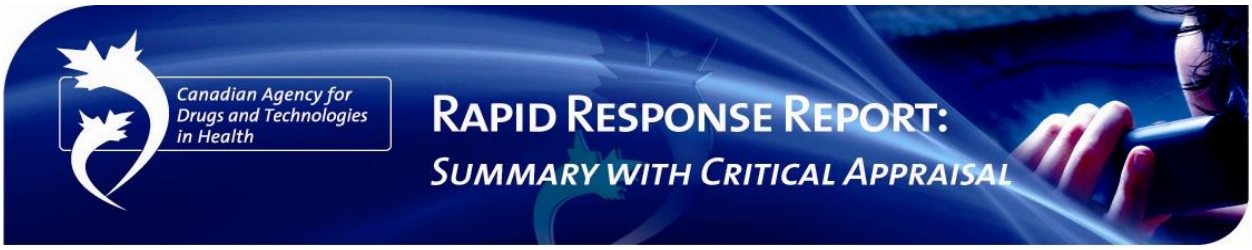

TITLE: Bioimpedance Devices for the Assessment of Body Fluid Volume for Patients Undergoing Dialysis: A Review of the Clinical Effectiveness, Cost-Effectiveness and Guidelines – An Update

DATE: 25 August 2015

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. According to 2013 estimates, the number of Canadians receiving dialysis treatment has more than tripled in 20 years and of the 40,385 patients being treated for kidney failure, 58% were on dialysis.[1]

Management of ESRD patients undergoing dialysis is complicated by the occurrence of hemodynamic instability which may be manifested as volume-related hypotension or as hypertension or fluid overload.[2] These may lead to cardiac stiffness, left ventricular hypertrophy and an increased risk of death.[2,3] Fluid management is an important consideration during dialysis and for this an accurate assessment of the fluid status is necessary. Traditionally assessment was based on clinical examination, however, this may be confounded by vascular stiffness, cardiac dysfunction, hypoalbuminemia, and multimorbidity.[4] Hence, more objective methods were developed. These include blood volume monitoring, natriuretic peptide measurements, extravascular lung water indices, and bioimpedance methods.[2]

Bioimpedance is a non-invasive simple technique for determining fluid accumulation. It uses the electrical properties of body tissues.[5] The technology used in bioimpedance devices is based on the passing of a bioelectrical current through the body and estimating the body fluid volume from the extent of resistance this current endures in the body tissues.[2] Bioimpedance methods can be of various types depending on frequency of current used and site of measurement.[6] The single frequency bioimpedance analysis (BIA) uses current of a single frequency such as 50 kilohertz (kHz).[7] The multi-frequency BIA uses current of multiple frequencies such as 5, 50 and 100 kHz and bioimpedance spectroscopy (BIS) uses a range of frequencies such as 5 kHz to 1,000 kHz to measure extracellular and intracellular resistance.[6] Compared to single frequency BIS, the multifrequency BIS can provide a more precise estimate of total body water and

extracellular water.[8] The site based bioimpedance methods include whole body (wrist to ankle) and segmental (arm, trunk, and leg) measurements including calf BIS.[6] The segmental method uses more electrodes than the whole body method. [8] In dialysis centres, bioimpedance devices for assessment of fluid status in dialysis patients have been used to guide clinical decision making.[9] These methods are thought to be more objective than clinical assessments based on patient examination and calculation of body dry weight. However, it is unclear if there is a difference in patient outcomes achieved, depending on the assessment method used.

The purpose of this report is to review the clinical effectiveness, cost-effectiveness and evidence-based guidelines for use of bioimpedance devices for the assessment of body fluid volume status in patients undergoing hemodialysis or peritoneal dialysis. This current report is an update of a previous CADTH rapid response report[2] on bioimpedance devices for the assessment of body fluid volume for patients undergoing peritoneal dialysis or hemodialysis.

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

There appears to be improvement in some patient outcomes such as decreased blood pressure and reduced fluid overload with patient management guided by bioimpedance spectroscopy assessments. However, patient outcomes using bioimpedance spectroscopy and conventional methods were not always statistically significantly different.

No cost-effectiveness studies or evidence-based guidelines on 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 were identified.

METHODS

Literature Search Strategy

This report makes use of a literature search conducted for a previous CADTH report.[2] The original literature search was conducted in February 2014 using key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2009 and February 12, 2014. For the

current report, database searches were rerun on July 21, 2015 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since February 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with renal disease requiring peritoneal or hemodialysis
Intervention	Bioimpedance devices for the assessment of body fluid volume
Comparator	Clinical assessment of body fluid volume without the device; No comparator
Outcomes	Q1: Clinical effectiveness (e.g., blood pressure, fluid overload, left ventricular mass index, body weight, antihypertensive drug use); Safety Q2: Cost-effectiveness outcomes; Q3: Evidence-based guidelines regarding the use of bioimpedance devices for the assessment of body fluid volume
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), observational studies, economic studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to February 2014. Studies were excluded if they evaluated body fluid status in patients with renal disease who were not receiving hemodialysis or peritoneal dialysis. An additional exclusion criterion was for studies that focused on nutritional status rather than body fluid management.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The Downs and Black checklist[10] was used for RCTs and observational studies.

For the critical appraisal, a numeric score was not calculated. Instead, the strengths and limitations of the study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 129 citations were identified in the literature search. Following screening of titles and abstracts, 108 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 20 publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. These three publications were comprised of two randomized controlled trials (RCTs) and one observational study. No relevant systematic reviews, cost-effectiveness studies or evidence-based guidelines were identified. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references that did not meet the inclusion criteria but may be of potential interest are included in Appendix 2.

Summary of Study Characteristics

Characteristics of the included RCTs and observational study are summarized below and details are provided in Appendix 3.

Randomized controlled trials

Two relevant RCTs[3,11] were identified. Both RCTs involved adults undergoing hemodialysis.

One RCT[3] was published in 2014 from Romania. It compared BIS (with body composition monitor [BCM]) with clinical methods (assessment based on reference clinical criteria such as blood pressure, presence of edema, and cramps) and included a total of 131 patients with 62 in the bioimpedance group and 69 in the clinical methods group. The mean ages of patients were 52 years and 54 years and proportions of males were 54% and 52% in the bioimpedance and clinical groups respectively. The study duration was 2.5 years. Outcomes reported included blood pressure (BP), pulse wave velocity (PWV), relative fluid overload (RFO), death, and adverse events such as hypotensive events and cramps.

One RCT[11] was published in 2014 from Portugal. This RCT[11] compared BIS (with body composition monitor [BCM]) with conventional methods. Both groups appeared to have access to BCM and one group was referred to as BCM-open and the other group as BCM-blind (which was considered as the conventional group). In both groups, the hydration status was measured monthly using BCM, at the mid-week dialysis treatment session, prior to dialysis. These pre-dialysis measurements were available to the treating physician for the BCM-open group but not to the treating physician or nurse for the BCM-blind group. The BCM measurements in the BCM-blind group were recorded by a research nurse. It was unclear if or how the BCM measurements in the BCM-blind group were used. The study included a total of 189 severely over-hydrated patients with 101 in the BCM-open group and 88 in the BCM-blind group (or conventional group). An absolute fluid overload between the 10th and 90th percentile for health individuals i.e. between -1.1 L and 1.1L was defined as normal hydration; and volumes below or above this range was defined as under- and over-hydration, respectively. Fluid overload above 2.5 L was defined as severe over hydration. The mean ages of the patients were 66 years and 67 years and proportions of males were 71% and 82% in the BCM-open and BCM-blind groups,

respectively. The study duration was one year. Outcomes reported included hydration status, BP, hypotensive events, hospitalization, and death.

Observational study

One relevant observational uncontrolled before and after study[12] was identified. It was published in 2014 from Spain. The study included adult patients undergoing hemodialysis for more than two months and in stable condition and without hospital admission in the previous two months The mean age of patients was 59 years and the proportion of males was 64%. The study started with 110 patients and the study duration was 36 months. Bioimpedance spectroscopy was used and bioimpedance was assessed using a BCM. Outcomes reported included weight, body mass index (BMI), serum creatinine, albumin, and C-reactive protein (CRP), lean tissue index (LTI), fat mass index (FTI), body cell mass, extracellular water (ECW), intracellular water (ICW), and total body water (TBW).

Summary of Critical Appraisal

The strength and limitations of the included RCTs and observational study are summarized below and details are provided in Appendix 4.

Randomized controlled trials

Both RCTs clearly stated the objectives, inclusion and exclusion criteria and described patient characteristics, the intervention, and outcomes. The studies were randomized but details of the randomization methods were lacking and it was unclear if allocation was concealed. A sample size calculation based on power was undertaken in one RCT.[3] This study was powered to detect significant differences between the two assessment methods with respect to PWV and RFO. It was, however, underpowered to detect significant difference in the primary outcome i.e., mortality. In both RCTs the number of withdrawals was numerically less in the bioimpedance group compared to the clinical methods group. In one RCT,[3] withdrawals were 6.5% and 15.9% in the BIS and clinical assessment groups respectively and reasons for withdrawal were death, kidney transplant or transfer to another dialysis centre. However, all patients were considered in the analysis. In one RCT, [11] withdrawals were high; it was unclear if all patients were included in the analysis. One RCT[3] reported *P*-values for between group differences in outcomes and one RCT[11] did not. In both RCTs, one or more authors had either received honorarium or were employees of the manufacturer of the bioimpedance device and potential for bias cannot be ruled out. Generalizability was limited as both RCTs had restrictive exclusion criteria such as life expectancy less than one year, patients with implanted defibrillators and pacemakers, patients with metal prosthetic joints and pregnant women. Hence results reported may not be applicable for these patient groups. However, it should be noted that use of BIS is contraindicated in some patient groups such as those with implants and pregnant women.

Observational study

One relevant observational study[12] was identified. It was a before and after study and there was no independent comparator group. In the absence of an independent comparator group it is difficult to judge if BIS offers an advantage over conventional clinical methods. The study clearly stated the objectives, inclusion and exclusion criteria and described patient characteristics, intervention and outcomes. *P*-values for outcomes were reported. The authors mentioned that there was no conflict of interest. Sample size calculations were not mentioned. The number of

patients remaining in the study declined over time. Results presented for each intervention period included only those patients who completed the specific intervention periods, therefore it is unclear to what extent patients who did not complete a specified time period could impact the results. Generalizability is limited as the study inclusion criteria were restrictive and excluded sicker patients such as those with implanted electronic devices or amputations. However, it should be noted that use of BIS is contraindicated in some patient groups such as those with implants and pregnant women.

Summary of Findings

The findings are summarized below and the details are provided in Appendix 5.

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?

Randomized controlled trials

One RCT[3] compared BIS with clinical methods and reported no statistical difference in change in BP from baseline between the two groups (mean difference [MD] = -2.43, *P* = 0.4), and a statistically significant difference from baseline for PWV and RFO between the groups (MD = -2.78, *P* < 0.001 for PWV and MD = -2.99, *P* = 0.05 for RFO). There was a statistically significant decrease in the number of patients requiring antihypertensive drugs in the bioimpedance group and there was no significant change in the number of patients requiring hypertensive drugs in the clinical group. There was no statistically significant between group difference for hypotension and cramps. There was one death (1.6%) in the bioimpedance group and eight (11.6%) in the clinical group.

The other RCT[11] compared BIS with a BCM with conventional methods, defined by study authors as a BCM-blind group. Compared to baseline values, the hydration status was lower at 12 months for both groups and the between group difference was statistically significant with greater decrease in the BCM-open group (mean difference -0.42 L and 95% confidence interval [-0.02 L to -0.86 L]). Compared to baseline values, the pre- and post-dialysis blood pressures were reduced at 12 months for both groups (Appendix 5). The statistical significance of the between group differences were not reported. The number of hypotensive events (47.5% versus 46.6%) and the number of patients hospitalized (39.6% versus 31.8%) were numerically higher in the BCM-open group compared to the BCM-blind group. There were eight deaths (7.9%) in the BCM-open group and 12 deaths (13.6%) in the BCM-blind group.

Observational study

Of the 110 patients included in the study, 68 completed one year, 47 completed two years ,and 39 completed three years of follow-up.[12] In this before and after study, there was a statistically significant decrease in weight, LTI, ICW, TBW, and body cell mass, compared to baseline at the end of each year of the three years of the study).

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?

No relevant cost-effectiveness studies were identified.

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?

No relevant evidence-based guidelines were identified.

Limitations

There appears to be no real gold standard to measure fluid overload to use as a comparator for people receiving dialysis. In addition, the included studies used mostly surrogate measures to evaluate the effectiveness of bioimpedance, and while hard endpoints like hospitalization and death were included, the number of events was small and it is unclear whether bioimpedance measurement impacts hard endpoints in people on dialysis.

Study duration ranged between one and three years, hence beyond this time duration the effectiveness of BIS for the management of patients on dialysis is unclear. Also,the criteria for selecting the study populations were restrictive and sicker patients such as those with implants, major amputation and those with a life expectancy of less than one year, were excluded. Hence, generalizability of the study findings is limited. In addition, only patients receiving hemodialysis were included in the studies, therefore it is unclear whether the results apply to patients receiving peritoneal dialysis. It also must be noted that the use of bioimpedance devices are contraindicated in many instances such as patients with pacemakers, children, and pregnant women.[5]

Not all studies reported the same outcomes hence comparability of findings between the studies was difficult. In addition, all included studies reported findings with the use of a particular bioimpedance technique: BIS. Relevant studies with other types of bioimpedance techniques were not identified. None of the studies were conducted in Canada, hence the applicability of the study findings to the Canadian context is unclear. Lastly, no cost-effectiveness studies or evidence-based guidelines on 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 were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Three relevant studies comprising of two RCTs and one observational study and involving patients undergoing hemodialysis and evaluating BIS were identified. Based on limited evidence there appears to be a suggestion of improvement in some patient parameters such as decreased blood pressure and reduced fluid overload with patient management guided by BIS assessments. However, patient outcomes using BIS and conventional methods were not always statistically significantly different. Also, it is unclear what, if any, impact the reduction in blood pressure and fluid overload would have on hard endpoints like the need for hospitalization or death. Considering there is limited evidence on the impact of fluid management based on assessments with BIS with respect to patient outcomes such as morbidity and mortality, further research in this area would be useful. Findings reported in this update are similar to that of the previous CADTH report.[2] The previous CADTH report included four studies on hemodialysis and one study on peritoneal dialysis. It reported that use of bioimpedance devices in fluid management might be associated with better patient outcomes such as decreased blood pressure, reduced fluid overload, and decreased left ventricular mass index. No evidence on the

use of bioimpedance devices for evaluation of fluid volume in patients undergoing peritoneal dialysis was identified in this update.

No cost-effectiveness studies or evidence-based guidelines on 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 were identified in the previous CADTH report or in this update.

Considering there is limited evidence on the impact of fluid management based on assessments with BIS with respect to patient outcomes such as morbidity and mortality, and no information on cost-effectiveness, further research in this area would be useful.

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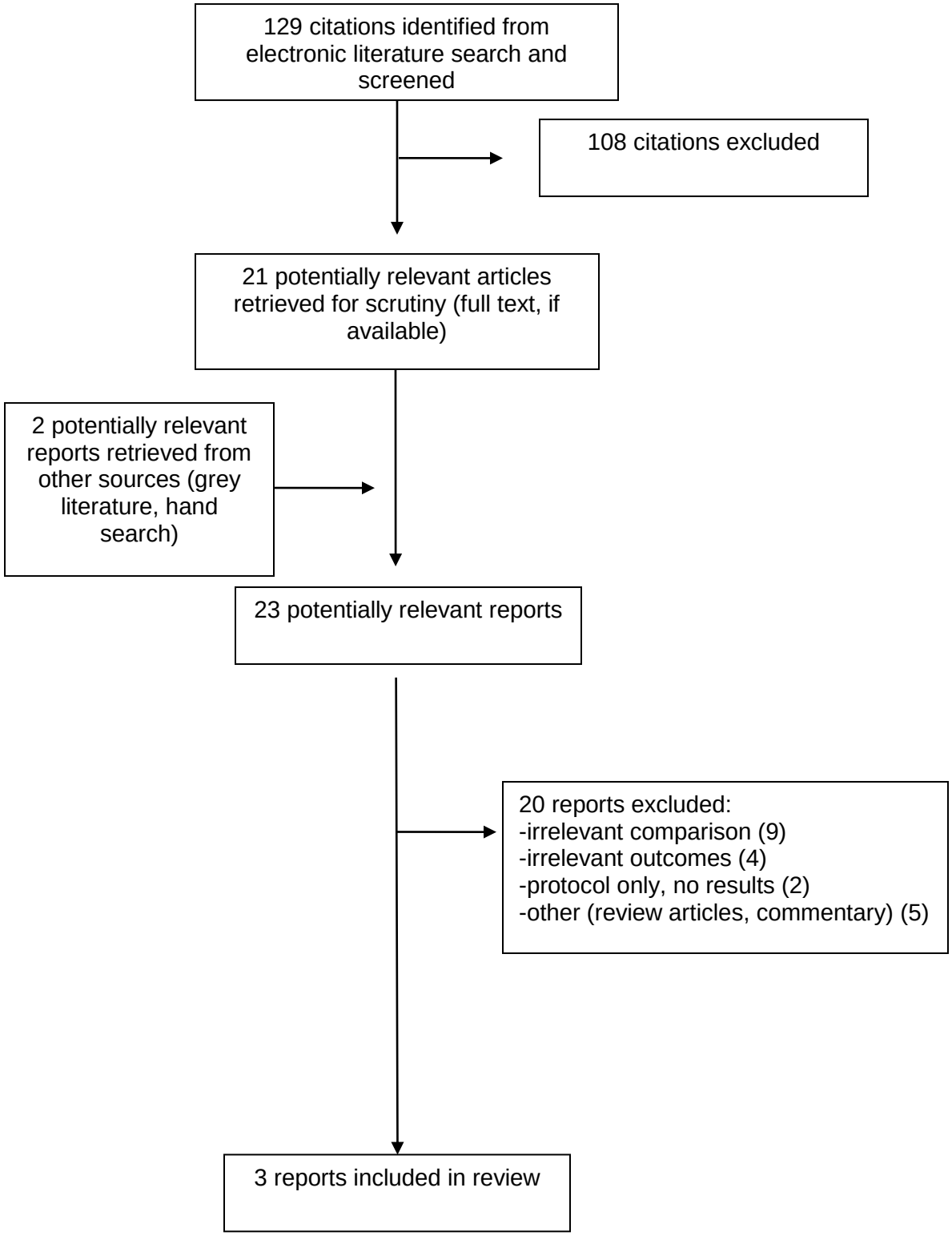
ABBREVIATIONS

AE	adverse event
B	bioimpedance group
BCM	body composition monitor
BIA	bioimpedance analysis
BIS	bioimpedance spectroscopy
BMI	body mass index
BP	blood pressure
C	clinical methods group
CI	confidence interval
CRP	C-reactive protein
DBP	diastolic blood pressure
ECW	extracellular water
ESRD	end stage renal disease
FTI	fat mass index
HD	hemodialysis
HR	hazard ratio
ICW	intracellular water
L	litre
LTI	lean tissue index
m	metre
mg	milligram
mo	month
NR	not reported
PWV	pulse wave velocity
RFO	relative fluid overload
RCT	randomized controlled trial
s	second
SBP	systolic blood pressure
SD	standard deviation
TBW	total body water

APPENDIX 1: Selection of Included Studies



APPENDIX 2: References of potential interest

No results reported/Study protocol

Baek SH, Oh KH, Kim S, Kim DK, Joo KW, Oh YK, et al. Control of fluid balance guided by body composition monitoring in patients on peritoneal dialysis (COMPASS): study protocol for a randomized controlled trial. Trials [Internet]. 2014 [cited 2015 Jul 30];15:432. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4233087

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APPENDIX 3: Characteristics of Included Studies

Study objectives and Design	Inclusion criteria, Sample size, and Patient Characteristics	Intervention, Comparator, and Study conduct	Clinical Outcomes
Randomized controlled trials			
Onofriescu et al.[3] 2014 - Romania			
Objective: To compare strict volume control based on bioimpedance versus clinical methods for guiding ultrafiltration prescription in patients undergoing HD. **Design:** RCT, parallel group, single centre, patients blinded to intervention	**Inclusion criteria**: Patients ≥ 18 years, already on maintenance HD for at least 3 months. **Exclusion criteria**: Patients with limb amputations, metallic joint prosthesis, absence of a permanent vascular access, decompensated cirrhosis, stent or pacemaker, and pregnant women as bioimpedance assessments cannot be accurately performed in such cases. Patients with life expectancy < 1 year. **Sample size**: 131 (62 in B & 69 in C) **Characteristics**: Age (years) 52 in B, 54 in C % Male: 54% in B, 52% in C Duration of dialysis (mo): 107 in B, 104 in C Diabetes: 10% in B, 9% in C Hypertension: 65% in B, 73% in C	**Intervention**: BIS (BCM, Fresenius Medical Care) Bioimpedance recommended dry weight to be achieved ± 1.1 Kg in the next month **Comparator**: Clinical methods. **Duration**: 2.5 years	Primary: Death Secondary: BP, PWV, RFO Other: AE
Ponce, [11] 2014, Portugal			
Objective: To compare the performance using bioimpedance spectroscopy versus conventional	**Inclusion criteria**: Incident and prevalent HD patients ≥ 18 years with a relative predialytic over hydration (OH) at baseline of > 15% (on average > 2.5 litres). Patients had to be	**Intervention**: BIS (with BCM, Fresenius Medical Care) **Comparator**: BIS but blinded so similar to conventional clinical methods.	Hydration status, BP, hypotensive events, hospitalization, death

Study objectives and Design	Inclusion criteria, Sample size, and Patient Characteristics	Intervention, Comparator, and Study conduct	Clinical Outcomes
clinical judgement in assessing the hydration status of HD patients. **Design:** RCT, multicentre study. Patients were randomly divided into B-open-label group and B-blinded group (similar to conventional clinical judgement)	treated by HD three times a week with each session being ≥4 hours. **Exclusion criteria**: Patients with metal prosthetic joints or metal implants such as implanted defibrillators, cardiac pacemakers; patients with major amputation or symptomatic aortic valve stenosis or pregnant women. **Sample size**: 189 (101 [B-open] + 88 [B-blinded]) **Characteristics**: In groups B-open and B-blind respectively Age (years): 65.8 and 66.7 % Male:71.3% and 81.8% Duration of dialysis (mo): NR Diabetes: 38.6% and 39.8% Hypertension:72.3% and 73.9%	**Duration**: 1 year. All patients underwent three times weekly HD treatment of ≥ 4 hours per session.	
Observational study			
DiGioia, [12] 2014, Spain			
Objective: To monitor body composition changes (BCC) in hemodialysis (HD) patients and to relate BCC to mortality. **Design:** Prospective observational study (before and after study)	**Inclusion criteria:** HD patients ≥ 18 years with more than 2 months on HD and in stable condition and without hospital admission in the previous two months. **Exclusion criteria:** Patients with implanted electronic device, metallic prostheses of any type, patients with amputation, pregnant or lactating women	**Intervention:** BIS with BCM **Comparator:** None **Duration:** 3 years Of the 110 patients, 68 completed one year, 47 two year and 39 three year follow-up.	Weight, BMI, creatinine, albumin, CRP, LTI, FTI, body cell mass, ECW, ICW, TBW

Study objectives and Design	Inclusion criteria, Sample size, and Patient Characteristics	Intervention, Comparator, and Study conduct	Clinical Outcomes
	Sample size: 110 **Characteristics:** Age (years): 59 % Male: 64% Duration of dialysis (days): 682 (250 to 1011) Diabetes: 32.7% Hypertension: NR		

AE = adverse event, B = bioimpedance group, B-blind = bioimpedance spectroscopy and blinded, BCM = body composition monitor, BMI = body mass index, B-open = bioimpedance spectroscopy and open-label, BIS = bioimpedance spectroscopy, BP = blood pressure, C = clinical method group, CRP = C-reactive protein, ECW = extracellular water, FTI = fat mass index, HD = hemodialysis, ICW = intracellular water, LTI = lean tissue index, mo = months, NR = not reported, PWV = pulse wave velocity, RFO = relative fluid overload, TBW = total body water

APPENDIX 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Randomized controlled trials		
Onofriescu et al.[3] 2014, Romania	• Objectives were clearly stated • Inclusion/exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described • Randomized parallel group trial. Block randomization technique was used, no further details were provided • No patients were lost to follow-up and all patients were included in the analysis. However, number of patients discontinuing intervention was 4 (6.5%) in the bioimpedance group and 11 (15.9%) in the clinical group. Reasons for discontinuation were death, kidney transplant or transfer to another centre • Sample size calculation based on power was provided • *P*-values were provided but not always • The authors disclosed conflict of interest	• Assessors were not blinded • Generalizability limited as study conducted at a single centre in Romania • One of the authors received speaker honorarium from the manufacturer. The other authors declared they had no relevant financial interest
Ponce, [11] 2014, Portugal	• Objectives were clearly stated • Inclusion/ exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described • Randomized parallel group trial. Details of randomization method not provided • Number of patients prematurely withdrawing from the study was 29 (28.7%) in the open group and 42 (47.7%) in the blind group. Withdrawals were due to no availability of valid data, death, kidney transplant or transfer to another centre	• Sample size calculation was not provided • P-values were not reported, 95% CI were reported in one instance only • In the BCM-blind group (i.e. conventional clinical assessment group), the BCM measurements were recorded by a research nurse and were unavialable to the treating physician or nurse. However, it was unclear how these measurements were used, if at all • Some of the authors were employees of the manufacturer of the device. Authors mentioned that there were no other relevant financial interests • Generalizability limited to centres in Portugal

First Author, Publication Year, Country	Strengths	Limitations
Observational study		
DiGioia, [12] 2014, Spain	• Objectives were clearly stated. • Inclusion/exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described • *P*-values were reported • Number of patients completing a specified treatment period were reported and appeared to decline over time. Reasons for this decline were not stated • The authors mentioned there was no conflict of interest	• Not randomized and no independent comparator group (before and after study) • Sample size calculation was not provided • Results presented for each intervention period considered only those patients who completed the specific intervention periods. Hence it is unclear to what extent patients who did not complete a specified period could impact the results • Generalizability limited to the study population

APPENDIX 5: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Randomized controlled trials</td></tr>
<tr><td>Onofriescu et al.[3]
2014 - Romania</td><td>
Main Findings:
Comparison of outcomes using bioimpedance or conventional clinical methods for assessing HD patients
<table>
<tr><th colspan="2">Outcome</th><th>Bioimpedance</th><th>Clinical method</th><th>Between group mean difference (95% CI), P value</th></tr>
<tr><td rowspan="3">BP (mm Hg)</td><td>Baseline</td><td>145.4 ± 14.5</td><td>144.6 ± 15.2</td><td>-0.76 (-7.66 to 6.13),
P = 0.9</td></tr>
<tr><td>End of intervention</td><td>138.9 ± 14.7</td><td>140.5 ± 11.4</td><td>1.67 (-5.24 to 8.60),
P = 0.9</td></tr>
<tr><td>Change from baseline</td><td>-6.50 (-13.62 to -4.53)
P = 0.04</td><td>-4.00 (-10.83 to 2.63)
P = 0.4</td><td>-2.43 (-7.70 to 2.84)
P = 0.4</td></tr>
<tr><td rowspan="3">PWV (m/s)</td><td>Baseline</td><td>8.22 ± 2.33</td><td>7.63 ± 2.35</td><td>-0.58 (-2.35 to 1.18)
P = 0.9</td></tr>
<tr><td>End of intervention</td><td>6.68 ± 1.89</td><td>8.88 ± 3.23</td><td>2.19 (0.42 to 3.96)
P = 0.005</td></tr>
<tr><td>Change from baseline</td><td>-1.50 (-2.80 to -0.30)
P < 0.001</td><td>1.20 (-0.10 to 2.38)
P = 0.10</td><td>-2.78 (-3.75 to 1.80)
P < 0.001</td></tr>
<tr><td rowspan="3">RFO (%)</td><td>Baseline</td><td>9.52 ± 7.67</td><td>10.30 ± 7.70</td><td>0.78 (-2.38 to 4.36)
P = 0.9</td></tr>
<tr><td>End of intervention</td><td>7.46 ± 5.77</td><td>11.24 ± 7.62</td><td>3.77 (2.20 to 7.35)
P = 0.03</td></tr>
<tr><td>Change from baseline</td><td>-2.05 (-5.70 to -1.10)
P = 0.03</td><td>0.94 (-2.50 to 4.40)
P = 0.9</td><td>-2.99 (-5.00 to -0.89)
P = 0.05</td></tr>
<tr><td>Use of antihypertensive drugs by end of intervention period</td><td>Change from baseline</td><td>Increase in number of patients not requiring drugs from 34 to 45,
P = 0.05</td><td>No significant change in number of patients not requiring drugs</td><td>NR</td></tr>
<tr><td colspan="5">Results expressed as mean ± standard deviation or mean (95% confidence interval)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Comparison of incidences of death and adverse events in the bioimpedance and conventional clinical methods groups
<table>
<tr><td>Event</td><td>Bioimpedance N = 62</td><td>Clinical method N = 69</td><td>P value</td></tr>
<tr><td>Death</td><td>1</td><td>8</td><td></td></tr>
<tr><td>Hypotension, cramps (events/patient/year) (mean [95% CI])</td><td>6 (4.59 to 7.41)</td><td>6.48 (4.59 to 7.41)</td><td>0.6</td></tr>
</table>
Authors' Conclusion:
"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." Page 111
</td></tr>
<tr><td>Ponce, [11] 2014, Portugal</td><td>
Main Findings:
Comparison of hydration status and blood pressure in open and blind groups
<table>
<tr><td colspan="2" rowspan="2">Category</td><td colspan="2">Data (mean ± SD)</td><td rowspan="2">Between group mean difference (95% CI)</td></tr>
<tr><td>B-open</td><td>B-blind</td></tr>
<tr><td rowspan="2">Hydration status (L)</td><td>Baseline</td><td>3.77 ± 1.23</td><td>3.81 ± 1.35</td><td>NR</td></tr>
<tr><td>At 12 month</td><td>2.92 ± 1.47</td><td>3.36 ± 1.75</td><td>-0.42 (-0.02 to -0.86)</td></tr>
<tr><td rowspan="2">Predialysis SBP (mm Hg)</td><td>Baseline</td><td>144.8 ± 24.1</td><td>145.9 ± 26.8</td><td>NR</td></tr>
<tr><td>At 12 month</td><td>134.6 ± 27.3</td><td>136.5 ± 24.7</td><td>NR</td></tr>
<tr><td rowspan="2">Predialysis DBP (mm Hg)</td><td>Baseline</td><td>68.3 ± 14.4</td><td>69.73 ± 16.7</td><td>NR</td></tr>
<tr><td>At 12 month</td><td>65.4 ± 15.8</td><td>64.5 ± 16.2</td><td>NR</td></tr>
<tr><td rowspan="2">Post-dialysis SBP (mm Hg)</td><td>Baseline</td><td>145.0 ± 25.4</td><td>142.5 ± 29.4</td><td>NR</td></tr>
<tr><td>At 12 month</td><td>132.8 ± 28.6</td><td>129.3 ± 24.0</td><td>NR</td></tr>
<tr><td rowspan="2">Post-dialysis DBP (mm Hg)</td><td>Baseline</td><td>65.8 ± 14.4</td><td>66.1 ± 14.2</td><td>NR</td></tr>
<tr><td>At 12 month</td><td>63.4 ± 15.0</td><td>61.4 ± 12.9</td><td>NR</td></tr>
</table>
Comparison of hypotensive events, hospitalization, and death in open and blind groups
<table>
<tr><th colspan="2">Category</th><th>B-open</th><th>B-blind</th></tr>
<tr><td rowspan="2">Hypotensive events</td><td>Baseline</td><td>39 in 17 patients</td><td>28 in 12 patients</td></tr>
<tr><td>12 month</td><td>48 in 20 patients</td><td>41 in 15 patients</td></tr>
<tr><td>Proportion of patients hospitalized</td><td>12 month</td><td>39.6%</td><td>31.8%</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Deaths	12 month	8 Cause: acute myocardial infarction (3), sepsis (1), and unspecified (4)	12 Cause: acute myocardial infarction (1), mesenteric ischemia (1), cardiac arrest (1), cerebral infarction (1), chronic respiratory failure (1), prostate carcinoma (1),pulmonary embolism (1), septicaemia (2), unspecified (3).

Authors' Conclusion:
"Our results confirm a marginal better performance of fluid management when using BCM for assistance to prescribe dry weight. On the other hand, we have to consider that although the BCM recommendation is accurate for the ideal extracellular volume, clinically we may not always be able to reach that fluid status. Cardiovascular impairment and subsequent morbidity caused by end-organs hypoperfusion may occur if we try to decrease volume status as low as recommended, even if rightly so." Page 247

Observational study (before and after study)

DiGioia, [12] Spain

Main Findings:
Results for patients completing 12 months of treatment

Parameter	Data (mean ± SD) for patients (N = 68) who completed 12 months		*P* value
	Baseline	12 months	
Weight (kg)	67.42±13	66.2±13.6	0.011
BMI (kg/m^2)	25.54±4.85	25.07±4.88	0.007
Creatinine (mg/dL)	8.21±2.32	8.35±2.53	0.548
Albumin	3.82 ± 0.34	3.96 ± 0.37	0.002
CRP Log n	1.87 ± 1.23	1.78±1.11	0.463
LTI (kg/m^2)	12.1 ± 2.8	11.62±2.53	0.013
FTI (kg/m^2)	12.70±6.09	12.88±6.09	0.517
Body cell mass (kg)	17.61 ± 5.9	16.18 ±5.47	0.001
TBW (L)	31.75 ± 5.27	30.36±5.10	0.000
ECW (L)	15.2 4±2.42	14.78 ± 2.32	0.003
ICW (L)	16.51±3.34	15.74±3.08	0.000

BMI = body mass index, CRP = C-reactive protein, ECW = extracellular water, FTI = fat mass index, ICW = intracellular water, LTI = lean tissue index, SD = standard deviation, TBW = total body water.

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Results for patients completing 24 months of treatment

Parameter	Data (mean ± SD) for patients (N = 47) who completed 24 months		*P* value
	Baseline	24 months	
Weight (kg)	68.22±12.03	65.98±12.03	0.00
BMI (kg/m^2)	26.01±4.52	25.14±4.29	0.00
Creatinine (mg/dL)	8.40±2.17	8.42±2.46	0.947
Albumin	3.80±0.31	3.79±.0.51	0.843
CRP Log n	2.09±1.18	2.09±1.18	0.674
LTI (kg/m^2)	11.93±2.66	11.93±2.66	0.06
FTI (kg/m^2)	12.97±5.37	12.97±5.37	0.22
BCM (kg)	17.00±5.97	17.00±5.97	0.04
TBW (L)	31.35±5.38	31.35±5.38	0.02
ECW (L)	15.16±2.51	15.16±2.51	0.24
ICW (L)	16.20±3.35	16.20±3.35	0.009

BCM = body cell mass, BMI = body mass index, CRP = C-reactive protein, ECW = extracellular water, FTI = fat mass index, ICW = intracellular water, LTI = lean tissue index,SD = standard deviation, TBW = total body water.

Results for patients completing 36 months of treatment

Parameter	Data (mean ± SD) for patients (N = 39) who completed 36 months		*P* value
	Baseline	36 months	
Weight (kg)	66.62±11.93	64.12±11.83	0.004
BMI (kg/m^2)	25.10±3.39	23.93±3.49	0.014
Creatinine (mg/dL)	9.05±1.53	8.27±2.59	0.061
Albumin	3.76±0.31	3.74±.39	0.691
CRP Log n	1.94±1.09	2.14±1.05	0.408
LTI (kg/m^2)	11.81±2.52	10.86±2.91	0.044
FTI (kg/m^2)	13.15±5.50	12.07±4.5	0.017
BCM (kg)	16.86±5.87	15.06±6.5	0.05
TBW (L)	31.35±5.65	29.75±6.32	0.02
ECW (L)	14.93±2.50	14.98±2.53	0.854
ICW (L)	16.10±3.97	15.05±3.97	0.021

BCM = body cell mass, BMI = body mass index, CRP = C-reactive protein, ECW = extracellular water, FTI = fat mass index, ICW = intracellular water, LTI = lean tissue index, SD = standard deviation, TBW = total body water.

Authors' Conclusion:

"Lean mass loss was the most important change during follow-up; we have not observed association between BCC with mortality. PA was the main mortality predictor." P. 1

(BCC = body composition changes)

B-blinded = bioimpedance spectroscopy and blinded, BMI = body mass index, BP = blood pressure, B-open = bioimpedance spectroscopy and open-label, CRP = C-reactive protein, DBP = diastolic blood pressure, ECW = extracellular water, FTI = fat mass index, ICW = intracellular water, LTI = lean tissue index, PWV = pulse wave velocity, RFO = relative fluid overload, SD = standard deviation, SBP = systolic blood pressure, TBW = total body water