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Original Investigation

Bioimpedance-Guided Fluid Management in Maintenance Hemodialysis: A Pilot Randomized Controlled Trial

Mihai Onofriescu, MD, PhD,[1] Simona Hogas, MD, PhD,[1] Luminita Voroneanu, MD, PhD,[1] Mugurel Apetrii, MD,[1] Ionut Nistor, MD,[1] Mehmet Kanbay, MD, PhD,[2] and Adrian C. Covic, MD, PhD, FRCP[1]

Background: Chronic subclinical volume overload happens very frequently in hemodialysis patients and is associated directly with hypertension, increased arterial stiffness, left ventricular hypertrophy, and ultimately higher mortality.

Study Design: Randomized controlled parallel-group trial.

Setting & Participants: 131 patients from one hemodialysis center, randomly assigned into 2 groups.

Intervention: Dry weight prescription using results derived from repeated 3-month bioimpedance measurements to guide ultrafiltration for strict volume control (bioimpedance group; n = 62) compared with clinical judgment without bioimpedance measures (clinical-methods group; n = 69) for 2.5 years.

Outcomes: The primary outcome was all-cause mortality over 2.5 years (the duration of the intervention). Secondary outcomes were change in relative arterial stiffness, fluid overload, and blood pressure (BP) over 2.5 years.

Measurements: Bioimpedance measurements were performed using a Body Composition Monitor device. Pulse wave velocity analysis was performed at baseline, 2.5 years (end of intervention), and 3.5 years (end of study). Relative fluid overload and BP were assessed at 3-month intervals.

Results: The unadjusted HR for all-cause death in the bioimpedance group (vs the clinical-methods group) was 0.100 (95% CI, 0.013-0.805; $P = 0.03$). After 2.5 years, we found a greater decline in arterial stiffness, relative fluid overload, and systolic BP in the bioimpedance group than the clinical-methods group. Between-group differences in change from baseline to the end of intervention were −2.78 (95% CI, −3.75 to 1.80) m/s for pulse wave velocity ($P < 0.001$), −2.99% (95% CI, −5.00% to −0.89%) for relative fluid overload ($P = 0.05$), and −2.43 (95% CI, −7.70 to 2.84) mm Hg for systolic BP ($P = 0.4$).

Limitations: Echocardiography was not performed as cardiovascular assessment and the caregivers were not masked to the intervention.

Conclusions: Our study showed improvement in both surrogate and hard end points after strict volume control using bioimpedance to guide dry weight adjustment. These findings need to be confirmed in a larger trial.

INDEX WORDS: Bioimpedance; hemodialysis; pulse wave velocity; survival.

Patients with end-stage renal disease treated with maintenance dialysis have alarmingly high mortality, similar to that seen with aggressive forms of cancer.[1] Chronic subclinical volume overload occurs very frequently and may be ubiquitous in hemodialysis (HD) patients receiving the standard thrice-weekly treatment. It is associated directly with hypertension, increased arterial stiffness, left ventricular hypertrophy, heart failure, and eventually, higher mortality and morbidity.[2]

To routinely determine patients' hydration status, clinical surrogate parameters, such as ultrafiltration rate or blood pressure (BP), are used. Unfortunately, clinical parameters often are unreliable and not always conclusive. Currently, we are not even certain of the optimal BP target for HD patients.[3] The classic empirical approach of gradually "drying out" the patient until the symptomatic hypotension ceiling is reached is difficult in one-third of patients (particularly for those with low cardiac reserve/cardiac failure) or even deleterious, leading to cardiac stunning[4] and sustained increases in brain natriuretic peptide (BNP; infraclinic myocardial damage) levels. Theoretically, these problems could be solved with a valid method for assessment of individual volemia and detection of changes in fluid volume/fluid compartments.

A promising and increasingly validated avenue to objectively assess (over)hydration is the use of electrical bioimpedance, a technique that has been

From the [1]Nephrology Department, "Dr. C.I. Parhon" University Hospital, University of Medicine and Pharmacy "Gr. T. Popa," Iasi, Romania; and [2]Department of Medicine, Division of Nephrology, Istanbul Medeniyet University School of Medicine, Istanbul, Turkey.

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Address correspondence to Mihai Onofriescu, Nephrology Department, "Dr. C.I. Parhon" University Hospital, Bld Copou, No. 50, Iasi, Romania. E-mail: onomihai@yahoo.com

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used in various forms (single/multiple frequency and segmental/whole-body bioimpedance) and validated by isotope-dilution methods, accepted reference body composition methods, and techniques that measure relative changes in fluid volumes.[5] In addition, overhydration determined by multiple frequency bioimpedance recently was identified as an important and independent mortality predictor in maintenance HD patients.[6] Bioelectrical impedance analysis (BIA) also has been used successfully to guide HD patients toward normohydration and better BP control.[7]

Despite this increasingly large body of evidence, clinicians are reluctant to adopt bioimpedance-based technologies. This is mainly because of the lack of a definitive randomized controlled trial with hard end points and adequate follow-up demonstrating the superiority of BIA to usual clinical best practice.

The objective of this prospective randomized trial was to compare strict volume control based on bioimpedance versus clinical methods for guiding ultrafiltration prescription in HD patients. In the intervention arm, ultrafiltration goals were derived exclusively from BIA readouts. Most importantly, we investigated the medium-term impact of strict volume control on patient survival, arterial stiffness, and BP values.

METHODS

Study Design

During a 2-month enrollment phase, we considered for inclusion in the trial all adult patients (aged ≥18 years) from the "Dr. C.I. Parhon University Hospital" Dialysis Center already on maintenance HD therapy for more than 3 months (N = 277). Patients with limb amputations, metallic joint prostheses, absence of a permanent vascular access, decompensated cirrhosis, pregnancy, or a cardiac stent or pacemaker were excluded from the study because bioimpedance assessment cannot be performed accurately in such cases. In addition, patients with life expectancy less than 1 year were not considered. The study finally included 131 patients who were eligible and willing to participate, with follow-up of 3.5 years (July 2008 to December 2011). The hospital ethics committee approved the study and all participating patients signed written informed consent.

The final study population of 131 patients fulfilled initial power calculations for detecting a significant difference between groups in pulse wave velocity (PWV) of 1 m/s and in relative fluid overload of 1%. Such a change in PWV and relative fluid overload (computed in regard to mean baseline values of 7.1 m/s and 8.8%, respectively, which were reported previously for HD populations by Covic et al[8] and Wabel et al[9]) would require 60 patients in each arm for 85% power, with 2-tailed $\alpha = 0.05$. At the same time, Wizemann et al[6] previously demonstrated that overhydrated patients have an increased hazard ratio (HR) for death of 2.1. Therefore, in order to show a 50% decrease in mortality from our center's expected death rate of 6% per year,[10] 620 patients in each arm followed up for 2.5 years would have been required (80% power, 2-tailed $\alpha = 0.05$) to be included.[11]

The overall study design is shown in Fig 1A and B. All patients were assigned using the block randomization technique to either the bioimpedance (intervention) group or the clinical-methods (control) group (Fig 1A and B). During the first 2.5 years of the study (the intervention period), dry weight was determined/adjusted in the clinical-methods group by clinical reference criteria (BP value, presence of edema, intradialytic hypotension, cramps etc), whereas in the bioimpedance group, target dry weight was prescribed exclusively based on readouts from the bioimpedance device measurements. The primary end point was all-cause mortality and secondary end points were change in arterial stiffness, BP, and hydration status, assessed at 2.5 years. After this period, during the last year of the study, all patients were left free of any intervention and managed according to the standard medical practice of the dialysis center. At the end of the study, at 3.5 years, a third PWV measurement was performed in all patients.

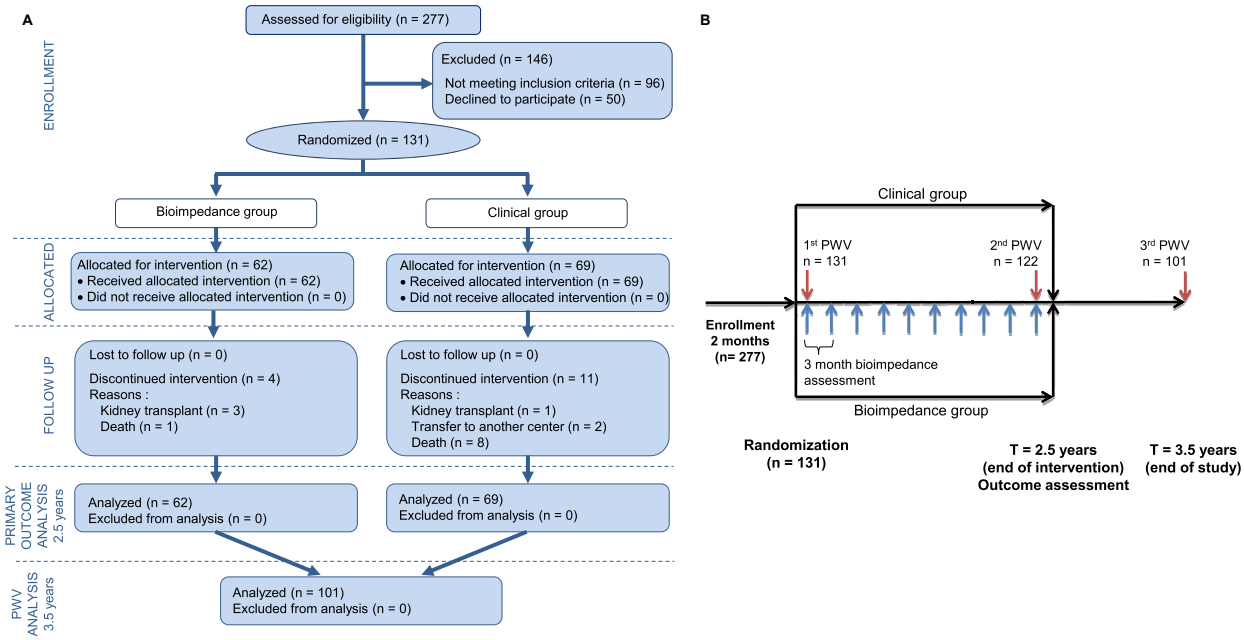

Figure 1. Study (A) flow chart and (B) design. Abbreviation: PWV, pulse wave velocity.

All patients underwent serial body composition measurements every 3 months by bioimpedance spectroscopy (Body Composition Monitor; Fresenius Medical Care), but results were disclosed to clinicians for only the bioimpedance (intervention) arm, in the form of a strict target interval (bioimpedance-recommended dry weight ± 1.1 kg) to be achieved during the next month. Thus, in the bioimpedance arm, all patients, either under- or overhydrated, were brought to the bioimpedance-recommended dry weight, with 200-g weight adjustments per dialysis session. Patients included were blinded to the intervention. All patients received standard medical care according to current guidelines throughout the study period.

Body Composition

Body composition was determined before dialysis using the Body Composition Monitor, a portable whole-body multifrequency bioimpedance analysis device. The technique involves attaching electrodes to the patient's nonfistula forearm and ipsilateral ankle, with the patient in a supine position. The Body Composition Monitor measures body resistance and reactance to electrical currents of 50 discrete frequencies, ranging from 5-1,000 kHz. Based on a fluid model using these resistances, extracellular water, intracellular water, and total-body water are calculated. These volumes then are used to determine the amount of fluid overload. All calculations are performed automatically by the software of the Body Composition Monitor. Absolute fluid overload is defined as the difference between the patient's expected extracellular water under normal physiologic conditions and actual extracellular water, whereas relative fluid overload is defined as the absolute fluid overload to extracellular ratio. Normohydration is defined when absolute fluid overload is between the 10th and 90th percentiles for healthy age- and sex-matched individuals from the reference population, that is, −1.1 to 1.1 L, with volumes below and above this range defining under- and overhydration, respectively.

Blood Pressure

BP was measured in patients after 10 minutes of recumbence, using a standard mercury sphygmomanometer with cuffs of appropriate size in the arm without an arteriovenous fistula. We used predialysis BP, as an average measurement from the previous 3 consecutive HD sessions.

Arterial Stiffness

Applanation tonometry was done with a SphygmoCor device (AtCor Medical). Radial arterial waveforms during 40 cardiac cycles were recorded in each patient. The averaged composite radial waveform was calculated and the aortic BP waveform then was derived by the device's software, using a validated transfer function algorithm. PWV was computed from carotid and femoral artery waveforms recorded consecutively, using an electrocardiogram-gated signal and anthropometric distances. All measurements were done twice in a row on each occasion and results were averaged.

Adverse Events

Because the intervention involved frequent changes in dry weight, hypotension-related intradialytic adverse events were recorded. Intradialytic hypotension was defined as a decrease in systolic BP > 20 mm Hg and/or a decrease in BP that is perceived as symptomatic and requires an intervention to be corrected (modifying dialysate temperature, stopping ultrafiltration, or using Trendelenburg position and saline solution boluses to increase systolic BP to 100-110 mm Hg). These events were assessed by the nephrologist on call in the dialysis unit and written in the patient's protocol.

Statistical Analysis

Mean values and frequencies of the parameters were compared by analysis of variance or χ^2 test, as appropriate. Sample size and power calculations were performed with the IBM SPSS SamplePower software. Differences in survival were assessed using log-rank test and Kaplan-Meier plot. Cox regression survival analysis also was performed using a backward stepwise model adjusting for demographic data (age, sex, and body mass index), comorbid conditions (diabetes and cardiovascular disease), and dialysis vintage. Proportional hazards assumptions were checked using the graphical method (log minus log) and Schoenfeld residuals test. Both Kaplan-Meier curves and the Cox model used the same end point (time of death). Patients were censored when they were transferred to another center, received a kidney transplant, or were still on HD therapy by the final observation date (December 31, 2010). In order to test for significant differences in change in PWV at 3 separate times, a mixed linear model analysis was performed. The significance level was set to $P = 0.05$. All statistical analyses were performed using SPSS software, version 15 (SPSS Inc).

RESULTS

From 277 patients dialyzed in the dialysis center, 131 patients who were eligible and gave consent to participate were included in the study. Reasons for exclusion for the other 146 patients were metallic joint prostheses (n = 4), cardiac pacemakers (n = 3), decompensated cirrhosis (n = 2), limb amputations (n = 10), twice-weekly HD schedules (n = 10), refusal to participate (n = 50), life expectancy less than 1 year (terminal illness or diagnosed cancer), or absence of a permanent vascular access (n = 67).

Baseline characteristics of the randomly assigned patients are listed in Table 1. Mean ages were 54 years in the clinical-methods group and 52 years in the bioimpedance group. Mean dialysis vintages were 104 months and 107 months, respectively. At baseline, there were no significant differences between the 2 groups in terms of demographic parameters, comorbid conditions, biochemical profiles, dry weight, body composition (total-body, extracellular, and intracellular water), and predialysis overhydration, as measured by bioimpedance.

We compared relative fluid overload in the 2 groups at baseline and end of the intervention period (2.5 years). In the bioimpedance group, we found a significant decrease in relative fluid overload, from 9.52% to 7.46% (mean difference, 2.05%; 95% confidence interval [CI], 1.10%-5.70%; $P = 0.03$), while in the clinical-methods group the change in relative fluid overload (10.30% to 11.24%) was not statistically significant (Fig 2; Table 2).

In the bioimpedance group, systolic BP significantly decreased from 145.4 to 138.9 (mean difference, −6.54; 95% CI, −13.62 to −4.53) mm Hg ($P = 0.04$), while in the clinical-methods group the reduction in systolic BP from 144.6 to 140.5 mm Hg was not statistically significant (Table 2).

To better estimate the treatment effect on relative fluid overload and predialysis systolic BP, we compared

Table 1. Baseline Characteristics of Study Population by Randomization Group

Characteristic	Clinical Methods (n = 69)	Bioimpedance (n = 62)	*P*
Age (y)	54 ± 13	52 ± 13	0.5
Male sex	52%	54%	0.7
Dry weight (kg)	66 ± 13	65 ± 13	0.7
Overhydration			
Pre-HD (L)	2 ± 2	2 ± 1	0.4
Post-HD (L)	−0.16 ± 2	0.03 ± 1	0.06
TBW	35 ± 7	33 ± 5	0.2
ECW	17 ± 3	16 ± 3	0.4
ICW	18 ± 4	17 ± 3	0.2
Lean tissue index	13 ± 3	13 ± 2	0.3
Fat tissue index	12 ± 6	10 ± 4	0.1
Lean tissue mass	36 ± 9	36 ± 8	0.1
Fat tissue mass	25 ± 12	21 ± 9	0.2
BMI (kg/m^2)	25 ± 5	24 ± 3	0.09
Systolic BP (mm Hg)	145 ± 15	145 ± 15	0.7
Diastolic BP (mm Hg)	83 ± 9	82 ± 10	0.2
Dialysis vintage (mo)	104 ± 57	107 ± 60	0.4
Albumin (g/dL)	4	5	0.7
PTH (pg/mL)	372	317	0.3
Hemoglobin (g/dL)	12	12	0.2
Phosphorus (mmol/L)	1.79	1.85	0.6
Diabetes	9%	10%	0.8
Cause of ESRD			
Diabetic nephropathy	9%	8%	
Glomerular nephropathy	42%	47%	
Tubulointerstitial nephropathy	20%	21%	
Congenital nephropathy	15%	11%	
Unknown	15%	13%	
Comorbid conditions			
Peripheral vascular disease	10%	11%	0.8
Ischemic cardiomyopathy	25%	24%	0.9
Stroke	3%	8%	0.2
Hypertension	73%	65%	0.3

Note: Values for categorical variables are given as percentages; values for continuous variables, as mean or mean ± standard deviation.

Abbreviations: BMI, body mass index; BP, blood pressure; ESRD, end-stage renal disease; HD, hemodialysis; ECW, extracellular water; ICW, intracellular water; PTH, parathyroid hormone; TBW, total-body water.

the differences between the 2 groups from baseline to the end of intervention (delta − delta). The differences between randomly assigned groups for the changes from baseline to the end of intervention were −2.43 (95% CI, −7.70 to 2.84) mm Hg for systolic BP ($P = 0.4$) and −2.99% (95% CI, −5.00% to −0.89%) for relative fluid overload ($P = 0.05$; Table 2).

The number of patients on antihypertensive drugs in both study groups was compared at the beginning and at the end of the intervention period. There was no statistically significant change from baseline to end

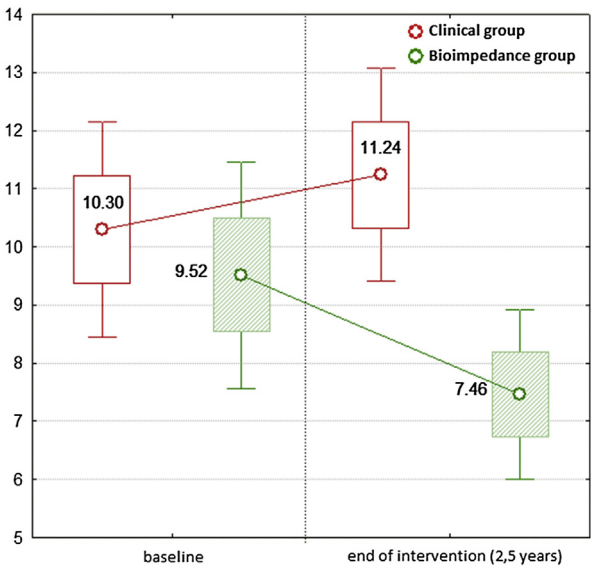

Figure 2. Mean relative fluid overload at baseline and at the end of intervention (box, mean ± standard error; whiskers, 95% confidence interval).

of the intervention in the number of patients receiving or not treated with antihypertensive drugs in the clinical-methods group. In contrast, in the bioimpedance group, there was a significant increase in patients not treated with antihypertensive medication, from 34 to 45 ($P = 0.05$). We found no difference in intradialytic signs of hypovolemia (hypotension and cramps) between the 2 groups. These adverse events are listed in Table 3.

PWV was measured at baseline, end of the intervention period (2.5 years), and end of the study (3.5 years). At the end of the intervention period, in the clinical-methods group, PWV significantly increased from 7.63 to 8.88 m/s ($P = 0.01$), whereas in the bioimpedance group, it decreased from 8.22 to 6.68 (mean difference, 1.53 [95% CI, 0.30-2.80] m/s; $P < 0.001$). The difference between the 2 groups for changes in PWV from baseline to end of the intervention was −2.78 (95% CI, −3.75 to 1.80) m/s ($P < 0.001$; Table 2).

Further analysis was performed using the third PWV measurement, assessed 1 year after the end of the intervention period. A longitudinal model was developed to look at all 3 time points simultaneously and describe the change at each time point adjusted for the others in a single model. One year after the intervention period, without strict volume control, PWV increased in both groups, to 12.07 m/s in the clinical-methods group and 12.35 m/s in the bioimpedance group (Fig 3). Using a fixed-effects model for longitudinal data analysis showed that when looking at all 3 time points simultaneously, the group variable does not influence the overall change in PWV and the last

Table 2. Outcomes

Primary Outcome		Clinical Methods (n = 69)	Bioimpedance (n = 62)	*P*
No. of deaths		8	1	
Kaplan-Meier cumulative survival[a]		78%	96%	0.008[a]
Unadjusted HR for death (95% CI)[b]			0.100 (0.013 to 0.805)	0.03
HR for death (95% CI)[c]			0.112 (0.014 to 0.918)	0.04
Secondary Outcomes				
		Clinical Methods	Bioimpedance	Between-Group Mean Difference
Baseline	PWV (m/s)	7.63 ± 2.35	8.22 ± 2.33	−0.58 (−2.35 to 1.18); *P* = 0.9
	BP (mm Hg)	144.6 ± 15.2	145.4 ± 14.5	−0.76 (−7.66 to 6.13); *P* = 0.9
	RFO (%)	10.30 ± 7.70	9.52 ± 7.67	0.78 (−2.80 to 4.36); *P* = 0.9
End of intervention	PWV (m/s)	8.88 ± 3.23	6.68 ± 1.89	2.19 (0.42 to 3.96); *P* = 0.005
	BP (mm Hg)	140.5 ± 11.4	138.9 ± 14.7	1.67 (−5.24 to 8.60); *P* = 0.9
	RFO (%)	11.24 ± 7.62	7.46 ± 5.77	3.77 (2.20 to 7.35); *P* = 0.03
Change from baseline to end of intervention	PWV (m/s)	1.20 (−0.10 to −2.38); *P* = 0.01	−1.50 (−2.80 to −0.30); *P* < 0.001	−2.78 (−3.75 to 1.80); *P* < 0.001
	BP (mm Hg)	−4.00 (−10.83 to 2.63); *P* = 0.4	−6.50 (−13.62 to −4.53); *P* = 0.04	−2.43 (−7.70 to 2.84); *P* = 0.4
	RFO (%)	0.94 (−2.50 to 4.40); *P* = 0.9	−2.05 (−5.70 to −1.10); *P* = 0.03	−2.99 (−5.00 to −0.89); *P* = 0.05

Note: Secondary outcomes data shown as mean ± standard deviation or mean difference (95% CI); *P* value.
Abbreviations: BP, blood pressure; CI, confidence interval; HR, hazard ratio; RFO, relative fluid overload; PWV, pulse wave velocity.
[a]End of intervention; log-rank *P*.
[b]Bioimpedance versus clinical-methods group.
[c]Bioimpedance versus clinical-methods group; adjusted for age, sex, hemodialysis vintage, cardiovascular disease, systolic BP, body mass index, RFO > 15%, albumin level, and diabetes.

measurement (third PWV) is statistically significantly higher compared with both baseline PWV (estimated difference, −4.26 [95% CI, −5.00 to −3.5] m/s; $P < 0.001$) and second PWV (estimated difference, −4.33 [95% CI, −5.15 to −3.51] m/s; $P < 0.001$).

Nine deaths were recorded during the intervention period, one in the bioimpedance group and 8 in the clinical-methods group. In the clinical-methods group, 4 patients died of hemodynamic shock (either septic shock or cardiogenic shock): one death was from acute myocardial infarction, one death was classified as sudden cardiac death, and 2 deaths were of unknown cause. In the bioimpedance group, the only death was attributed to septic shock. All-cause mortality (both unadjusted and multivariate adjusted) was significantly lower in the bioimpedance group compared to the clinical-methods group (Table 2). After adjusting in the Cox model for age, sex, cardiovascular disease, diabetes, dialysis vintage, body mass index, systolic BP, albumin level, and relative fluid overload, the HR for mortality in the bioimpedance group was 0.100 (95% CI, 0.013-0.805; $P = 0.04$) compared to the clinical-methods group. Kaplan-Meier survival analysis also showed significantly higher survival in the bioimpedance group (log-rank test $P = 0.008$; Fig 4).

Of interest is whether the superior outcomes for bioimpedance are related mostly to avoidance of overhydration or to inclusion in a weight target interval (ie, avoiding both chronic over- and underhydration). The proportion of patients maintained within 1.1 kg of the bioimpedance-recommended dry weight was

Table 3. Adverse Events

Adverse Event	Clinical Methods	Bioimpedance	*P*
Hypotension, cramps (events/ patient/y)	6.48 (4.59-7.41; 0.65)	6 (4.59-7.41; 0.71)	0.6

Note: Values given as mean (95% confidence interval; standard error).

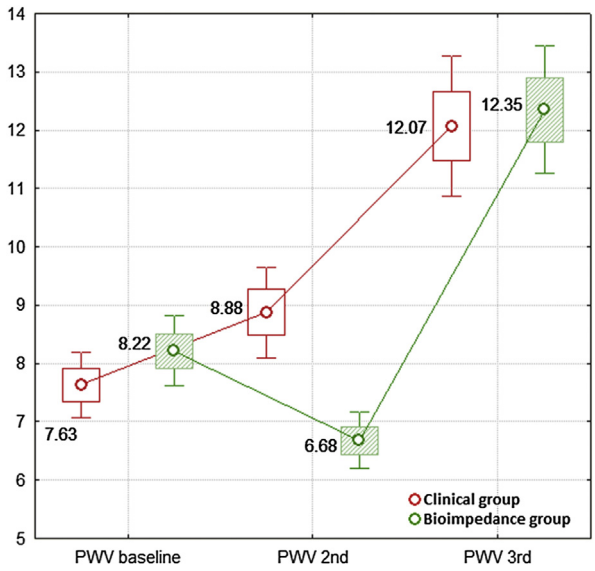

Figure 3. Pulse wave velocity (PWV) mean values (m/s) at baseline, end of intervention (2nd PWV), and end of study (3rd PWV; box, mean ± standard error; whiskers, 95% confidence interval).

statistically significantly higher in the bioimpedance group than in the clinical-methods group (Fig S1, available as online supplementary material).

DISCUSSION

Our study was set up to use an established objective method for determining body composition and hydration status in a randomized trial that analyzed powerful surrogate (PWV) and hard (all-cause mortality) end points. The study showed a significant difference in survival, PWV, BP, and fluid overload between the bioimpedance group and the clinical-methods (control) group after a 2.5-year intervention period. In addition, 1 year after the end of the intervention, stopping bioimpedance-guided fluid management led to loss of the initial improvement in PWV and a decrease in the difference in arterial stiffness between study groups (Fig 3).

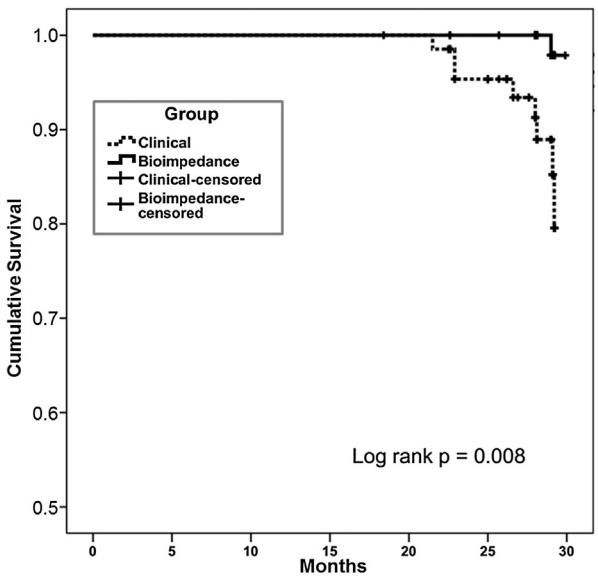

Figure 4. Kaplan-Meier survival analysis.

This is one of the first randomized studies to compare strict exclusive use of bioimpedance versus usual clinical methods for the adjustment of dry weight in HD patients and to our knowledge is the first study reporting survival benefits of strict volume control guided by bioimpedance.

Although bioimpedance has been used in clinical studies for more than 20 years, knowledge of the electrical properties of body tissues is still evolving: only recently has the technique gained momentum following the advent of new bedside easy-to-use devices and recent significant trials describing the deleterious impact of overhydration on survival.[6]

Wabel et al,[9] using the same previously validated bioimpedance technique used in our trial, analyzed 500 HD patients to describe and compare different profiles of BP and hydration status.[5] The results were surprising: besides the expected group of overhydrated hypertensive patients (25%), there was a significant proportion (~25%) of normotensive or even hypotensive, but overhydrated, patients; this finding suggests the need for different therapeutic approaches. In a subsequent prospective study, using the same technique, Wizemann et al[6] measured baseline overhydration in 269 HD patients who were followed up for 3.5 years. The extracellular water to total-body water ratio (as a marker of overhydration) was shown to be an independent predictor of mortality, with an HR for all-cause mortality of 2.1, second only to that related to diabetes (HR, 2.7). Similarly, extracellular to intracellular water ratio was identified as the only significant predictor for patient survival (relative risk, 1.37 for every 0.1-unit increase in extracellular to intracellular water ratio) in 227 incident peritoneal dialysis patients.[12]

Chazot et al[13] analyzed baseline hydration status in 208 patients using bioimpedance and reported mortality after a 6.5-year follow-up period. Fifty patients were considered as a reference population and were selected from the town of Tassin (France), while 158 patients were selected from Giessen (Germany) and were stratified further (using BIA) as nonhyperhydrated and hyperhydrated. The Tassin patients were considered as having optimal fluid status by clinical criteria. After 6.5 years, no difference in mortality was found between the Tassin reference group and the nonhyperhydrated Giessen subgroup (35 patients), whereas multivariate-adjusted all-cause mortality was increased significantly in the hyperhydrated Giessen patient group (HR, 3.41).

The only randomized prospective study in which dry weight was prescribed and reached based exclusively on impedance-derived measurement was published recently by Hur et al.[14] During the course of 12 months, this study showed a significant decrease in left ventricular mass index, BP values, and arterial stiffness in the strict volume control arm. Our trial not only confirms these results, but also adds survival analysis over a longer period (30 months).

Our findings are in agreement with previous data that identified an important relationship in dialysis populations between overhydration and death[6,12] and/or between arterial stiffness and death.[15,16] It is well known that BP is dependent on volume status and it is thought that volume overload also plays an important role in the progression of arterial stiffness.[17] Therefore, controlling volume status improves BP levels and possibly could reverse arterial stiffness. Our study shows in the bioimpedance (strict volume control) group an improvement in both BP and PWV, the latter being offset after abandoning the strict policy of bioimpedance-guided volume control. Thus, we hypothesize that the significant difference in survival may be attributed to the positive impact of bioimpedance-guided fluid management (maintenance in a weight target interval, with avoidance of both chronic over- and underhydration) on BP and vascular health.

A few very small studies have investigated whether, by using bioimpedance instead of clinical judgment, a "true" dry weight is reached (ie, leads to changes in volume status that have clinically relevant effects). Machek et al[7] used bioimpedance-guided fluid management in 52 patients, of whom 12 had been overhydrated and 13 had experienced intradialytic adverse events suggesting underhydration. Over the course of 1 year, all patients were successfully brought into the normohydration range.[7] Zhu et al[18] used continuous calf bioimpedance in 15 HD patients. After gradually decreasing post-HD dry weight, a significantly lower predialysis BP was achieved compared to the initial clinically assessed dry weight, but at the same time, the incidence of clinical symptoms suggesting underhydration in the same patients was increased significantly. Our randomized controlled trial clarifies these single-arm reports, recording a similar amount of intradialytic adverse events between groups, although fluid overload was reduced significantly in the bioimpedance group (Fig 2; Table 3).

One of the major study limitations of this randomized controlled trial is the lack of echocardiography; this would have given important information related to cardiac structure and function and inferior vena cava filling. However, echocardiographic measurements are influenced highly by the training of the people performing them and are associated with substantial intra- and interobserver variability.[19]

Designed as a pilot trial in a single center, this study is underpowered regarding mortality outcomes and registered only a 6.9% mortality rate. This is a low figure compared to the US population and European Renal Association–European Dialysis and Transplant Association reports.[20] However, this value is closer to that recorded by the Romanian Renal Registry[10] and by recent reports showing that Romania has one of the highest survival rates in the world for dialysis, comparable only to that of Japan.[11] Major explanations are the younger age of the dialysis population and lower diabetes prevalence. Moreover, due to limitations of the bioimpedance measuring technique, sicker patients (with cardiac stents, limb amputations, severe ascites, or hip prosthetics) were excluded from enrollment.

However, the study was powered for PWV measurements, which is considered a strong cardiovascular end point,[15,16] because both sample-size calculations and previous reproducibility studies show that a small number of patients is needed to detect significant changes in PWV.[21]

Finally, although patients were blinded during the randomized phase, it was difficult to mask the intervention for the caregivers. However, all decisions regarding adjustment of dry weight, in either the bioimpedance-guided interventional arm or clinical-methods arm (based on clinical judgement alone), were discussed and approved by a decision committee. None of the study investigators was involved directly in care of the patients. In addition, we expect that this limitation would only decrease the difference between the bioimpedance and clinical-methods groups because it is conceivable that additional interest in establishing the clinical correct dry weight was present in the clinical-methods group.

Although these limitations might lead to questions about the generalizability of the data, we believe that in a sicker more compromised cardiovascular population, results from this randomized controlled trial will only be magnified. Nevertheless we acknowledge that this is a pilot trial and results should be confirmed by larger trials.

During the last few years, bioimpedance has come a long way as a noninvasive, simple, and reproducible method of determining body composition and hydration status in dialysis patients. Our study showed improvement in both surrogate and hard end points after bioimpedance-guided strict volume control. More randomized trials are needed to prove whether this method is really useful for reaching a true dry weight that improves BP control, arterial stiffness, or left ventricular hypertrophy, consequently improving mortality. The results are promising and, with enough compelling evidence, this method could become part of future guidelines in treating HD patients.

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SUPPLEMENTARY MATERIAL

Figure S1: Proportion of patients under, over, or within the target dry weight range, by study arm.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.01.420) is available at www.ajkd.org

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