study was powered until after the study data lock applied we were able to minimize the effect of clinician bias. Third, there are very large databases giving normal values for vectors in the general population,[19] as well as the dialysis population, in which both phase angle and vector length have been shown to be highly predictive of survival.[4] At the time of study design, these data were not available for other methods, in particular the overhydration index. Finally, the BI devices that we used have a well-established record in reproducibility and were relatively inexpensive. Of interest, a similar approach has been adopted in the FLUID study protocol.[14]

One of the purposes of our study was to capture information on decision-making by clinicians in an attempt to see how the use of BI informs practice. Overall, most clinical assessments did not lead to a change in target weight, and it should be recognized that spontaneous changes in weight without a change in hydration will have occurred in many patients, reflecting, for example, changes in body fat. In the control groups, the decision to increase or decrease target weight was remarkably symmetric, whereas increasing the weight in the intervention groups was less likely. It is possible that for the UK clinicians the tendency to make greater weight reductions in the intervention group so as to achieve better blood pressure control was because of study bias. The types of intervention used, although recorded, proved difficult to analyze, as these were usually multiple—i.e., of several types and repeated within patients and not demonstrably different between control and BI groups. The relative maintenance of urine volume, despite a reduction in target weight, could be explained by diuretics, as observed in a previous trial comparing diuretic use with placebo,[20] but this could not be clearly shown here because of the fact that most patients were already on diuretics and that most interventions were complex. In any case, this did not translate into improvements in hydration status, as judged by ECW volume, ECW/TBW, phase angle, or blood pressure management. However, this does support observational data, indicating that preservation of residual urine volume does not depend on maintaining overhydration.[21] There is a concern that the loss of weight might reflect a reduction in muscle mass, but the change in TBW was not associated with a significant change in the raw electrical data, e.g., resistance, and is therefore dominated by the weight change fed into the algorithm used to extrapolate TBW, and thus it might be because of loss in body fat. This complex effect deserves further evaluation and a better understanding of how patients respond to requests to reduce their target dry weight that should inform future trial design. The trend to reduce weight, especially for the purpose of blood pressure control, was also seen in the Shanghai patients, but the absolute changes were not so great, perhaps reflecting the overall better blood pressure measurements in the Chinese patients. The value of BI in the anuric intervention group here appears to have been a better targeting of decision-making combined with a significant increase in glucose prescription, thus preventing the drift toward worsening tissue edema. This increase in glucose use will also have increased calorie intake, thus protecting against loss of lean tissue, which was less severe in this group.

This study has a number of limitations. Although we went to great lengths to conceal the allocation process and to blind clinicians to the control BI data and outcomes, it was by definition impossible to avoid the knowledge of randomization group and thus eliminate decision bias by clinicians. It may well be, for example, that the more aggressive weight reduction in the UK-nonanuric intervention group reflected this rather than specific information obtained from the BI measurements *per se*. Reasons not to be included in the study differed by country, being planned modality transfer, especially transplantation, in the UK versus greater likelihood of failing to achieve stability in the run-in period in Shanghai, which suggests that the Chinese anuric patients could be more selected. However, it can equally be argued that this selection applied to the UK even more so given the greater

Table 3 | | Multilevel analysis of determinants of BI-derived fluid volumes (TBW and ECW/TBW) incorporating all visits (level 1), patients (level 2), and centers (level 3)

	Control (all)	BI intervention (all)	Controls (nonanuric)	BI intervention (nonanuric)	Controls (anuric)	BI intervention (anuric)
Number of patients	**158**	**149**	**115**	**100**	**44**	**49**
Number of visits	**666**	**637**	**491**	**435**	**175**	**202**
Mean TBW (l, 95% CI)						
Baseline constant	34.7 (31.6, 37.8)	34.1 (31.1–37.0)	33.7 (31.0, 36.5)	33.6 (30.4, 36.7)	31.8 (29.3, 34.3)	33.1 (29.6, 36.7)
Gender (male)	**10.1*** (8.4, 11.9)	**8.8*** (7.2–10.4)	**11.7*** (9.6, 13.9)	**9.2*** (7.1, 11.3)	**8.6*** (5.8, 11.4)	**8.8*** (6.4, 11.3)
Age (year)	0.06 (0.0, 0.12)	−0.01 (−0.07–0.05)	0.00 (−0.07, 0.07)	−0.01 (−0.09, 0.06)	**0.21*** (0.09, 0.32)	−0.03 (−0.12, 0.06)
Comorbidity Grade 1[a]	−0.84 (−2.81, 1.13)	0.73 (−1.13, 2.60)	0.38 (−1.91, 2.67)	1.86 (−0.42, 4.14)	−2.46 (−5.55, 0.63)	−1.70 (−4.59, 1.18)
Comorbidity Grade 2[a]	−1.96 (−6.27, 2.4)	0.95 (−3.63, 5.53)	−1.53 (−5.86, 2.80)	1.43 (−3.33, 6.20)	None in this category	
Visit 2 versus baseline[b]	0.40 (−0.07, 0.86)	−0.12 (−0.55, 0.30)	0.44 (−0.08, 0.96)	−0.44 (−0.91, 0.03)	0.23 (−0.72, 1.19)	0.57 (−0.30, 1.43)
Visit 3 versus baseline[b]	0.11 (−0.36–0.59)	−0.41 (−0.83, 0.0)	0.12 (−0.41, 0.65)	**−0.57**† (−1.03, −0.10)	0.06 (−0.91, 1.03)	−0.08 (−0.92, 0.76)
Visit 4 versus baseline[b]	−0.45 (−0.95–0.05)	**−0.51**† (−0.9, −0.06)	−0.13 (−0.68, 0.42)	**−0.52**† (−1.01, −0.02)	**−1.49*** (−2.58, −0.41)	−0.46 (−1.35, 0.42)
Visit 5 versus baseline[b]	−0.45 (−0.96–0.06)	**−0.79**† (−1.24, −0.4)	−0.15 (−0.71, 0.41)	**−0.81***(−1.30, −0.31)	**−1.52*** (−2.67, −0.37)	−0.79 (−1.70, 0.12)
ECW/TBW (ratio, expressed as percentage, 95% CI)						
Baseline constant	46.3 (43.8, 48.7)	46.4 (43.9, 48.8)	46.9 (45.1, 48.7)	46.3 (43.8, 48.9)	47.6 (42.1, 53.1)	46.8 (43.0, 50.5)
Gender (male)	**−2.78*** (−4.37, −1.18)	**−3.32*** (−4.97, −1.67)	**−3.53*** (−5.36, −1.69)	**−2.58*** (−4.54, −0.62)	**−3.68**† (−7.00, −0.36)	**−4.26*** (−7.37, −1.14)
Age (year)	**0.07**† (0.01, 0.12)	**0.14*** (0.08, 0.20)	**0.06**† (0.00, 0.12)	**0.12*** (0.05, 0.19)	0.05 (−0.08, 0.18)	**0.17*** (0.05, 0.28)
Comorbidity Grade 1[a]	1.54 (−0.28, 3.36)	**2.30**† (0.43, 4.16)	1.15 (−0.79, 3.08)	1.31 (−0.81, 3.42)	1.21 (−2.62, 5.05)	**3.97**† (0.33, 7.62)
Comorbidity Grade 2[a]	**8.81*** (4.83, 12.78)	1.61 (−2.96, 6.18)	**8.72*** (4.97, 12.46)	1.71 (−2.69, 6.11)	None in this category	
Visit 2 versus baseline[b]	0.08 (−0.89, 1.04)	0.57 (−0.43, 1.57)	−0.29 (−1.37, 0.79)	0.32 (−0.93, 1.57)	1.05 (−0.97, 3.06)	1.11 (−0.51, 2.72)
Visit 3 versus baseline[b]	0.52 (−0.46, 1.51)	−0.09 (−1.07, 0.89)	0.44 (−0.67, 1.55)	−0.26 (−1.49, 0.97)	0.74 (−1.29, 2.78)	0.35 (−1.22, 1.91)
Visit 4 versus baseline[b]	−0.49 (−1.53, 0.55)	0.45 (−0.58, 1.48)	−0.39 (−1.54, 0.76)	0.37 (−0.94, 1.67)	−0.83 (−3.10, 1.45)	0.71 (−0.94, 2.36)
Visit 5 versus baseline[b]	0.96 (−0.10, 2.03)	0.85 (−0.19, 1.90)	0.31 (−0.85, 1.47)	0.50 (−0.81, 1.81)	**3.25*** (0.85, 5.66)	**1.79**† (0.09, 3.48)

BI, bioimpedance; CI, confidence interval; ECW, extracellular water; TBW, total body water.

6 models are presented; in each case, the BI fluid volume is adjusted for baseline age, gender, and comorbidity; TBW at baseline is greater by 8.5–10 liters in men and falls over visits (spontaneously in anurics, because of target weight reduction in nonanurics), whereas the ECW/TBW at baseline is elevated by age, female gender, and comorbidity and increases over visits in anuric patients. Values significantly different from baseline constant are shown in bold.

†$P < 0.05$.

*$P < 0.01$.

[a]Compared with Grade 0 = no comorbid conditions, Grade 1=1–2, Grade 2 = 3 or more comorbidities.

[b]Change from baseline visit.

Table 4 | Longitudinal changes in secondary outcomes and dialysis prescription

	UK nonanuric						Shanghai nonanuric						Shanghai anuric					
	Control			BI intervention			Control			BI intervention			Control			BI intervention		
	Baseline	12 Months	*P*	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value	Baseline	12 Months	*P*-value
Systolic BP (mm Hg)	144 ± 25	140 ± 20	0.209	137 ± 20	136 ± 20	0.845	133 ± 16.2	135 ± 18.4	0.375	131 ± 15	130 ± 21	0.637	128 ± 24	123 ± 27	0.638	130 ± 22	128 ± 26	0.776
Diastolic BP (mm Hg)	81.2 ± 13	79.1 ± 10	0.235	79.7 ± 11	79.2 ± 11	0.815	85.5 ± 8	86.1 ± 13	0.991	83.3 ± 11	81.9 ± 11	0.410	79.7 ± 9	76.2 ± 16.2	0.246	79.8 ± 13.1	81.6 ± 14.9	0.613
Input volume (l)	8.8 ± 2.5	9.4 ± 3	0.032	8.7 ± 2.7	9.0 ± 3	0.079	6.1 ± 1.8	6.5 ± 1.8	0.025	6.6 ± 1.5	6.9 ± 1.4	0.025	8.3 ± 1.3	8.6 ± 1.4	0.083	7.8 ± 1.2	8.0 ± 1.2	0.157
Total glucose (g)	121.7 ± 5	126.7 ± 6	0.395	119.1 ± 51	126.8 ± 57	0.067	104.2 ± 35	120.0 ± 39	0.001	116.0 ± 31	130.0 ± 36	0.003	181.2 ± 41	186.7 ± 51	0.398	167.5 ± 39	176.3 ± 46	0.037
Average (glucose; g/l)	1.36 ± 0.28	1.3 ± 0.4	0.257	1.31 ± 0.37	1.34 ± 0.39	0.417	1.71 ± 0.32	1.86 ± 0.34	0.009	1.75 ± 0.27	1.87 ± 0.34	0.006	2.16 ± 0.31	2.15 ± 0.39	0.888	2.13 ± 0.33	2.19 ± 0.39	0.342
Daily UF	326 ± 629	446 ± 435	0.113	339 ± 539	439 ± 418	0.203	160 ± 437	352 ± 487	0.003	166 ± 514	316 ± 568	0.012	876.4 ± 296	792 ± 402	0.384	833 ± 327	831 ± 363	0.819
Urine volume (ml)	1,298 ± 746	1,007 ± 599	0.003	1,165 ± 661	1,170 ± 896	0.957	1,084 ± 621	746 ± 559	0.000	1,005 ± 571	723 ± 654	0.000	NC	NC		NC	NC	
Renal Ccr (L/week/1.73 m^2)	94.6 ± 63	78.1 ± 57	0.020	93.1 ± 66.1	72.3 ± 62.6	0.001	40.1 ± 35.3	33.9 ± 38.7	0.012	41.7 ± 33.1	27.2 ± 26.5	0.000	NC	NC		NC	NC	
Renal Kt/V	1.3 ± 0.8	1.1 ± 0.7	0.023	1.2 ± 0.8	1.0 ± 0.8	0.006	0.8 ± 0.6	0.6 ± 0.6	0.007	0.7 ± 0.5	0.5 ± 0.5	0.000	NC	NC		NC	NC	
Albumin (g/l)	33.5 ± 4.0	32.9 ± 3.7	0.301	33.2 ± 4.7	33.2 ± 5.0	1.00	38.0 ± 3.4	38.2 ± 4.6	0.466	37.8 ± 2.8	38.4 ± 3.3	0.307	38.9 ± 3.3	38.2 ± 4.3	0.548	39.2 ± 3.0	38.0 ± 3.5	0.130
UF capacity	274 ± 216	244 ± 220	0.572	226 ± 266	279 ± 294	0.357	253 ± 111	291 ± 138	0.147	221 ± 174	266 ± 130	0.299	274 ± 139	252 ± 153	0.701	241 ± 196	267 ± 129	0.247
Solute transport	0.66 ± 0.11	0.68 ± 0.10	0.156	0.70 ± 0.14	0.73 ± 0.11	0.175	0.58 ± 0.11	0.60 ± 0.12	0.231	0.60 ± 0.10	0.62 ± 0.10	0.255	0.64 ± 0.11	0.67 ± 0.11	0.032	0.62 ± 0.11	0.67 ± 0.11	0.001

BI, bioimpedance; BP, blood pressure; Ccr, creatinine clearance; Kt/V, urea clearance (weekly); NC, not collected; UF, ultrafiltration from peritoneal equilibration test.

Table 5 | Proportion of 1394 clinical assessments associated with interventions that were not uniformly distributed by type, and thus, on many occasions more than one intervention was implemented, or by patient, as some had multiple interventions during the course of the study

Intervention	UK centers	Shanghai	Total
Reduce fluid intake	14.8%	29.9%	22.5%
Increase fluid intake	6.8%	1.8%	4.4%
Commence/increase diuretics[a]	2.4%	2.2%	2.3%
Reduce/stop diuretics	1.0%	-	0.05%
Increase dialysate glucose prescription	14.5%	7.9%	11.3%
Decrease dialysate glucose prescription	1.0%	0.07%	0.085%
Commence icodextrin	0.04%	NA	
Decrease icodextrin	0.03%	NA	

NA, not applicable as it is unavailable in China.
There was no apparent difference in the pattern of interventions between active and control groups, and the proportion of assessments does not necessarily reflect the magnitude—e.g., there were more recorded episodes of increasing the glucose prescription in the UK, but the actual average increase in prescription in Shanghai was greater.
[a]Denominator adjusted for the number of interventions in nonanuric patients.

difficulty in recruiting anuric patients. The unequal numbers in the UK randomization, which in retrospect should have been stratified by center, did not affect the balance of measured baseline patient characteristics, and the failure to recruit sufficient anuric patients from the UK has been partially addressed by including a multivariate analysis incorporating both data from both countries. This analysis showed that age, gender, and comorbidity are the main determinants of body composition and that any differences between centers were a function of patient-level characteristics and interventions available. More detail in describing the dietetic interventions would have been desirable—e.g., patient-level data on salt intake, as this turned out to be more important than was initially appreciated; we considered measuring sodium losses, but these have previously been shown to be an unreliable indicator of dietary change in PD patients.[22] The strengths of the study were its multicenter, pragmatic design, which enhances its generalizability.

In conclusion, routine use of longitudinal BI to inform fluid management in PD patients had minimal impact over 12 months. Although this was partly because body composition is very stable in nonanuric patients, it could be because we chose to maintain a stable BI vector rather than intervene more aggressively to normalize fluid status. Future studies are needed to evaluate such an approach, but they will require careful choice of clinically relevant outcomes such as residual kidney function and blood pressure control. Importantly, this study demonstrates just how difficult it is to capture and interpret the complex interventions and practice patterns associated with fluid management and thus attribute cause and effect. An increase in glucose prescription was the only intervention associated with benefit.

MATERIALS AND METHODS

Study design

The study design was a pragmatic, nested, controlled trial based on the PROBE principles[23]—i.e., prospective, randomized, open-label,

Table 6 | Analysis of interventions according to changes in target dry weight defining ≥ ± 1 kg as being clinically significant

Clinical decision		UK-NA				S-NA				S-A				All groups			
Change in target weight	Randomization	↓	=	↑	*P*-value	↓	=	↑	*P*-value	↓	=	↑	*P*-value	↓	=	↑	*P*-value
Reason given for changing weight to achieve lower blood pressure	BI intervention	10	30	1		6	27	1		6	29	3		22	86	5	
	Controls	13	31	12	0.004	11	36	4	0.03	2	26	1	0.002	26	93	17	0.008
Reason given for changing weight to achieve better fluid status based on clinical examination	BI intervention	6	20	1		9	33	1		8	21	2		23	74	4	
	Controls	7	23	4	0.24	8	37	0	ND	4	28	2	0.056	19	88	6	0.15
Overall decision to change weight in either direction regardless of reason	BI intervention	38	159	19		27	135	13		24	110	13		89	404	45	
	Controls	31	177	36	0.003	25	142	16	0.58	19	109	13	0.51	75	428	65	0.006

A, anurie; NA, nonanuric; ND, not done; S, Shanghai.
↓, target weight decreased by ≥1 kg; =, change in target weight <1 kg; t, target weight increased by ≥1 kg.
P-values are for the X^2-test.

blinded end-point in which patients were allocated 1:1 either to an active arm in which BI measurements were available to clinicians in their assessment of fluid status or to a control arm in which measurements were taken but concealed. Complete blinding of control BI data was achieved by using vector analysis, which requires two-dimensional plotting (Figures 1 and 4) before their interpretation. In addition, clinicians were blinded to the primary body composition outcome for all participants, as BI-derived fluid compartment volumes (ECW, TBW) were only calculated after completion of the study and data lock.

Within this overarching design, four groups of patients were recruited each using an independent, concealed, and randomly generated centralized allocation procedure. The four groups were nonanuric and anuric, defined as a 24-h urine volume <200 ml, with patients recruited from three medium-sized UK centers, and one large Chinese Center. The rationale underpinning the need for four independent patient groups nested within a common trial design is that (i) clinical decisions are likely to be affected by the presence of residual kidney function; (ii) that the options for therapeutic intervention are different in the UK, where automated PD and icodextrin are available, compared with China, where options are more limited despite a higher proportion of anuric patients; and (iii) that there were anticipated important differences in case mix between the two countries—e.g., body weight and comorbidity.

Pragmatic inclusion and exclusion criteria were used to mirror routine practice. Clinicians were asked to include sequential patients attending clinic who were willing to be enrolled, only excluding patients unlikely be on PD for more than 6 months for whatever reason. All subjects gave fully informed consent, and the trial was preregistered with ClinicalTrials.gov Number: NCT00801112.

After obtaining consent, clinicians were allowed up to 3 months to stabilize fluid status using standard clinical assessment (but not BI) and to ensure that the patients had recovered from any intercurrent illness—e.g., peritonitis. Immediately after randomization, fluid assessments (including BI measurements) were undertaken a minimum of every 3 months over the following year, unless the subject left the study. Additional assessments were permitted,

Table 7 | Summary for practice patterns used to manage fluid status by the participating centers

Center	Dietetic support and advice	Use of diuretics	Use of ACE/ARBs	Use of icodextrin
UK: Stoke-on-Trent	Dietician available in clinic. Advice on fluid restriction tailored to the individual aiming for salt intake of 5–7.5 g depending on the nutritional state	Continued on commencing PD. Usually furosemide 240 mg. Dose maximized before using >1.5% dialysate glucose. Stopped when anuric.	Used in all patients unless intolerant; antihypertensive drugs of choice	Used in all patients requiring a long dwell. Only replaced by glucose if clinically volume depleted.
UK: Leeds	Dietician available at clinic with periodic review of all patients. Salt restricted to <6 g/24h and fluid intake allowance individualized to patient	Continued on commencing PD, and start/increase dose used before more hypertonic exchanges, except where there is negative UF. Stopped when anuric.	First choice of antihypertensive agent where one is required.	Used in a majority of patients having a long dwell.
UK: Sheffield	Dietician available in clinic with periodic review of all patients. Aim for 6 g salt intake per day and no added salt.	Continued on commencing PD. Furosemide dose titrated up to 240 mg daily. Dose maximized before using >1.5% dialysate glucose. Stopped when anuric.	Used in all patients unless intolerant; antihypertensive drugs of choice	Used in majority of patients having a long dwell.
China: Shanghai	Dietician not available in clinic. Nursing staff and physician give advice on fluid restriction and salt intake. Rather than giving fixed target of salt and fluid intake, the advice is to alter to be more or less than the patient's current intake levels.	Usually used if urine volume less that 500 ml and start/increase dose before changing PD regime to achieve more daily fluid removal. Maximum dose is 100 mg. Stopped when anuric.	First choice of antihypertensive agent where required, unless for economic reason, as short-acting calcium channel blocker and clonidine are cheaper options.	Not available

ACE, angiotensin-converting enzymes; ARB, angiotensin receptor blocker; PD, peritoneal dialysis.

including the use of BI in the active limb at the clinician's discretion. The primary outcome was body composition, as calculated from BI. Secondary outcomes included blood pressure, residual kidney function, peritoneal membrane function (solute transport and ultrafiltration capacity), and prescribed dialysis dose.

Standard assessment of fluid status was recorded using an electronic database (Figure 1) that included weight, physical examination (e.g., edema), and blood pressure. In the BI groups, a vector plot was automatically generated to guide decisions, and clinicians were trained before the study in how this could be used to maintain stable fluid status (Supplementary Material online). Using this format, an increase in height^2/resistance indicates increasing total fluid content ($\approx$TBW), whereas a change in height^2/reactance causes a change in the vector such that a wider angle denotes increased tissue hydration ($\approx$ECW) and vice-versa. In this way, changes (or not) in actual bodyweight and clinical examination can be interpreted alongside trends, but not absolute measures of body composition. The interventions used by clinicians were at their discretion and availability, but included adjustment of dry weight (e.g., by asking the patient to reduce salt and fluid intake), altering the dialysis prescription of glucose or icodextrin, changing modality (continuous ambulatory or automated peritoneal dialysis), or altering diuretic prescription (see Table 7 for summary of practice patterns). These were recorded along with the rationale behind the decision.

BI measurements

All units were issued with BI 101 ASE (Anniversary Sport Edition, Akern, Italy) body composition analyzers. These devices measure resistance and reactance at a single (50 MHz) frequency using the RJL Quantum technology previously validated in dialysis patients.[24–26] BI measurements were taken using a standardized protocol, with documentation of the placement of electrodes, without draining the abdomen of dialysate and after the patient had been lying recumbent for at least 5 min. Using this approach we have previously documented within patient on the same day coefficient of variation of $<$1% and inter-class correlations to determine intra-observer error of $>$0.96.

Clinical measurements

Comorbidity was characterized using the externally validated Stoke scoring system.[27] Blood pressure was measured in clinic attendance using standard equipment. Residual renal function was determined from 24-h urine collections and calculated as the mean urea and creatinine clearance normalized to body surface area of 1.73 m^2. Dialysis dose was determined from 24-h collections and expressed as weekly Kt/V_{urea}. Membrane function was determined using the peritoneal equilibration test and expressed as the 4-h dialysate: plasma creatinine ratio (solute transport rate) and net ultrafiltration corrected for overfill (ultrafiltration capacity). Glucose utilization was calculated from the product of the volume and the concentration and expressed as grams used per day. Plasma albumin was determined using the bromocresol purple (BCP) colorimetric method in the UK and bromocresol green (BCG) method in Shanghai. The systematic difference between these methods is $Alb_{BCG} = 5.5 + Alb_{BCP}$[28], but data here are expressed after correction to the BCG method to enable comparison.

Statistical analysis and power calculations

The trial was powered so as to be able to detect a clinically meaningful longitudinal change in body composition from baseline, specifically ECW volume, with an *a priori* assumption that spontaneous changes would occur in the control group that would be prevented in the active group. On the basis of pilot data obtained from longitudinal studies of body composition in PD patients over 12 months in which the SD of the difference in ECW was 1.22 L, detecting a 1-L difference in ECW, assuming a 5% type 1 error with 80% power, would require 25 patients per group with 1:1 randomization, and detecting a 0.8-L change would require 38 patients in each arm (SAS Institute, Cary, NC). The plan was to recruit sufficient numbers to detect a 1-kg difference, but to allow over-recruitment within the predefined window. For nonanuric and anuric patients, the anticipated dropout was 25 and 35%, respectively, necessitating $\sim$130-150 patients enrolling per country.

The predefined primary analysis was planned as follows: after study completion and data lock (August 2012), the R and X data were converted to estimates of ECW, TBW (and ECW/TBW) using an algorithm based on the software provided with the BI device and the change at 12 months from baseline determined by paired *t*-tests, to include changes in target and actual weight and secondary outcomes. To assess dropout between groups, differences in patient and study survival were determined from Kaplan–Meier survival curves and the log-rank test. Mean values and frequencies of parameters including fluid assessments and interventions were compared using ANOVA or χ^2-tests as appropriate. A secondary multilevel regression analysis with BI-derived fluid volumes as the dependent variables was undertaken to include all observations (level 1), individuals (level 2), and centers (level 3), and adjustment for the baseline covariates associated with BI volumes on exploration of the data set: age, gender, and comorbidity. Models were fitted separately for active and control limbs in anuric and nonanuric groups, with random intercepts at individual and center. All statistical analyses were undertaken using SPSS software version 20 (IBM, Armonk, NY), except for the multilevel analysis for which we used MLwin (Version 2.22, Centre for Multilevel Modelling, University of Bristol, UK).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Kaplan–Meier survival plots for patient dropout by group. Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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