TITLE: **Bioimpedance Devices for the Assessment of Body Fluid Volume for Patients Undergoing Dialysis: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines**

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CONTEXT AND POLICY ISSUES

Patients with terminal or end stage renal disease (ESRD) require lifetime renal replacement therapy. Depending on the medical condition of the patient, local clinical guidelines, and the availability of different therapeutic options, patients can be treated with hemodialysis or peritoneal dialysis modalities. Hemodynamic instability is a challenge that complicates the management of ESRD, and it can present as volume-related hypotension during the dialysis sessions or as hypertension or fluid overload due to insufficient fluid clearance through dialysis.[1] The chronic exposure to fluid overload and hypertension may lead to cardiac stiffness and left ventricular hypertrophy; some studies have reported an increased risk of death due to inadequate total body fluid removal.[2-4] Therefore, fluid management should be based on accurate estimation of patients' dialysis needs. These estimates can be obtained clinically by patient examination and the calculation of body dry weight; however, they are subjective and operator-sensitive methods.[1] Objective methods have been developed to provide reliable and accurate estimates of the dry weight and fluid clearance needs; of these are blood volume monitoring, natriuretic peptide measurements, extravascular lung water indices, and bioimpedance methods.[1]

Bioimpedance devices are a technology based on passing a bioelectrical current through the body, and it estimates the body fluid volume by the amount of resistance this current endures in the body tissues. The bioelectrical current used in these devices can have segmental, spectral, or multi-bioelectrical frequencies.[5] Several studies have showed that this method is accurate and reliable for the assessment of body fluids.[6-9] The objective of this report is to review the evidence on the clinical effectiveness, cost-effectiveness, and evidence-based clinical guidelines on the use of bioimpedance-based fluid management in renal dialysis patients.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of bioimpedance devices for the assessment of body fluid volume status in patients with renal disease who are on peritoneal dialysis or hemodialysis?

2. What is the cost-effectiveness of bioimpedance devices for the assessment of body fluid volume status in patients with renal disease who are on peritoneal dialysis or hemodialysis?

3. What are the evidence-based guidelines regarding the use of bioimpedance devices for the assessment of body fluid volume status in patients with renal disease who are on peritoneal dialysis or hemodialysis?

KEY FINDINGS

Five studies on the effectiveness of bioimpedance spectrometry devices were included in the review. The literature search did not identify any cost-effectiveness analyses or clinical guidelines. The included studies showed limited evidence that the use these devices as adjunctive tools in fluid-management might be associated with better patient outcomes such as decreased blood pressure, reduced fluid overload, and decreased left ventricular mass index.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and February 12, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles/abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients requiring peritoneal or hemodialysis
Intervention	Bioimpedance devices for the assessment of body fluid volume
Comparator	Clinical assessment of body fluid volume without the device or no comparator
Outcomes	Clinical effectiveness, clinical benefit or harm, safety, cost, and evidence-based guidelines
Study Designs	Health technology assessment, systematic review, meta-analysis, randomized- or non-randomized-controlled trials, and evidence based clinical guidelines

Exclusion Criteria

Studies were excluded if they evaluated body fluid status in patients with renal disease but not receiving hemodialysis or peritoneal dialysis. An additional exclusion criterion was for studies that focused on body nutrients rather than body fluid management.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was based on study design.

The methodological quality of the included randomized controlled trials was evaluated using the SIGN50 checklist for controlled studies.[10] The uncontrolled trials included in this review were evaluated using the SIGN50 checklist for cohort studies.[11]

For the included studies a numeric score was not calculated. Instead, the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A PRISMA diagram demonstrating the study selection process is presented in APPENDIX 1

A total of 264 potential citations were identified by searching the bibliographic database, with 256 citations being excluded during the title and abstract screening based on their irrelevance to the questions of interest. The full text documents of the remaining eight articles were retrieved. One additional article was identified by grey literature and hand search. Of the nine articles, four did not meet the inclusion criteria and were excluded; leaving five articles that reported three randomized-controlled trials and two uncontrolled studies.

Additional reference of potential interest is provided in APPENDIX 2.

Summary of Study Characteristics

Details on study characteristics are tabulated in APPENDIX 3

Five studies that addressed the clinical effectiveness of bioimpedance devices were included in this report; the search did not identify any relevant literature related to the cost-effectiveness of these interventions or clinical guidelines for their use.

Fluid management in hemodialysis patients was evaluated in four studies: two randomized-controlled studies[12,13] and two studies that had a before-after design with no control group.[14,15] One randomized controlled study evaluated fluid management in peritoneal dialysis patients.[16]

The five included studies evaluated fluid management using a bioimpedance spectrometer (Body Composition Monitor [BCM]; Fresenius Medical Care, Germany). The device is based on bioimpedance analysis which uses a spectrum of currents ranging from 5 to 1,000 kHz.

Studies on hemodialysis patients

The four studies included patients stabilized on at least three sessions per week of maintenance hemodialysis therapy for at least three to six months.[12-15] Three of these studies excluded patients with major health problems, which included patients with a pacemaker or defibrillator,[12-14] having catheters or access problems,[12,14] infections,[14] severe intradialytic blood pressure instability,[14] or major amputations.[13,14] The fourth study included all patients who had been receiving hemodialysis therapy at the study centre; the published article on this study did not report exclusion criteria.[15] However, this study was the only one to report the causes of renal failure for the included patients; the article reported that the following reasons for renal failure in the included patients: nondiabetic nephropathy, diabetic nephropathy, glomerulonephritis, interstitial nephritis, polycystic kidney disease[15] The two RCTs by Hur et al.[12] and Onofriescu et al.[13] had one year trial duration; the study by Moissl et al.[14] was three months long, and the one by Vujicic et al. had a six-month duration.[15]

Studies on peritoneal dialysis patients

Luo et al.[16] used the bioimpedance spectrometry to estimate over-hydration values in peritoneal dialysis patients. These values in turn were relied on in the management of body volume and arterial hypertension. The study included patients who were stabilized on continuous ambulatory dialysis for at least three months and at least three fluid exchanges per day. The study adopted a randomized-controlled design in which the bioimpedance technique was provided for both groups; however, over-hydration results were withheld from the patients and their primary nurses, who then based patient management solely on the unit's prior protocols.[16] The study was planned for six months, but the article reported that the study was terminated at three months without reporting the reasons.[16]

Summary of Critical Appraisal

Details on study appraisal are tabulated in APPENDIX 4.

In general, the included studies provided detailed descriptions of the evaluated interventions. Three studies used a randomized controlled design in order to compare patients' outcomes between bioimpedance-based fluid management and clinical-based fluid management;[12,13,16] the remaining two studies used one-group interventional cohort in which patients' outcomes at the end of the study were compared with the baseline values of the same patients.[14] Although this design provides comparative estimates of bioimpedance-based effectiveness, it has several limitations: it does not allow for direct comparison with standard of care, and it may be liable to a potential bias due to confounding factors which otherwise would be offset by the control group in the randomized-controlled trials.

Hur et al. estimated the sample size was based on statistical power calculation;[12] however, the remaining four studies included a convenience sample, but without any statistical power estimation.[13-16]

The generalizability of findings from the included studies might be limited due to the extensive exclusion criteria adopted in four studies.[12-14,16] The remaining study by Vujicic et al.[15] included all patients treated at the hemodialysis center at which the study was conducted. Therefore, this study might have a good representation of the hemodialysis population seen in clinical practice.[15]

Two studies defined several outcomes in their methodologies, but they only report the results for some of the defined outcomes. This might be a source of reporting bias because it is unknown whether the unreported outcomes confirm or contradict the reported ones.[12,13]

Summary of Findings

Details on studies' findings are tabulated in APPENDIX 5.

Studies on hemodialysis patients

Hur et al. reported that patients who received 12-month bioimpedance-based fluid management had statistically significant more reduction in left ventricular mass index than those who had clinically-based fluid management.[12] However, the authors did not report the comparative difference in patients with left ventricular hypertrophy, and therefore it is unclear whether the reported reduction in left ventricular mass index is clinically significant. Similarly, the authors reported that the post dialysis blood pressure was statistically significantly reduced more in the bioimpedance-based fluid management patient; however, they did not report the incidence or the comparative difference in patients achieving normal blood pressure.[12] The article did not report the results for the following defined outcomes: antihypertensive drugs use, left atrial volume index, hemoglobin, erythropoietin, albumin and c-reactive protein.[12]

Moissl et al. compared patients' clinical and laboratory values at baseline with the values obtained after three months of bioimpedance-based fluid management.[14] The authors reported that at the end of the trial patients had a reduction in time-averaged fluid overload that was no statistically significant; however, this reduction was statistically significant in subgroups of patients who were either dehydrated or overloaded at baseline.[14] The authors also reported a statistically significant reduction in pre- and post-dialysis fluid overload, serum albumin and c-reactive protein, but the results were not consistent among the defined subgroups. In contrast, the trial failed to show statistically significant differences in quality of life, post-dialytic blood pressure, serum hemoglobin or residual renal functions.[14]

Vujicic et al. compared patients' clinical and laboratory values at baseline with those obtained after six months of bioimpedance-based fluid management.[15] The study showed that at the end of study, patients had statistically significant reductions in body weight, dry weight, overhydration, and predialysis blood pressure.[15]

The study by Onofriescu et al. reported that patients who had 12 months bioimpedance-based fluid management had a statistically significant reduction in blood pressure when compared with their values at baseline. Patients who received clinically-based fluid management also had reduction in their blood pressure, but this change was not statistically significant. However, the study did not report the difference between groups, and the individual results for each group does not permit the direct comparison between the two groups.[13] Furthermore, the study did not report the results for the following defined outcomes: serum hemoglobin, total protein, calcium, phosphate, or intact parathormone.[13]

Studies on peritoneal dialysis patients

The study by Luo et al.[16] reported a statistically significant greater reduction in systolic blood pressure and over-hydration volume in the bioimpedance group compared with the clinical management group. However, the differences between groups were not statistically significant

in diastolic blood pressure, total fluid or sodium removal, and total defined daily doses of peritoneal dialysis.

Limitations

None of the included studies was conducted in Canada or North America and might not reflect the Canadian context and clinical practice. Clinical practice and guidelines might have impact on the dialysis regimens and the clinical evaluation relative to fluid management. Therefore, the generalizability of findings from the included studies might be limited to the Canadian context. However, the literature search detected a protocol of a three-year Canadian study dated in 2011, with the results of this trial likely to be available by the end of 2014 or early 2015.[17] A summary of the protocol is provided in APPENDIX 2.

All the included studies evaluated bioimpedance spectrometry technology; however, the bioimpedance technology can also be used with segmental or multibioelectrical frequencies.[5] The findings of the current review are limited to the bioimpedance spectrometry devices only; furthermore, the evaluated bioimpedance spectrometry devices were of the same mark. Another gap in the research is related to the cost-effectiveness and clinical guidelines.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report aimed to evaluate effectiveness of bioimpedance devices for the management of body fluids in patients requiring renal dialysis. The clinical guidelines for use and cost-effectiveness of these devices were also searched for. A total of five effectiveness studies were retrieved, but the literature search did not identify any cost-effectiveness studies or clinical guidelines.

With respect to the effectiveness of bioimpedance devices, the included reports evaluated devices that used spectrometry of bioelectrical frequency only. Therefore, no conclusions could be made on devices that use segmental or multi-bioelectrical frequencies. Evidence from the included randomized controlled studies showed that the use bioimpedance-based fluid management was associated with signs of better blood pressure control than the standard of care; however, the significance of these results was not consistent. One included study also indicated that the use of these devices was associated with a reduction of the left ventricular mass index.

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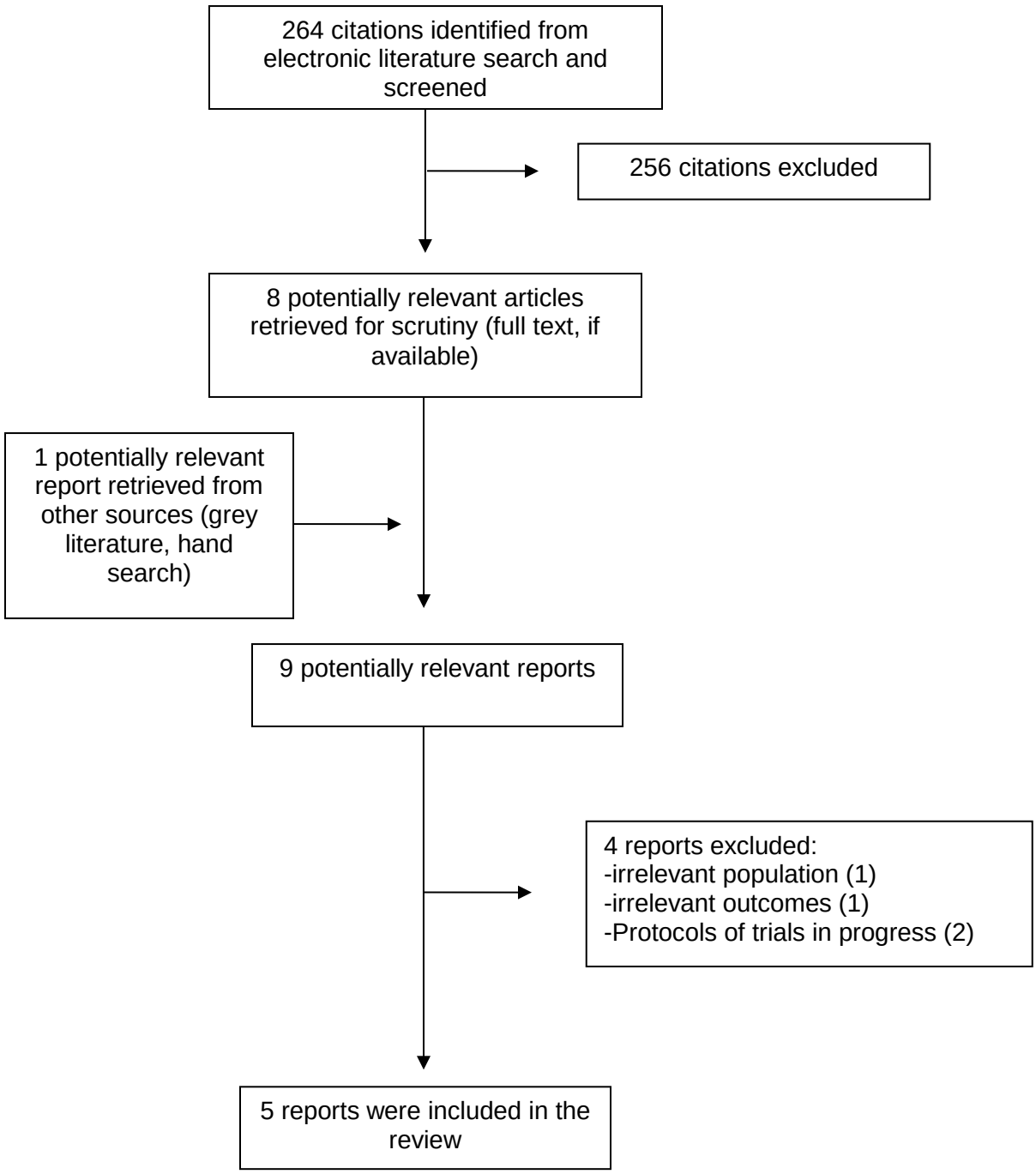
APPENDIX 1: SELECTION OF INCLUDED STUDIES



APPENDIX 2: REFERENCE OF INTEREST BUT NOT IINCLUDED IN THE REVIEW

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
Su et al. 2011[17] – Canada (Randomized Controlled Trial - Protocol)			
To evaluate the effects of bioimpedance analysis–guided fluid management and vitamin D supplementation on volume overload and left ventricular mass in peritoneal dialysis patients RCT	**Inclusion Criteria:** • Patients receiving peritoneal dialysis *The trial excluded patients with* • peritonitis in preceding 3 months	**Intervention: (N = 70)** o Fluid management is based on bioimpedance evaluation (non-blinded); the target of dialysis is to achieve euvolemia, AND ▪ vitamin D3 50 000 U weekly for 8 doses, and then 10 000 U weekly, or ▪ placebo for 1 year (double-blinded) **Comparators: (N = 70)** o Fluid management is based on usual care (non-blinded), AND ▪ vitamin D3 50 000 U weekly for 8 doses, and then 10 000 U weekly, or ▪ placebo for 1 year (double-blinded) **Study Conduct:** • Study duration is 3 years o Bioimpedance assessment was conducted as the following: ▪ Control group: at baseline and at 2-month intervals for 12 months; ▪ Intervention group: monthly for 12 months. After 12 months, bioimpedance assessment was repeated every 3 months until the end of the planned 3-year study.	**Primary outcome**: • Changes in left ventricular mass **Secondary outcome:** • Composite of death, non-fatal cardiovascular event, and transfer to hemodialysis for dialysis inadequacy or ultrafiltration failure. **Other outcomes**: • mean and pulse arterial pressure, • quality of life (measured using the Kidney Disease Quality of Life Short Form), • 6-minute walk test, • residual renal function.

Strengths	Limitations
Su et al. 2011[17] – Canada (Randomized Controlled Trial - Protocol)	
• The trial adopted a randomized approach with a control group; randomization was computer generated. • The intervention is described in details. • The sample size is based-on power calculation relative to the trial's primary outcome • Outcomes were centrally adjudicated by the Events Adjudication Committee, using standardized definitions and blinded to treatment assignment.	• The volume management is not blinded; however, the results of the bioimpedance measures obtained in the control group will be unavailable to the primary nephrologists and to other health care providers delivering peritoneal dialysis care. • Although the volume management arm of the study will be unblinded by necessity, the results of the bioimpedance measures obtained in the control group will be unavailable to the primary nephrologists and to other health care providers delivering PD care.

APPENDIX 3: CHARACTERISTICS OF INCLUDED STUDIES

Characteristics of the Included Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
Hur et al. 2013[12] – Turkey (Randomized Controlled Trial)			
To evaluate the impact of bioimpedance spectroscopy (BIS)-guided fluid management on cardiac health and blood pressure in hemodialysis patients. RCT	**Inclusion Criteria:** • Patients receiving maintenance hemodialysis therapy three times weekly • On maintenance therapy for at least 3 months • Patients with pacemaker or defibrillator, permanent or temporary catheters were excluded **Sample size:** • 156 patients **Patients characteristics:** • Average age was 52 years • 87 (69%) male patients • More smoking patients in the control group (19% vs 26%; p-value =0.4)	**Intervention:** • N=78 o Body-fluid management was based on BIS device (Body Composition Monitor [BCM]; Fresenius Medical Care, Germany) o BIS estimates were used to achieve neutral (zero) time-averaged fluid overload[a] **Comparators:** • N=78 o Body-fluid management was based on dry weight estimates o Dry weight was estimated clinically, and chest radio graph was used to evaluate the cardiothoracic index o BIS was used to estimate the pre-dialysis fluid overload at baseline and 3-monthly intervals during follow-up **Study Conduct:** • Study duration was 12 months o Laboratory parameters were evaluated monthly	Primary outcome: • Regression of left ventricular mass index **Secondary outcomes:** • Change in postdialytic weight • Achievement of normal blood pressure without antihypertensive medications • Change in atrial volume • Hemoglobin level • Recombinant human erythropoietin dose • Serum levels of albumin and C-reactive protein **Additional outcomes:** • Ambulatory blood pressure • Femoral pulse wave velocity • Augmentation index

BIS= bioimpedance spectroscopy;
[a] Time-averaged overload (TAFO) was used to account for the different amounts of fluid overload during the interdialytic period. TAFO was based on the measured predialysis fluid overload and interdialytic weight gain. TAFO was estimated form the following formula:
$TAFO = FO_{pre} – IDWG/2$; FO_{pre} = fluid overload and IDWG = interdialytic weight gain. These measures were taken at mid- or end-week dialysis session, and they excluded the first dialysis session in the week.

Characteristics of the Included Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
Moissl et al. 2013[14] – Spain (Before-After study with no control group)			
To evaluate the clinical consequences of bioimpedance spectroscopy (BIS)-guided fluid management in hemodialysis patients Uncontrolled trial	**Inclusion Criteria:** • CKD-5 patients who underwent three times per week in-center dialysis treatments for at least 6 months before study start **Exclusion criteria:** • Acute or chronic infections, • Severe diseases, • Access problems, • Severe intradialytic BP instabilities in the month before study start, • Major amputations, or pacemakers. **Sample size:** • 56 patients **Patients characteristics:** • Average age was 65 years • 37 (66%) were male patients • Dialysis vintage: 26 (6–180) months • Patients with diabetes: 17 (31%) • Antihypertensive medication: 33 (60%)	**Intervention:** • N=56 o Fluid overload (FO) was estimated using BIS device (Body Composition Monitor [BCM]; Fresenius Medical Care, Germany) o FO readings were used to estimate the time-averaged fluid overload (TAFO)[a] o The treatment target was to achieve TAFO of 0.5L. **Comparators:** • None **Study Conduct:** • Study duration was 3 months • Results were analysed for 55 patients, and the analysis considered 3 subgroups: dehydrated at baseline, normovolemic at baseline, and overloaded at baseline.	Primary outcome: • Intra-individual difference in TAFO between baseline and study end Secondary outcomes: • changes in predialysis fluid overload • Short-Form (SF-36) Health Survey • Brain natriuretic peptide, • Blood pressure, • Laboratory parameters, • Medication, • Intradialytic events (hypotension or cramps), • Residual renal function, and • Hospitalization

[a] TAFO was defined as the average cardiovascular fluid load over 1 complete week, assuming linear fluid accumulation in the interdialytic period. It was estimated from the following formula:
Average weekly TAFO = $(FO_{pre}1 + FO_{pre}2 + FO_{pre}3 + FO_{post}1 + FO_{post}2 + FO_{post}3)/6$; FO = fluid overload

Characteristics of the Included Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
Vujicic et al. 2013[15] – Croatia (Before-After study with no control group)			
To evaluate the effect of bioimpedance spectroscopy (BIS)-guided fluid management on volume-dependent hyrpertension in hemodialysis patients Uncontrolled trial	**Inclusion Criteria:** • The trial included all ESRD patients in on dialysis centre, • Patients were on maintenance HD for at least six months, three times a week, four hours each treatment. **Sample size:** • 65 patients **Patients characteristics:** • 36 (55%) male patients **Etiology:** • Nondiabetic nephropathy: 18 (28%) • Diabetic nephropathy: 14 (22%) • Glomerulonephritis: 12 (18%) • Interstitial nephritis: 10 (15%) • Polycystic kidney disease: 6 (9%) • Other: 5 (8%)	**Intervention:** • N= 65 o Volume status was evaluated using BIS device (Body Composition Monitor [BCM]; Fresenius Medical Care, Germany) o Volume status was assessed before the midweek HD session at months 0, 1, 3 and 6 **Comparators:** • None **Study Conduct:** • Study duration was 6 months • Results were analysed for 65 patients, and the analysis considered 5 subgroups: o patients with volume-dependent hypertension o patients with hypertension and normal volume status o patients with hypovolemic and hypotensive patients o hypervolemic but normotensive patients o patient with normovolemic - normotensive patients	The trial did not declare a primary outcome; the reported outcomes were: • Weight • Dry weight • Hemoglobin • Overhydration • Blood pressure
BIS = bioimpedance spectroscopy; ESRD = end stage renal disease; HD = hemodialysis			
Onofriescu et al. 2013[13] – Romania (Randomized Controlled Trial)			
To compare the effect of multi-frequency bioimpedance analysis (BIA)-guided versus clinical-guided ultrafiltration on clinical outcomes in hemodialysis patients RCT	**Inclusion Criteria:** • Patients with ESRD treated by HD for at least 3 months • Patients with metallic joint prostheses, cardiac pacemakers and limb amputations were excluded **Sample size:** • 135 patients **Patients characteristics:** • The mean age was 52.4 years • Dialysis vintage: 51 months • Hypertension: 69 (51.5%) patients • Coronary artery disease: 25	**Intervention: (N=71)** • Bioimpedance group o Target dry weight was determined by BIA measurements.[a] **Comparators: (N=64)** • Clinical group o Target dry weight was set according to clinical criteria o target BP equal to or less than 140/90 mm Hg, o absence of edema, and o absence of intra-dialytic or inter-dialytic hypotension or other symptoms) **Study Conduct:** • One year trial duration • Laboratory and blood pressure were assessed before mid-week session	The trial did not declare a primary outcome; the reported outcomes were: • Blood pressure, • hemoglobin, • total protein, • calcium, phosphate, • intact parathormone • B-type natriuretic peptide (NT-proBNP)

Characteristics of the Included Trials

Study Objectives and Design	Inclusion Criteria, Sample Size, and Patient Characteristics	Intervention, Comparator, and Study Conduct	Clinical Outcomes
	(18.5%) • Diabetes: 14 (10.3%) • Congestive heart disease: 16 (11.8%)	• During the trial, bioimpedance analysis were done at baseline, 3, 6, 9 and 12 months • Investigators were blinded to patients' randomization	
Luo et al. 2010[16] – Germany (Randomized Controlled Trial)			
To evaluate the effect of over hydration value provided by bioimpedance spectroscopy in volume and hypertension management in peritoneal dialysis patients RCT	**Inclusion Criteria:** • Stable continuous ambulatory peritoneal patients for at least 3 months • Patients who had been on 1 or 2 exchanges a day due to economic limitation were not included in the present study **Sample size:** • 165 patients **Patients characteristics:** • 74 (44.8%) male patients • Dialysis vintage: 34 months • Diabetes mellitus: 44 (26.7) • Daily defined doses: 2.5	**Intervention: (N = 78)** • Patients and primary nurses were informed of OH values provided by a body composition monitor.[a] **Comparators: (N = 82)** • Over hydration values were withheld from the patients and the primary nurses, who then based their patient management solely on the unit's prior protocols. **Study Conduct:** • The trial was planned for 6 months, but it was terminated at 3 months • Patients were followed and assessed about every 6 weeks or less • Bioimpedance was done during each clinical visit • Residual renal function and sodium removal was assessed every 3 months. • The treatment allocation was not blinded	The trial did not declare a primary outcome; of the reported outcomes: • Over hydration • Blood pressure • Total fluid removal • Total sodium removal • Total defined daily dose

[a] Body Composition Monitor [BCM]; Fresenius Medical Care, Germany

APPENDIX 4: CRITICAL APPRAISAL OF THE INCLUDED STUDIES

Strengths	Limitations
Hur et al. 2013[12] – Turkey (Randomized Controlled Trial)	
• The trial adopted a randomized approach with a control group. • The sample size was based-on power calculation relative to the trial's primary outcome • The intervention was described in details.	• The nature of the evaluated intervention did not permit its blinding to the operator; however, patients could be blinded to offset the placebo effect. • The trial's main objectives were to evaluate the effect of bioimpedance spectroscopy-guided fluid management on cardiac health and blood pressure; however, only 23% of the included patients had cardiovascular disease history, 80% of patients had left ventricular hypertrophy (main outcome measure), and the average blood pressure was 140/79. The results should have been analysed in a manner that differentiate between the therapeutic impact of BIS and its preventive benefit. • Smoker status was different in the two groups; the control group had more smoker patients than the intervention group (26% versus 19%, p-value = 0.4). The analysis for the main outcome was adjusted for several variables, but the model did not adjust to the smoking status.
Moissl et al. 2013[14] – Spain (Before-After study with no control group)	
• The intervention was described in details.	• The trial did not use statistical power calculation to estimate the required sample size; instead inclusion was based on convenience. • The trial did not include a control group; instead the effects of the evaluated intervention was assessed intra-individually (before and after the application of the intervention). • The trial was conducted on relatively stable hemodialysis patients with no major health issues such interdialytic blood pressure instability. Hemodialysis patients, in general, have many comorbid health issues, and the generalizability of this trial is uncertain.
Vujicic et al. 2013[15] – Croatia (Before-After study with no control group)	
• The trial included all patients receiving hemodialysis treatment at the included center. Inclusion was not limited to patients' health status; therefore, results from this trial can be generalized to other center with similar patient population. • The intervention was described in details.	• The trial did not use statistical power calculation to estimate the required sample size; instead inclusion was based on convenience. • The trial did not include a control group; instead the effects of the evaluated intervention was assessed intra-individually (before and after the application of the intervention).
Onofriescu et al. 2013[13] – Romania (Randomized Controlled Trial)	
• The trial adopted a randomized approach with a control group; randomization was computer generated. • The investigator, who assessed patients' outcomes, was blinded to the allocated group	• The trial did not use statistical power calculation to estimate the required sample size; instead inclusion was based on convenience. • The results were analyzed for each group separately i.e., in each group the comparison was made between the baseline and end for trial values. However, there was no direct comparison between the two groups, and the comparative effectiveness of the bioimpedance-guided fluid management with the standard of care is unknown. • The method used to estimate the target dry weight was not provided; therefore, results obtained from this trial can't be compared to other trials or adopted for different settings

Strengths	Limitations
Luo et al. 2010[16] – Germany (Randomized Controlled Trial)	
• The trial adopted a randomized approach with a control group • The intervention was described in details.	• The trial did not use statistical power calculation to estimate the required sample size; instead inclusion was based on convenience. • The treatment allocation was not blinded

APPENDIX 5: SUMMARY OF THE FINDINGS

Study Findings								Authors' Conclusions
Hur et al. 2013[12] – Turkey (Randomized Controlled Trial)								
								The authors concluded that the use of bioimpedance spectroscopy for fluid management in hemodialysis patients resulted in lower fluid status and improved cardiovascular parameters. Reviewer's comment: the article not report the results for all specified outcomes; this might be a source of reporting bias.
	BIS-guided group (N = 64)			**Clinical fluid management (N = 64)**			**Mean difference (95% CI)**	
	Baseline	**12 mo**	**Change P-value**	**Baseline**	**12 mo**	**Change P-value**		
LVMI, g/m^2	131 (36)	116 (29)	-14.5 (32.1) <0.001	121 (35)	120 (30)	-1.3 (33.2) 0.9	-10.2 (-19.2 to -1.17)	
LVH, n (%)	43 (67)	28 (13.1)	0.03	29.0 (9.8)	27.4 (10.0)	0.3	Not reported	
PDBW, KG	67.6 (8.6)	67.0 (9.4)	-0.5 (2.4) 0.05	67.9 (13.7)	68.0 (15.3)	0 (3.2) 0.9	-0.6 (-1.6 to 0.4)	
Normal BP	Not reported							
Predialysis ABP, mmHG								
• Systolic	129 (17)	120 (19)	-9.4 (11) <0.001	130 (17)	125 (19)	-5.0 (13) 0.006	-4.5 (-8.9 to 0.1)	
• Diastolic	76 (7)	73 (9)	-3.5 (5.9) <0.001	77 (7)	76 (9)	-0.9 (6.4) 0.2	-2.6 (-4.8 to -0.3)	
Postdialysis ABP, mmHG								
• Systolic	116 (16)	105 (18)	-11 (11) <0.001	117 (20)	113 (21)	-4.8 (15) 0.03	-6.6 (-11.1 to -1.9)	
• Diastolic	70 (8)	65 (9)	-5.3 (6.2) <0.001	71 (9)	70 (10)	-1.7 (6.9) 0.07	-3.7 (-6.0 to -1.4)	
Antihypertensive drugs use, %	23%	11%	0.008	24%	21%	0.6	Not reported	
LAVI, mL/m^2	28.6 (8.4)	26.9 (8.7)	0.03	27.2 (8.4)	27.7 (9.1)	0.8		
Hemoglobin, g/dL	11.7 (1.1)	12.0 (1.1)	0.01	11.9 (1.1)	12.1 (1.1)	0.1		
Erythropoietin IU/kg/mo	267 (138)	294 (130)	0.5	246 (131)	270 (150)	0.6		
Albumin, g/dL	4.13 (0.23)	4.25 (0.25)	<0.001	4.16 (0.22)	4.21 (0.30)	0.08		
CRP, mg/dL	1.05 (1.44)	1.41 (2.16)	0.2	1.16 (2.37)	1.30 (1.94)	0.9		

Values between brackets = (standard deviation) unless otherwise indicated
BP = blood pressure; CPR = C-reactive protein; LAVI = left atrial volume index; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; PDBW = post-dialytic body weight;

<table>
<tr><th>Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td colspan="2">Moissl et al. 2013[14] – Spain (Before-After study with no control group)</td></tr>
<tr><td colspan="2">
Study duration was three months
<table>
<tr><th></th><th colspan="2">All patients (N = 55)</th><th colspan="2">Dehydrated (N = 12)</th><th colspan="2">Normovolemic (N = 26)</th><th colspan="2">Overloaded (N = 17)</th></tr>
<tr><th></th><th>Baseline</th><th>End</th><th>Baseline</th><th>End</th><th>Baseline</th><th>End</th><th>Baseline</th><th>End</th></tr>
<tr><td>TAFO, L</td><td>0.9 (1.6)</td><td>0.6 (1.1)</td><td>-1.1 (0.7)</td><td>-0.5 (0.7)</td><td>0.6 (0.4)</td><td>0.5 (0.8)</td><td>2.8 (1.3)</td><td>1.6 (1.0)</td></tr>
<tr><td>p-value</td><td colspan="2">0.08</td><td colspan="2">0.02</td><td colspan="2">0.59</td><td colspan="2"><0.001</td></tr>
<tr><td>FO predialysis, L</td><td>2.1 (1.6)</td><td>1.8 (1.1)</td><td>0.3 (0.6)</td><td>0.7 (0.6)</td><td>1.7 (0.5)</td><td>1.7 (0.8)</td><td>4.0 (1.3)</td><td>2.7 (1.0)</td></tr>
<tr><td>p-value</td><td colspan="2">0.03</td><td colspan="2">0.13</td><td colspan="2">0.70</td><td colspan="2"><0.001</td></tr>
<tr><td>FO postdialysis, L</td><td>-0.3 (1.8)</td><td>-0.5 (1.2)</td><td>-2.4 (0.9)</td><td>-1.6 (0.9)</td><td>-0.6 (0.7)</td><td>-0.7 (0.9)</td><td>1.5 (1.5)</td><td>0.4 (1.1)</td></tr>
<tr><td>p-value</td><td colspan="2">0.2</td><td colspan="2"><0.001</td><td colspan="2">0.5</td><td colspan="2"><0.001</td></tr>
<tr><td>SF-36 mental health</td><td>64 (23)</td><td>68 (18)</td><td>65 (28)</td><td>66 (20)</td><td>63 (21)</td><td>65 (17)</td><td>64 (24)</td><td>74 (19)</td></tr>
<tr><td>p-value</td><td colspan="2">0.14</td><td colspan="2">0.76</td><td colspan="2">0.75</td><td colspan="2">0.08</td></tr>
<tr><td>BNP, pg/ml</td><td>185</td><td>193</td><td>64</td><td>111</td><td>134</td><td>160</td><td>472</td><td>265</td></tr>
<tr><td>p-value</td><td colspan="2">0.78</td><td colspan="2">0.003</td><td colspan="2">0.97</td><td colspan="2">0.31</td></tr>
<tr><td colspan="9">Predialysis BP, mmHG</td></tr>
<tr><td>Systolic</td><td>137 (26)</td><td>137 (25)</td><td>116 (30)</td><td>127 (34)</td><td>137 (19)</td><td>139 (20)</td><td>150 (23)</td><td>139 (26)</td></tr>
<tr><td>p-value</td><td colspan="2">0.95</td><td colspan="2">0.20</td><td colspan="2">0.56</td><td colspan="2">0.02</td></tr>
<tr><td>Diastolic</td><td>63 (12)</td><td>66 (14)</td><td>54 (11)</td><td>60 (17)</td><td>65 (11)</td><td>69 (13)</td><td>66 (12)</td><td>65 (12)</td></tr>
<tr><td>p-value</td><td colspan="2">0.04</td><td colspan="2">0.12</td><td colspan="2">0.02</td><td colspan="2">0.39</td></tr>
<tr><td colspan="9">Postdialysis BP, mmHG</td></tr>
<tr><td>Systolic</td><td>135 (28)</td><td>137 (26)</td><td>111 (25)</td><td>130 (34)</td><td>136 (23)</td><td>140 (22)</td><td>149 (27)</td><td>138 (27)</td></tr>
<tr><td>p-value</td><td colspan="2">0.37</td><td colspan="2"><0.01</td><td colspan="2">0.32</td><td colspan="2">0.02</td></tr>
<tr><td>Diastolic</td><td>66 (12)</td><td>66 (12)</td><td>56 (10)</td><td>60 (13)</td><td>68 (14)</td><td>70 (12)</td><td>69 (8)</td><td>66 (11)</td></tr>
<tr><td>p-value</td><td colspan="2">0.59</td><td colspan="2">0.21</td><td colspan="2">0.41</td><td colspan="2">0.31</td></tr>
<tr><td>Hemoglobin, g/L</td><td>117 (17)</td><td>115 (15)</td><td>120 (16)</td><td>110 (16)</td><td>119 (15)</td><td>116 (14)</td><td>113 (21)</td><td>118 (17)</td></tr>
<tr><td>p-value</td><td colspan="2">0.35</td><td colspan="2">0.02</td><td colspan="2">0.21</td><td colspan="2">0.51</td></tr>
<tr><td>Albumin, g/L</td><td>37.2 (3.3)</td><td>36.5 (3.4)</td><td>38.2 (3.9)</td><td>37.2 (5.0)</td><td>37.2 (3.1)</td><td>36.0 (2.9)</td><td>36.5 (3.3)</td><td>36.6 (3.0)</td></tr>
<tr><td>p-value</td><td colspan="2">0.06</td><td colspan="2">0.19</td><td colspan="2">0.02</td><td colspan="2">0.89</td></tr>
<tr><td>CRP, mg/dL</td><td>6.9 (1.9)</td><td>6.6 (1.7)</td><td>7.7 (1.8)</td><td>6.8 (1.7)</td><td>6.7 (2.1)</td><td>6.4 (1.9)</td><td>6.6 (1.7)</td><td>6.7 (1.4)</td></tr>
<tr><td>p-value</td><td colspan="2">0.03</td><td colspan="2"><0.01</td><td colspan="2">0.07</td><td colspan="2">0.63</td></tr>
<tr><td>RRF, ml</td><td>500</td><td>500</td><td>500</td><td>750</td><td>500</td><td>500</td><td>600</td><td>300</td></tr>
<tr><td>p-value</td><td colspan="2">0.92</td><td colspan="2">NA</td><td colspan="2">0.80</td><td colspan="2">NA</td></tr>
</table>
Values between brackets = (standard deviation) unless otherwise indicated
BNP = brain natriuretic peptide; BP = Blood pressure; Hb = hemoglobin; FO = fluid overload; RRF = residual renal function; SF-36 = Short-Form Health Survey; TAFO = time-averaged fluid overload
</td><td>

The authors concluded that the use of fluid management guided by bioimpedance spectroscopy was associated with better fluid status and blood pressure.
The article highlighted the differences between the three subgroups analyzed in this study. Dehydrated patients at baseline had higher body mass index, preweight, and adipose tissue mass than the other groups, supporting the hypothesis that dehydration was driven by motivation to lose weight.

</td></tr>
</table>

<table>
<tr><th>Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td colspan="2">Vujicic et al. 2013[15] – Croatia (Before-After study with no control group)</td></tr>
<tr><td>
A total of 65 patients were included in the study
The study duration was 6 months
<table>
<tr><th></th><th>Baseline</th><th>End</th><th>p-value</th></tr>
<tr><td>Weight, kg</td><td>73.8 (17.3)</td><td>72.4 (16.9)</td><td>0.03</td></tr>
<tr><td>Dry weight, kg</td><td>71.5 (16.6)</td><td>70.0 (16.4)</td><td>0.02</td></tr>
<tr><td>Hemoglobin, g/L</td><td>111.8 (9.3)</td><td>113 (5)</td><td>0.38</td></tr>
<tr><td>Overhydration, L</td><td>1.73 (1.75)</td><td>1.12 (1.13)</td><td>0.004</td></tr>
<tr><td colspan="4">Predialysis BP, mmHG</td></tr>
<tr><td>• Systolic</td><td>140 (21)</td><td>130 (17)</td><td><0.0001</td></tr>
<tr><td colspan="4">Predialysis BP, mmHG</td></tr>
<tr><td>• Systolic</td><td>130 (21)</td><td>121 (14)</td><td>0.002</td></tr>
<tr><td colspan="4">Values between brackets = (standard deviation) unless otherwise indicated</td></tr>
</table>
</td><td>• The authors concluded that fluid overload management based on the bioimpedance spectrometer improved fluid status and blood pressure among hemodialysis patients.</td></tr>
<tr><td colspan="2">Onofriescu et al. 2013[13] – Romania (Randomized Controlled Trial)</td></tr>
<tr><td>
<table>
<tr><th></th><th colspan="3">BIS-guided group (N = 71)</th><th colspan="3">Clinical fluid management (N = 64)</th><th>Mean difference (95% CI)</th></tr>
<tr><th></th><th>Baseline</th><th>12 months</th><th>Change P-value</th><th>Baseline</th><th>12 months</th><th>Change P-value</th><th></th></tr>
<tr><td colspan="8">Blood pressure (average of three readings), mmHG</td></tr>
<tr><td>• Systolic</td><td>114.3 (14.5)</td><td>135.4 (17.8)</td><td>SS</td><td>146.6 (16.3)</td><td>142.8 (13)</td><td>NS</td><td>NR</td></tr>
<tr><td>• Diastolic</td><td>79.3 (9.5)</td><td>73.2 (11.1)</td><td>SS</td><td>77.7 (11.5)</td><td>75.3 (9.6)</td><td>NS</td><td>NR</td></tr>
<tr><td>Hemoglobin</td><td colspan="7">Not reported</td></tr>
<tr><td>Total protein</td><td colspan="7">Not reported</td></tr>
<tr><td>Calcium</td><td colspan="7">Not reported</td></tr>
<tr><td>Phosphate</td><td colspan="7">Not reported</td></tr>
<tr><td>Intact parathormone</td><td colspan="7">Not reported</td></tr>
<tr><td>NT-proBNP, pg/ml</td><td>7,552</td><td>4,552</td><td>SS</td><td>5,238</td><td>3,883</td><td>SS</td><td>NR</td></tr>
<tr><td colspan="8">Values between brackets = (standard deviation) unless otherwise indicated
NR = not reported; NS = not statistically significant; SS = statistically significant</td></tr>
</table>
</td><td>The authors concluded that fluid management guided by bioimpedance spectrometer was not inferior or even better than the standard of care.

Reviewer's comment: The reported analysis did not provide any direct comparison between the two methods to support the authors' conclusions. Furthermore, the article specified several outcomes, but it reported the results of two outcomes only; this might be a source of reporting bias.</td></tr>
</table>

<table>
<tr><th>Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td colspan="2">Luo et al. 2010[16] – Germany (Randomized Controlled Trial)</td></tr>
<tr><td colspan="2">
<table>
<tr><th rowspan="2"></th><th colspan="3">BIS-guided group (N = 80)</th><th colspan="3">Clinical fluid management (N = 85)</th><th rowspan="2">Mean difference (95% CI)</th></tr>
<tr><th>Baseline</th><th>12 weeks</th><th>Change P-value</th><th>Baseline</th><th>12 weeks</th><th>Change P-value</th></tr>
<tr><td colspan="8">Blood pressure (average of three readings), mmHG</td></tr>
<tr><td>• Systolic</td><td>137.6 (19.1)</td><td>133.0 (19.5)</td><td>SS</td><td>133.0 (22.4)</td><td>139.1 (22.4)</td><td>SS</td><td>SS</td></tr>
<tr><td>• Diastolic</td><td>80.7 (14.5)</td><td>77.6 (12.0)</td><td>SS</td><td>75.6 (14.7)</td><td>80.9 (14.2)</td><td>SS</td><td>NS</td></tr>
<tr><td>Over hydration, L</td><td>2.30 (1.95)</td><td>1.72 (1.51)</td><td>SS</td><td>2.20 (1.66)</td><td>2.52 (1.83)</td><td>SS</td><td>SS</td></tr>
<tr><td>TFR, L</td><td>1,342.1 (403.7)</td><td>1,385.0 (397.5)</td><td>NS</td><td>1,438.9 (451.9)</td><td>1,607.9 (369.8)</td><td>NS</td><td>NS</td></tr>
<tr><td>TSR, g/day</td><td>2.95 (1.03)</td><td>2.28 (0.95)</td><td>NS</td><td>2.81 (1.47)</td><td>284 (1.14)</td><td>NS</td><td>NS</td></tr>
<tr><td>Total DDD</td><td>2.51 (1.76)</td><td>2.33 (1.76)</td><td>NS</td><td>2.49 (1.42)</td><td>2.94 (1.87)</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="8">Values between brackets = (standard deviation) unless otherwise indicated
DDD = defined daily dose; NS = not statistically significant; SS = statistically significant, TFR = total fluid removal; TSR = total sodium removal;</td></tr>
</table>
</td><td>The authors concluded that information provided by the bio-impedance spectrometer overload facilitated volume management and blood pressure control in peritoneal dialysis patients.</td></tr>
</table>