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NEPHROLOGY – ORIGINAL PAPER

Randomized trial of bioelectrical impedance analysis versus clinical criteria for guiding ultrafiltration in hemodialysis patients: effects on blood pressure, hydration status, and arterial stiffness

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Abstract
Background Chronic fluid overload is common in maintenance hemodialysis (HD) patients and is associated with severe cardiovascular complications, such as arterial hypertension, left ventricular hypertrophy, congestive heart failure, and arrhythmia. Therefore, a crucial target of HD is to achieve the so-called dry weight; however, the best way to assess fluid status and dry weight is still unclear. Dry weight is currently determined in most dialysis units on a clinical basis, and it is commonly defined as the lowest body weight a patient can tolerate without developing intra-dialytic or inter-dialytic hypotension or other symptoms of dehydration. One of the most promising methods that have emerged in recent years is bioelectrical impedance analysis (BIA), which estimates body composition, including hydration status, by measuring the body's resistance and reactance to electrical current. Our objective was to study the effect BIA-guided versus clinical-guided ultrafiltration on various cardiovascular disease risk factors and markers in HD patients.
Materials and methods We included 135 HD patients from a single center in a prospective study, aiming to compare the long-term (12 months) effect of BIA-based versus clinical-based assessment of dry weight on blood pressure (BP), pulse wave velocity (PWV), and serum N-terminal fragment of B-type natriuretic peptide (NT-proBNP). The body composition was measured using the portable whole-body multifrequency BIA device, Body Composition Monitor—BCM® (Fresenius Medical Care, Bad Homburg, Germany).
Results In the "clinical" group there were no changes in BP, body mass index (BMI), and body fluids. The PWV increased from 7.9 ± 2.5 to 9.2 ± 3.6 m/s ($P = 0.002$), whereas serum NT-proBNP decreased from 5,238 to 3,883 pg/ml ($P = 0.05$). In the "BIA" group, BMI and body volumes also did not change; however, there was a significant decrease in both systolic BP, from 144.6 ± 14.7 to 135.3 ± 17.8 mmHg ($P < 0.001$), and diastolic BP, from 79.5 ± 9.7 to 73.2 ± 11.1 mmHg ($P < 0.001$). In this group, PWV also decreased from 8.2 ± 2.3 to 6.9 ± 2.3 m/s ($P = 0.001$) and NT-proBNP decreased from 7,552 to 4,561 pg/ml ($P = 0.001$).
Conclusion BIA is not inferior and possibly even better than clinical criteria for assessing dry weight and guiding ultrafiltration in HD patients.

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Keywords Hemodialysis · Ultrafiltration · Bioelectrical impedance analysis · Arterial stiffness · NT-proBNP

Introduction

Chronic fluid overload is very common in patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (HD) or peritoneal dialysis and is associated with severe complications, such as arterial hypertension, left ventricular hypertrophy, congestive heart failure, and arrhythmia—all of which are documented risk factors for cardiovascular (CV) mortality [1–7]. Overhydration can also lead to an increase in arterial stiffness, by amplifying arterial distension and systolic blood pressure [8]. In turn, this increase in arterial stiffness—which can usually be assessed noninvasively by measuring pulse wave velocity (PWV)—has been shown to independently predict mortality both in the general population [9] and in patients with ESRD [10]. On the other hand, excessive removal of fluid by ultrafiltration during dialysis may induce dehydration, intra-dialytic hypotension, and coronary hypoperfusion, which are also very frequent and equally unfavorable events [11, 12].

Therefore, the target of ultrafiltration by HD is to maintain this delicate balance between hypervolemia and hypovolemia. The concept of "dry weight" (which has a history of more than half a century now) is routinely used in current practice in virtually all HD centers worldwide [13, 14]. However, the best way to assess fluid status and dry weight is still an unsolved issue. The ideal method should be highly sensitive and specific, readily available, inexpensive, fast and easy to use by clinicians, and capable to predict clinical outcomes. Such a method still does not exist. Dry weight is currently determined in most dialysis units on a clinical basis, and it is commonly defined as the lowest body weight a patient can tolerate without developing intra- or inter-dialytic hypotension or other symptoms of dehydration [15, 16]. However, clinical findings have insufficient specificity, sensitivity, and objectivity; they are often contradictory and difficult to interpret, cannot detect small changes in hydration status, and cannot accurately predict the target dry weight [15, 17, 18]. Furthermore, this decades-old strategy has not contributed to reducing the notoriously high CV mortality in HD patients, which is ultimately one of the crucial long-term goals of renal replacement therapy.

Therefore, more objective and more sophisticated techniques of assessing hydration status have been proposed, each of these having its own advantages and limitations. For example, continuous blood volume monitoring during dialysis is often used to control ultrafiltration, as it is a safe and inexpensive procedure, although there are no norms to guide fluid removal by this method and its benefit for clinical outcomes is unknown [19, 20]. The echocardiographic measurement of inferior vena cava diameter and collapsibility can accurately predict both right atrial pressure and volume status in HD patients, and the adjustment of dry weight based on this technique was shown to prevent intra-dialytic adverse events, to reduce left ventricular mass and left atrial size, and to improve quality of life [21, 22]; however, its introduction in dialysis daily practice is strongly impeded by issues of cost, availability, need for specialized operators and confounding by intrinsic cardiac dysfunction [23]. The serum concentration of the N-terminal fragment of B-type natriuretic peptide (NT-proBNP) has also been suggested as a possible tool to guide fluid management, as it correlates with volume overload and predicts CV and all-cause mortality in HD patients; nevertheless, it is relatively expensive and its specificity is quite low, as it also depends on other factors than hydration status, such as renal and dialysis clearance, left ventricular structure and function, and systemic inflammation [24–29].

The most promising method of assessing dry weight that has emerged in recent years is probably bioelectrical impedance analysis (BIA). This method estimates body composition, including total body water (TBW), extracellular water (ECW), and intracellular water (ICW), by measuring the body's resistance and reactance to electrical current. It has been validated in healthy subjects and various patient populations by isotope dilution and other body composition techniques [12]. The procedure is safe, simple, and relatively inexpensive. There are two types of BIA: single-frequency BIA, which involves the application of a single 50-kHz frequency current, and multifrequency BIA, which uses multifrequency currents (ranging from 5 to 1,000 kHz). Although the former is more widely used because of the simpler

and less expensive device, the latter can make a more accurate distinction between ECW and ICW [30, 31]. A recently developed device, called Body Composition Monitor® (BCM, Fresenius), includes a computer software that uses a model of body composition for dialysis patients. This device is portable, easy to use, and enables the direct reading of the excess fluid volume on its display [32]. Several studies have proved the usefulness of BIA for the evaluation of dry weight in HD patients [11, 33–36]. Overhydration >15% of ECW as measured by BIA was demonstrated to predict mortality [37]. Very recently, Machek et al. showed that the adjustment of fluid status guided by BIA led to significant reductions in systolic BP and antihypertensive medications in overhydrated HD patients and prevention of adverse events in underhydrated ones [38].

In general, advocating the introduction of a new technique in any field of clinical practice requires evidence that this new technique is capable to improve, in some way, patient outcomes. The role of BIA in HD is currently unclear, as a direct comparison in terms of patient outcomes between this method and the clinical method of estimating dry weight has not been performed so far [39]. Therefore, our objective was to study for the first time in a randomized trial the effect of BIA-guided versus clinical-guided ultrafiltration on several end-points, such as blood pressure (BP), PWV, and NT-proBNP, regarded as CV disease risk factors or markers, in a group of patients from our HD center.

Patients and methods

Patients

We included in the study all prevalent patients ($n = 170$) with ESRD treated by HD for at least 3 months in the "Fresenius Nephrocare—Dr. C. I. Parhon Hospital" HD Center in Iaşi, Romania, in the period between 01.01.2008 and 01.01.2009. Of these patients, those with metallic joint prostheses ($n = 4$), cardiac pacemakers ($n = 5$), and limb amputations ($n = 10$) were subsequently excluded, as BIA cannot be performed in such cases. Another 16 patients were also excluded, as they refused to participate. The remaining patients ($n = 135$) completed the study.

During the study, all patients were treated by a standard HD regimen, consisting of three sessions per week and 5 h per session. Dialysis was performed using "Fresenius 4008" machines, F60 dialyzers, dialysate flows of 600 ml/min, dialysate sodium concentrations of 135–138 mmol/l, and dialysate calcium concentrations of 1.50 mmol/l. The patients also received intravenous iron and rHu-EPO, whenever indicated, in order to meet national and international guidelines for Hb targets.

The study was approved by the hospital ethics committee and all participating patients signed a written informed consent.

Study design

This was a prospective randomized study, aiming to compare the long-term (12 months) effect of BIA-based versus clinical-based assessment of dry weight on BP, PWV, and serum NT-proBNP, in our HD patients.

The patients were randomly assigned by the principal investigator to either group A (the "clinical" group), in which the target dry weight was set according to clinical criteria (i.e., target BP equal to or less than 140/90 mm Hg, absence of edema, and absence of intra-dialytic or inter-dialytic hypotension or other symptoms), or group B (the "BIA" group), in which target dry weight was determined by BIA measurements. The patients were randomized according to a computer-generated randomization list prepared by the chief investigator. Study subjects were randomized in blocks of 10; i.e., of every 10 subjects randomized, five were allocated group A, and five were allocated to group B, in a random manner. The target dry weight was then used to adjust ultrafiltration during all HD sessions throughout the study. Changes in target dry weight were only accepted in cases of rescue interventions by physicians from the dialysis unit, i.e., when compelling adverse events, such as hypotension or ischemia, occurred during HD.

Biochemistry and hematology analyses, serum NT-proBNP, anthropometric and BP measurements, BIA, and applanation tonometry were performed at baseline in all participants, before a mid-week HD session. During a 12-month follow-up period, three additional BIA measurements (at 3, 6, and 9 months) were done. At the end of the study (month 12), all the above-mentioned investigations were repeated. BIA

and tonometry were performed each by a single investigator, blinded to the patients' randomization. The patients' dry weights in group A were decided by the attending physicians from the dialysis unit.

Methods

Demographic characteristics and data concerning the etiology of ESRD, dialysis vintage, and associated CV conditions (including coronary artery disease, chronic heart failure, stroke, and peripheral vascular disease) were taken from the patients' electronic database.

For *BP*, the measurements from three consecutive HD sessions were taken and the average of these three measurements was used in the analysis. The BP was measured in patients after 10 min of recumbence, using a standard mercury sphygmomanometer, with cuffs of appropriate size, in the arm without arterio-venous fistula.

Laboratory data included serum hemoglobin (Hb), total protein, calcium, phosphate, intact parathormone (iPTH), and NT-proBNP. The iPTH was determined by ELISA assay (DRG Instruments®, GmBH, Germany) and the NT-proBNP was measured using an electrochemiluminescence immunoassay (ECLIA) system.

Applanation tonometry was done with a SphygmoCor® device (AtCor Medical, Westmead, Sydney, Australia). Radial arterial waveforms during 40 cardiac cycles were recorded in each patient. The averaged composite radial waveform was calculated and the aortic BP waveform was then derived by the device's software, using a validated transfer function algorithm [40]. The augmentation index (AIx) was calculated as the difference between the first and the second systolic peaks measured on the aortic pressure waveform, divided by the pulse wave height [41]. The PWV was computed from carotid and femoral artery waveforms recorded consecutively, using an electrocardiogram-gated signal and anthropometric distances [41]. All measurements were done twice in a row on each occasion and the results were averaged.

The *body composition* was measured using the portable whole-body multifrequency BIA device, Body Composition Monitor—BCM® (Fresenius Medical Care, Bad Homburg, Germany). The technique involves attaching electrodes to the patient's non-fistula forearm and ipsilateral ankle, with the patient in a supine position. The BCM measures the body resistance and reactance to electrical currents of 50 discrete frequencies, ranging between 5 and 1,000 kHz. Based on a fluid model using these resistances, the extracellular water (ECW), the intracellular water (ICW), and the total body water (TBW) are calculated. These volumes are then used to determine the amount of fluid overload. All calculations are automatically performed by the software of the BCM device. Absolute fluid overload (AFO) is the difference between the expected patient's ECW under normal physiological conditions and the actual ECW, whereas the relative fluid overload (RFO) is defined as the AFO to ECW ratio. Normohydration is defined when AFO is between the 10th and the 90th percentile for healthy, age- and gender-matched individuals from the reference population, i.e., between -1.1 to $+1.1$ L [35], while volumes below and above this range define underhydration and overhydration, respectively.

Statistical Analysis

Statistical analysis was done with the help of the SSPS 15.0 for Windows software (SPSS® Inc, Chicago IL). All values are expressed as mean ± standard deviation or as median and interquartile range (IQR), as appropriate, unless stated otherwise. Since iPTH values were not normally distributed, we used the natural logarithm as a method to normalize data. Continuous variables were compared using the t test. The ANOVA test was used for multiple group comparisons of normally distributed variables. Chi square was used to test differences in frequency distributions. All potential (physiologically meaningful) factors influencing PWV, AIx, and NT-proBNP were studied by univariate analyses, using the Pearson's coefficient of correlation test. Significant factors resulting from these analyses were further introduced in a stepwise multiple regression model, using the F statistic. The P values below 0.05 in the final model were considered as statistically significant.

Results

Baseline characteristics of the study population

A number of 135 HD patients actually took part in the study. Their mean age was 52.4 ± 13.1 years, 51.1%

were men, and their median dialysis vintage was 51 (22–102) months. The etiology of ESRD was chronic glomerulonephritis in 63 patients (46.6%); tubulointerstitial nephropathy in 19 (14.1%), polycystic renal disease in 19 (14.1%), diabetic nephropathy in 8 (5.9%), nephroangiosclerosis in 5 (3.7%), and others or unknown in 21 patients (15.5%).

There were 69 patients (51.5%) with hypertension, 25 (18.5%) with coronary artery disease, 14 (10.3%) with diabetes, and 16 (11.8%) with congestive heart failure. Antihypertensive treatment included betablockers in 44 (32.6%), angiotensin-converting enzyme inhibitors in 25 (18.5%), and angiotensin-receptor blockers in 16 patients (11.9%). Phosphate binders were given to 122 (90.3%) and vitamin D supplements to 51 (37.7%) patients. The patients' baseline clinical and laboratory characteristics are shown in Table 1.

During the study there were no deaths and no drop-outs for any reason among the study patients.

Changes in BP, BMI, and body water during follow-up

In group A, there were no changes in BP, BMI, and body fluids (TBW, ECW, AFO, and RFO) (Table 2a).

Table 1 Patients' characteristics at baseline

Characteristics	Mean ± standard deviation*
Age (years)	52.4 ± 13.1
Dialysis vintage (months)	51.0 (22–102)*
PWV (m/s)	8.1 ± 2.4
AIx (%)	33.6 ± 11.1
NT-proBNP (pg/ml)	6,125 (2,835–15,351)*
SBP (mm Hg)	145.2 ± 15.4
DBP (mm Hg)	78.4 ± 10.6
Serum hemoglobin (g/dl)	11.6 ± 1.6
Serum cholesterol (mg/dl)	176.5 ± 42.2
Serum triglycerides (mg/dl)	159.5 ± 110.2
Serum calcium (mg/dl)	8.3 ± 0.9
Serum phosphate (mmol/l)	1.9 ± 0.6
Serum iPTH (pg/ml)	351 ± 311.9

* All values are given as mean ± standard deviation, except for dialysis vintage and for NT-proBNP, which are given as median and IQR

PWV pulse wave velocity, *AIx* augmentation index, *NT-proBNP* N-terminal proB-type natriuretic peptide, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *iPTH* intact parathormone

In group B, BMI and volumes did not change either, but there was a significant decrease in both systolic BP, by 9.3 mm Hg, from 144.6 ± 14.7 to 135.3 ± 17.8 mmHg ($P < 0.001$), and diastolic BP, by 6.3 mm Hg, from 79.5 ± 9.7 to 73.2 ± 11.1 mmHg ($P < 0.001$) (Table 2b).

Changes in PWV, AIx, and NT-proBNP during follow-up

The PWV significantly increased in group A, from 7.9 ± 2.5 to 9.2 ± 3.6 m/s ($P = 0.002$), and it decreased in group B, from 8.2 ± 2.3 to 6.9 ± 2.3 m/s ($P = 0.001$). The AIx did not change in any of the two groups. The serum NT-proBNP significantly decreased in both groups: from 5,238 to 3,883 pg/ml (i.e., by 25.9%) in group A ($P = 0.05$) and from 7,552 to 4,561 pg/ml (i.e., by 39.6%) in group B ($P = 0.001$). These results are shown in Table 3.

Correlations between variables

At baseline, PWV correlated directly with systolic BP ($R = 0.184$; $P = 0.033$) and with total serum protein ($R = 0.216$; $P = 0.013$), and inversely with serum phosphate ($R = -0.174$; $P = 0.049$). However, at the end of the study, PWV did not correlate with any of the other variables.

The AIx inversely correlated with ECW ($R = -0.297$; $P = 0.001$), TBW ($R = -0.267$; $P = 0.002$), and with serum iPTH ($R = -0.179$; $P = 0.043$) at baseline. At the end of the study, the correlations between AIx and TBW ($R = -0.315$; $P = 0.001$) and ECW ($R = -0.299$; $P = 0.001$) were maintained.

Serum NT-proBNP did not correlate with any other variables at baseline, but it did correlate with BMI ($R = -0.237$; $P = 0.014$) and with the systolic BP ($R = 0.234$; $P = 0.012$) at the end of the study.

Discussions

Maintaining euvolemia is a key target of HD therapy; however, it is presently unclear which method of estimating dry weight in HD patients is the best.

In this study, we investigated if an objective tool such as BIA is better than clinical findings for guiding ultrafiltration in HD patients. Yet, the results

Table 2 Changes in BP, BMI, and body water

	Baseline	3 months	6 months	9 months	12 months
(a) Group A					
TBW (L)	34.1 ± 6.3	34.5 ± 6.3	34.1 ± 6.7	34.2 ± 6.6	34.2 ± 6.2
ECW (L)	16.4 ± 3.1	16.5 ± 3	16.5 ± 3.1	16.4 ± 3	16.5 ± 2.8
AFO (L)	1.7 ± 1.5	1.5 ± 1.6	1.8 ± 1.6	1.4 ± 1.7	1.7 ± 1.5
RFO (%)	9.5 ± 8.4	8.5 ± 9.1	10.4 ± 8.9	8.5 ± 9.5*	9.7 ± 8.3
BMI (kg/m^2)	25.4 ± 5.1	25.3 ± 5.1	25.6 ± 5.4	26.4 ± 5.5	26.2 ± 5.6
SBP (mm Hg)	146.6 ± 16.3	145.6 ± 14.9	146.3 ± 16.8	140.1 ± 14.5*	142.8 ± 13
DBP (mm Hg)	77.7 ± 11.5	82.7 ± 9.6*	79.7 ± 11.7	77.2 ± 10.5	75.3 ± 9.6
(b) Group B					
TBW (L)	33.3 ± 5.4	33.4 ± 5.4	32.9 ± 5.7	33.3 ± 5.6	33.5 ± 6
ECW (L)	15.7 ± 2.9	15.8 ± 2.7	15.9 ± 2.7	15.9 ± 2.6	16 ± 2.7
AFO (L)	1.4 ± 1.4	1.6 ± 1.3	1.6 ± 1.2	1.5 ± 1.3	1.5 ± 1.4
RFO (%)	7.8 ± 7.5	9.5 ± 7.3	9.8 ± 6.9	9.4 ± 7.6	9.3 ± 7.8
BMI (kg/m^2)	24.3 ± 3.7	24.1 ± 3.6	23.6 ± 4.7	24.1 ± 3.9	23.7 ± 4.9
SBP (mm Hg)	144.3 ± 14.5	144.9 ± 13.3	143.1 ± 14.5	141.5 ± 13.8	135.4 ± 17.8*#
DBP (mm Hg)	79.3 ± 9.5	82.5 ± 9.2	79.9 ± 9.5	77.3 ± 8.9	73.2 ± 11.1*#

* Significant difference from the very previous measurement

Significant difference between the final and the baseline measurements

TBW total body water, *ECW* extracellular water, *AFO* absolute fluid overload, *RFO* relative fluid overload, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 3 Changes in PWV, AIx, and NT-proBNP during follow-up: comparison between the two groups

Data	Group A ($n = 64$)		Group B ($n = 71$)	
	Baseline	End of study	Baseline	End of study
PWV (m/s)	7.9 ± 2.5	9.2 ± 3.6*	8.2 ± 2.3	6.9 ± 2.3*
AIx (%)	37.5 ± 26.1	35.6 ± 10.7	33.1 ± 11.5	30.9 ± 13.3
NT-proBNP (pg/ml)	5,238 (2,550–14,841)	3,883 (2,009–10,119)*	7,552 (3,591–15,429)	4,561 (2,815–10,269)*

* Significant difference between values at the end of the study versus baseline

PWV pulse wave velocity, *AIx* augmentation index, *NT-proBNP* N-terminal proB-type natriuretic peptide

of the study are not easy to interpret. When we look at the measurements of the patients' pre-dialysis body volumes (TBW, ECW, AFO, and RFO), we can conclude that, during the 12-month follow-up period, the hydration status was kept stable in all patients, irrespective of the method employed. It would thus seem that BIA is neither better nor worse than the clinical assessment in this regard. On the other hand, when we evaluate the BP (both SBP and DBP) and the PWV, we can see that they significantly decreased only in the "BIA" group, whereas the BP did not change and the PWV even increased in the "clinical" group. Additionally, the decrease in serum NT-proBNP was more important in the "BIA" group than in the "clinical" group (−39.6 vs. −25.9%). All in all, these findings seem to indicate a better sodium and fluid control in the "BIA" patients. In our opinion, these apparently paradoxical results could have one explanation: the patients in the "BIA" group might have got out from dialysis "dryer" than those in the "clinical" group and, therefore they might have had a lower average fluid overload, on long term, in comparison with the latter. Certainly, this explanation remains purely speculative, as we did not actually measure the post-dialysis hydration status.

Whatever the explanation, a more important question is whether these reductions in BP, PWV, and NT-proBNP could translate into an improvement in CV outcomes. Our study does not provide an answer to this question; however, based on previous studies, we can assume this might indeed be beneficial. The target BP in HD patients is currently unclear [42, 43]. An analysis of the HEMO data [44] showed that a pre-dialysis systolic BP below 120 mm Hg was associated with an increased mortality risk, compared to the reference range of 140–159 mm Hg, whereas higher BP levels did not affect this risk. However, in a younger cohort of HD patients [45], with a mean age of 54.9 (similar to our own patients, who were 52.4 years-old), the lowest mortality risk was found in those with a home systolic BP between 120 and 130 mm Hg. Arterial stiffness is also an important and independent predictive factor for survival in this population. The very recently published CORD study, performed in 1,084 patients from 47 European dialysis centers, showed that death risk increased by 15% for each 1 m/s increase in carotid-femoral PWV [10]. Finally, NT-proBNP has also been demonstrated as an independent risk factor for mortality in HD patients [28].

The strength of our study is, in our view, the fact that it was indeed the first randomized comparison between the utilization of BIA versus the clinical method in the adjustment of ultrafiltration in HD patients. In other words, the target dry weights in the "BIA" arm were established solely on the basis of BIA measurements, without any interference from the medical staff besides rescue interventions.

On the other hand, our study had several limitations that must be pointed out. First, we only performed BIA before the dialysis sessions but not afterward, in which case we would have been able to directly compare the two patient groups by their post-dialysis volumes. Second, it might have been useful to divide patients by their pre-dialysis ECW, into "overhydrated", "normohydrated", and "dehydrated", and to study their outcomes accordingly. Third, we did not take into account adverse events, such as hypotension episodes, and thus we could not compare the two groups in this regard. Fourth, we only studied surrogate end-points, such as BP, PWV, and NT-proBNP, but no hard end-points like CV events, hospitalizations or survival. Finally, it is worth pointing out that our study population was relatively younger and with a low prevalence of diabetes (5.9%), which makes it somewhat different from dialysis populations in most Western countries; these differences could limit the generalizability of our results.

We believe that, with all its limitations, our study proves that BIA is not inferior and possibly even better than clinical criteria for assessing dry weight and guiding ultrafiltration in HD patients. Being an accurate, simple, noninvasive, and relatively inexpensive technique, BIA could emerge as a useful tool in the management of HD patients—certainly, not to replace but to help clinical judgment. Further long-term BIA studies, with improved design and significant clinical end-points, are warranted in this population.

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