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Fluid Management in Haemodialysis

Studies on current practices and new methods

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Abstract
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Chronic fluid overload has been identified as an independent predictor of mortality in haemodialysis patients, and 30% remain fluid overloaded at dry weight. The use of bioimpedance spectroscopy (BIS) in fluid management may improve blood pressure control and cardiovascular status. However, the importance of regular and careful clinical assessment of fluid balance is repeatedly emphasised.

This thesis is based on five papers and the overall aim was to investigate current practices and new methods for fluid management in haemodialysis, and to develop a management tool for dry weight determination, based on multiple complementary methods. The purpose was to contribute to reduced prevalence of fluid overload and intradialytic symptoms in haemodialysis patients, by providing the healthcare team and the patient with a tool, that facilitates communication and enables informed decision-making in dry weight determination.

In the initial, cross-sectional study, clinical praxis for dry weight assessment in Sweden and Denmark was investigated. A wide variation in routines was found. Despite high access, BIS was sparsely used. Instead, nurses' authorisation to adjust haemodialysis patients' dry weight was associated with improved fluid status. The second study had a qualitative approach. Focus group interviews, with healthcare professionals, were carried out to achieve a deeper understanding of the factors preventing or facilitating the use of BIS. In the third study, the usefulness of a biomarker, brain natriuretic peptide (BNP), for assessing fluid status in haemodialysis patients, was investigated. An association between BNP and fluid overload was established. The between-individual variation in BNP levels was greater than the within-individual variation over time. Therefore, if BNP is to be used as a marker for fluid overload, repeated measurements are required. In the fourth study, we developed and validated a multifactorial decision aid, Recova®, that incorporates BIS in dry weight determination. Recova® is based on physiological parameters routinely measured in haemodialysis and provides guidance on when and how to respond to recognised fluid alterations. In the fifth study, the decision aid's effect on volume status was tested in a cohort of haemodialysis patients. Implementation of Recova® had effect on fluid status symptoms, BIS-measured hydration status and NT-proBNP levels.

Keywords: Haemodialysis, Fluid management, Fluid overload, Bioimpedance spectroscopy, Dry weight, Brain natriuretic peptide, Decision aid

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God, give me Grace to accept with serenity
the things that cannot be changed,
Courage to change the things
which should be changed,
and the Wisdom to distinguish
the one from the other.

Reinhold Niebuhr

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Stenberg J, Lindberg M, Furuland H. Clinical praxis for assessment of dry weight in Sweden and Denmark: A mixed-methods study. *Hemodial Int* 2016; 20: 111–119.

II Stenberg J, Henriksson C, Lindberg M, et al. Perspectives on clinical use of bioimpedance in hemodialysis: focus group interviews with renal care professionals. *BMC Nephrol* 2018; 19: 121.

III Stenberg J, Melin J, Lindberg M, et al. Brain natriuretic peptide reflects individual variation in hydration status in hemodialysis patients. *Hemodial Int* 2019; 23: 402–413.

IV Stenberg J, Keane D, Lindberg M, et al. Systematic Fluid Assessment in Haemodialysis: Development and Validation of a Decision Aid. *J Ren Care* 2020; 46: 52–61.

V Stenberg, J, Lindberg, M, & Furuland, H. Implementation of a decision aid for Recognition and Correction of Volume Alterations (Recova®) in haemodialysis. *Manuscript.*

Contents

Abbreviations

BP	Blood pressure
BIS	Bioimpedance spectroscopy
BNP	Brain natriuretic peptide
BVM	Blood volume monitoring
CKD	Chronic kidney disease
DW	Dry weight
ECW	Extra cellular water volume
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HD	Haemodialysis
HRV	Heart rate variability
ICC	Intraclass correlation coefficient
ICW	Intracellular water volume
IDH	Intradialytic hypotension
IDWG	Interdialytic weight gain
IRR	Inter-rater reliability
NT-proBNP	N-terminal pro brain natriuretic peptide
OH	Overhydration
RBV	Relative blood volume
RECOVA	Recognition and correction of volume alterations
RRF	Residual renal function
RRT	Renal replacement therapy
UFR	Ultrafiltration rate

Introduction

The prevalence of chronic kidney disease (CKD) was estimated at 9.1% in the world population in 2017. It resulted in 1.2 million deaths worldwide and was ranked as the 12th leading cause of death.[1] Dialysis and transplantation were established as treatments of CKD in the 1960s and have been developed and refined since. Renal replacement therapy (RRT) is lifesaving. Its purpose is to replace the vital functions of the failing kidneys, and it has two primary goals: to restore sodium and water homeostasis and to remove uremic toxins.[2,3] From having been reserved for a limited number of individuals, treatment can now be offered to all patients who are thought to benefit from it. The largest expansion took place in the 1990s, but the number of patients is still increasing. In 2010, 2.6 million people worldwide received RRT. However, a large number of people may have died prematurely because RRT could not be accessed. Worldwide use of RRT is projected to more than double to 5.4 million people by 2030, with the largest growth in Asia.[4,5] In Sweden, 10,025 people received RRT at the end of 2018. The transplanted made up the majority, 5,951 persons, 59% of the entire treatment group. There were 3,245 people treated with chronic haemodialysis, including 130 with home haemodialysis and 3,115 with maintenance haemodialysis. The number of peritoneal dialysis patients was 829.[6]

In the beginning of the 1990s, the yearly mortality in individuals with end-stage renal disease (ESRD) was almost 30%. Thanks to more efficient haemodialysers, more technically advanced haemodialysis machines, and wider use of ultrapure dialysis fluid, the efficiency and biocompatibility of RRT have improved over the past decades.[4,7] However, despite considerable technological advances, mortality among maintenance dialysis patients remains high, with a 20% yearly rate.[6]

To determine the adequacy of dialysis, clearance of uremic toxins is routinely assessed by measuring the clearance of a surrogate, urea.[8] However, the relevance of this measure of dialysis adequacy has been questioned. When high-efficiency dialysers with large surface area membranes are used, achieving a threshold of urea clearance is not difficult. It has been suggested that approaching normalisation of extracellular fluid volume should instead be a primary goal of dialysis care.[3,9] However, there is still no objective measure of adequacy of fluid control. This thesis focuses on the consequences of altered fluid status and management of fluid volume control via the assessment of dry weight.

Fluid status in healthy subjects

Total body water is made up of one-third extracellular water volume (ECW) and two-thirds intracellular water volume (ICW).[10] The cell membrane is highly permeable and water moves freely between ICW and ECW. Thus, an equal osmolality is maintained in all fluid compartments of the body. Osmoregulation involves thirst and antidiuresis. A decreased water intake increases osmolality, stimulating thirst and antidiuresis. However, this has no significant effect on ECW.[11]

The ECW is distributed between the intravascular and interstitial spaces. Overhydration (OH) is an excess fluid volume, above the ECW, found under physiological circumstances in healthy subjects. ECW expansion manifests itself in a variably increased intravascular volume. Hydrostatic and oncotic pressure, operating at the capillary level and in the interstitium, are key determinants of the filling status of the intravascular compartment. The complex interaction between blood volume and ECW depends predominantly on the oncotic pressures, and salt and fluid intake. However, the degree of intravascular volume increase is usually less than the rise in ECW.[12]

Fluid status in individuals with chronic kidney disease

Chronic kidney disease is defined as kidney damage or a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for a period longer than 3 months.[13] Based on the GFR level, renal failure is divided into five stages. In CKD stage five, GFR is < 15 ml/min/1.73 m^2. There are several causes of kidney diseases, but most CKDs are progressive and can lead to renal failure and development of uraemia. When GFR is < 10 mL/min/1.73 m^2, dialysis treatment may be initiated to replace the vital functions of the failing kidneys, one of which is regulation of body fluid.

During a dialysis session, excessive fluid is removed by ultrafiltration.[14] Maintenance haemodialysis is usually performed three times a week, with each session lasting between three and five hours.[6] Consequently, fluid status of anuric patients on intermittent haemodialysis therapy varies across the week. Body weight increases between dialysis sessions, when ingested fluids accumulate, and decreases during dialysis treatment, due to ultrafiltration,[15] Figure 1. Extreme interdialytic weight gain (IDWG) of > 5.0% in body weight is associated with adverse outcomes and mortality. However, it has been emphasised that chronic fluid overload is more strongly associated than IDWG with mortality risk.[15,16] Prevention of chronic fluid overload has been promoted as a primary goal of haemodialysis.[3] Still, evidence strongly suggests that avoiding both fluid overload and fluid depletion is highly important for improving the prognosis of haemodialysis patients.[17]

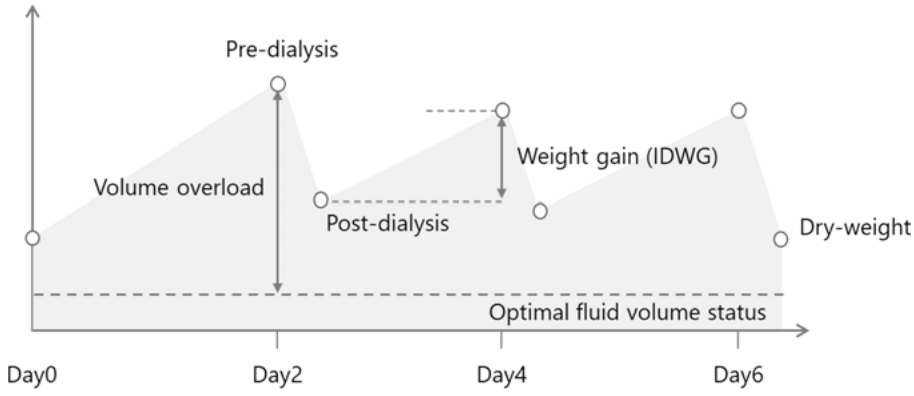

Figure 1. Variation in fluid status across the week in anuric patients on intermittent haemodialysis. The prescribed dry weight may not always correspond to optimal fluid status (from reference 26, used with the permission of John Wiley and Sons).

Clinical consequences of fluid depletion

The entire ultrafiltration volume removed during a haemodialysis session comes from the intravascular space; an ultrafiltration volume of several litres represents a substantial portion of the total blood volume. If the removal rate of ultrafiltration volume (UFR) exceeds the intravascular refill rate, the intravascular volume will drop, which could lead to decreased cardiac filling, reduced cardiac output, and intradialytic hypotension (IDH). IDH is associated with ischemic events, cardiac damage, loss of white matter in the brain, loss of residual renal function (RRF), and vascular access thrombosis.[2,7,18,19] A high frequency of IDH events carries a substantial death risk, and a rapid reduction in intravascular volume might result in IDH, even if ECW is normal or increased.[20] UFR > 10 ml/h/kg body weight is associated with increased mortality. In an individual with a body weight of 70 kg and a 4-hour dialysis treatment, this translates to a ultrafiltration volume of 2.8 L.[21–25] If the amplitude of IDWG is higher, adding extra dialysis sessions or extending dialysis treatment time may facilitate achievement of adequate fluid status.[3,26] However, it has been reported patients are generally averse to treatment time extension > 15 minutes.[27]

Clinical consequences of fluid overload

Chronic fluid overload, sometimes referred to as overhydration (OH), hypervolemia, or volume overload, has been identified as an independent predictor of mortality in chronic haemodialysis patients.[28–33] Among all haemodialysis patients, 25–45% have been found to be overhydrated.[18,32,34–37] Chronic fluid

overload is associated with left ventricular hypertrophy, left ventricular dilatation, arterial hypertension, and – over time – with the development of congestive heart failure. Fluid overload causes hypertension in dialysis patients via both increased cardiac output and increased systemic vascular resistance.[31,32,37] However, fluid overload can also partly explain the paradoxical relationship between low systolic blood pressure and outcome. In haemodialysis patients, a U-shaped association between systolic blood pressure and mortality has been reported.[37,38] Systolic blood pressure below 110 mmHg predialysis is associated with increased mortality when combined with either fluid overload or fluid depletion pre-dialysis. The highest all-cause mortality risk has been found in patients presenting with high fluid overload but low pre-dialytic blood pressure. The second highest mortality risk has been found in patients with both high blood pressure and fluid overload pre-dialysis.[39] High blood pressure pre-dialysis, but normal fluid status, is related to moderate mortality risk.[32,39] Already mild levels of fluid overload (1.1–2.5 L) are associated with increased mortality,[40] whereas post-dialysis fluid depletion appears to be protective.[37,40,41]

Fluid overload is related to mortality independently from cardiac damage, hypertension, and other risk factors, but is usually present in combination with malnutrition and/or inflammation.[34] The largest risk for mortality has been observed when all three risk factors are present, as compared with patients with fluid overload as the single risk factor.[37] Fluid overload and inflammation can be mutually reinforcing. Inflammation could contribute to fluid overload through hypoalbuminemia, capillary leakage, and a decline in lean and/or fat tissue mass, resulting in incorrect estimation of dry weight. Conversely, fluid overload could lead to inflammation caused by the translocation of endotoxins through a congested bowel wall or by a proinflammatory effect of tissue sodium.[42]

The association of fluid overload and malnutrition with outcome may also be reflected in the observation that the patients with the highest level of fluid overload and the lowest level of IDWG have the highest mortality risk. This may seem counterintuitive, but whereas a high IDWG may be causally related to mortality, a spontaneous decline in IDWG may reflect malnutrition.[30,34] It has been observed that hypertensive fluid overload patients often have low IDWG and when excessive fluid volumes are removed, their IDWG increases.[43] Thus, relatively large interdialytic weight gains in patients who are dehydrated at the end of dialysis are less of a risk signal than relatively small interdialytic weight gains in patients who are chronically fluid overloaded.[39]

Fluid management and haemodynamic management in haemodialysis

Optimal fluid volume and haemodynamic management in haemodialysis patients is considered an essential component of dialysis adequacy.[3,9] Management of fluid and sodium imbalance in dialysis patients consists of adjusting salt and fluid removal by dialysis and restricting salt intake and fluid gain between dialysis sessions.[7,9] High IDWG is associated with high UFR, which is associated with increased morbidity and mortality. Therefore, in order to prevent thirst, patients with consistently high IDWG should be advised to practice salt restriction.[3,16,44,45]

Sodium loading during dialysis should be avoided. In a large observational study initiative (the Dialysis Outcome and Practice Pattern Study, DOPPS), sodium modelling/profiling was associated with increased all-cause mortality. Therefore, prescription or routine use of sodium modelling/profiling in dialysis, to limit or prevent IDH, has been questioned.[46] Nor does lowering of dialysate sodium (< 138 mmol/L) have any proven effect on hard clinical endpoints such as cardiovascular or all-cause mortality.[47] Instead, the individual serum sodium level prior to haemodialysis treatment has been shown to be relatively constant,[48] and a personalised approach, through dialysate to serum sodium alignment, which is associated with reduced IDWG, is recommended.[16,39,45,49]

In haemodialysis, a dialysate temperature of 37 °C is widely used. However, the body temperature usually increases during standard dialysis, and it has been suggested that removal of heat with a cool dialysate might be beneficial to haemodynamic stability.[50] The use of cool dialysate, at 34–35.5 °C, has been shown to significantly reduce the rate of IDH, without affecting dialysis adequacy negatively. Although the intervention is quite simple to implement without any additional cost, cool dialysis is not frequently used.[50,51] One explanation may be its association with increase in discomfort symptoms of unclear severity.[52]

Definition of the dry weight concept

In order to manage fluid overload, the typical haemodialysis prescription includes a so-called dry weight. Prior to every dialysis session, the patient's body weight is measured, and the dry weight is used to calculate the IDWG, which is supposed to reflect the volume of ECW expansion. This volume is then translated into an ultrafiltration goal.[15]

The dry weight concept has evolved over time (Table 1). However, there is still no consensus on how the dry weight should be clinically defined. Earlier definitions of dry weight promoted aggressive volume removal strategies, causing a risk of cardiovascular stress and IDH.[53–55] Although these clinical

approaches have been associated with benefits on cardiovascular outcome, they are challenged by recent studies showing that intensity or aggressiveness of fluid removal during dialysis might induce excessive haemodynamic stress and organ damage, with potentially deleterious consequences in the long term. In later definitions, dry weight is assumed to coincide with normalisation of ECW,[56] and the importance of gradual change in post-dialytic weight and close monitoring of patient-reported symptoms of both hypovolemia and hypervolemia in achievement of dry weight are emphasised.[57] It has been argued that this approach may promote avoidance of the scenario where large and aggressive changes in post-dialysis weight provoke symptoms that lead both the caregiver and the patient to decide that further reductions in post-dialysis weight will be unsuccessful, which for some patients can be a lifelong conviction.[44,58]

Table 1. *Evolution of the dry weight definition over time.*

Author	Year	Definition of dry weight
Thomson et al.[55]	1967	The body weight at which blood pressure is reduced to hypotensive levels, associated with no obvious causes other than ultrafiltration.
Henderson[54]	1980	The weight obtained at the conclusion of a regular dialysis treatment, below which the patient more often than not will become symptomatic and go into shock.
Charra[53]	1996	The body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis despite the retention of saltwater (saline).
Sinha and Agarwall[57]	2009	The lowest tolerated post-dialysis weight achieved via gradual change in post-dialysis weight at which there are minimal signs or symptoms of either hypovolemia or hypervolemia.
van der Sande et al.[59]	2020	The body weight at which the patient is normotensive and has no clinical signs of fluid overload. In the presence of significant RRF, accept some degree of (BIS-defined) fluid overload.

BIS: bioimpedance spectroscopy; RRF: residual renal function.

Substantial differences may be observed between clinical judgment of symptoms and information obtained using additional technologies. Therefore, it has been suggested that some degree of hypervolemia should be allowed, instead of aiming for an "absolute" dry weight, as a slight ECW excess could prevent organ hypoperfusion and IDH, and contribute to preserved RRF.[19] Terms such as "functional dry weight", "estimated dry weight", or "target weight" have been suggested to replace the term dry weight. The purpose is to remind the caregiver that the prescribed dry weight is not an immutable physical constant like the patient's height, but rather the lowest achievable dry weight at any

given time.[44,59,60] In this thesis, we have chosen to use the term dry weight, as this is the term most commonly used at Swedish haemodialysis units.

Clinical assessment of fluid status

In everyday practice, dry weight is most commonly assessed using clinical methods, based on case history and physical examination.[11,61,62] Clinical signs of fluid overload, like peripheral oedema[63] and lung crackles,[64] are unfortunately not sensitive indicators. Therefore, using blood pressure as the assay variable is common practice when probing for dry weight. It is then assumed that blood pressure and ECW have a direct association in haemodialysis patients. However, as mentioned earlier, blood pressure has been shown to be an unreliable marker of fluid overload, and fluid removal in patients who are hypertensive with normal or reduced blood volume may induce or aggravate hypovolemia, resulting in IDH and cardiovascular complications.[65] Haemodialysis patients can be hypertensive without signs of fluid overload or normotensive (systolic blood pressure < 140 mmHg) despite fluid overload.[41,61,66] Patients with decompensated heart failure may even be hypotensive despite fluid overload.[65,66] Thus, IDH should not be confused with achieving or being below dry weight in all patients. In some patients, IDH is rather a consequence of excessive UFR, as large IDWGs require higher UFRs to achieve target weight within fixed dialysis treatment times.[23,67] Both inaccurately prescribed dry weight and failure to achieve prescribed dry weight can lead to volume overload.[60]

Because clinical assessment of volume status in dialysis patients is considered subjective and imprecise, utilisation of diagnostic tools aimed at complementing the current standard of care is suggested. These may include intradialytic blood volume monitoring (BVM), ultrasound of the lung and inferior vena cava, natriuretic peptide measurement, and bioimpedance spectroscopy (BIS).[21,68,69]

Blood volume monitoring

Blood volume monitoring measures intravascular volume changes, depending on ultrafiltration and plasma refilling rates. Despite the fact that most studies using BVM devices report positive feedback on blood pressure control and haemodynamic stability,[70] their clinical benefit is still a matter of controversy.[71] In a randomised controlled clinical trial (the CLIMB Study) of blood volume monitors, comparing BVM-guided treatment versus standard of care, BVM use was associated with higher nonvascular and vascular access-related hospitalisations and mortality.[12,67,72]

Since the degree of intravascular volume increase is usually less than the ECW rise, relative BV monitoring may be an unreliable indicator of ECW status and dry weight.[12] It has been shown that specific UFR, but not fluid overload, is associated with BV change in dialysis. This calls into question the assumptions that a rapid fall in relative BV (RBV) suggests fluid depletion and that the absence of an appreciable decrease indicates fluid overload. The link between refilling and fluid overload may not be as straightforward as previously assumed. BVM predicts the tolerance to dialysis treatment, but its use in dry weight determination is questioned.[71]

Ultrasound

Ultrasound measurement of inferior vena cava diameter and the derived collapsibility index have been shown to predict volume status, but they can only be used to assess intravascular volume, not real tissue hydration. In addition to significant inter-operator variability, the presence of diastolic dysfunction or right-sided cardiac failure is a major limitation.[73]

Lung ultrasonography through the assessment of extravascular lung water is receiving growing attention in clinical research. It has been suggested that BIS is probably sufficient for fluid assessment in the vast majority of patients with ESRD, but lung ultrasonography could be used in addition to BIS for dialysis patients with significantly compromised cardiac function.[74]

Cardiac biomarkers

Brain natriuretic peptide or B-type natriuretic peptide (BNP) is a polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells. It is secreted attached to N-terminal fragment in the prohormone called NT-proBNP, which is biologically inactive. NT-proBNP has a half-life of two hours, while BNP has a half-life of 18 minutes. The physiologic actions of BNP include decrease in systemic vascular resistance and central venous pressure, as well as increase in natriuresis. In patients with normal diuresis, the net effect of these peptides would be a decrease in blood pressure due to the decrease in systemic vascular resistance and, thus, after-load. Both BNP and NT-proBNP can be used for screening and prognosis of heart failure, and are also typically increased in patients with left ventricular dysfunction, with or without symptoms.[75]

Because BNP is secreted from the heart in response to volume overload, it has been suggested as a marker of fluid overload in haemodialysis. The vast majority of patients with ESRD, including those without a prior diagnosis of cardiac failure, have markedly elevated levels of BNP,[76,77] and in incident hae-

modialysis patients, it has been related to both fluid overload and cardiac status.[78–84] BNP is associated with mortality, and in haemodialysis patients significantly higher mortality has been shown with high BNP and high OH, but this association does not remain in patients with high BNP and low OH.[83,85] However, BNP is difficult to interpret in the dialysis context. A patient's degree of heart failure, fluid overload, and dialysis treatment modalities can all affect the levels of BNP,[77] as can the occurrence of adverse events, since IDH during dialysis can cause secretion of BNP.[86] Because a number of factors, beyond fluid status, affect BNP (and NT-proBNP), some argue that BNP is not a marker of fluid overload in haemodialysis.[87]

The between-person variation of NT-proBNP has been found to be large and markedly greater than the within-person variation, indicating that NT-proBNP testing might be applied better in this population using a relative change strategy.[88] Serial NT-proBNP levels need to double or halve for confident exclusion of changes due to analytic and biologic variation alone.[77] BNP levels in dialysis patients differ from those in non-dialysis subjects less than NT-proBNP levels, and have also been found to be less affected by dialysis treatment modalities.[86]

Bioimpedance spectroscopy

Bioimpedance spectroscopy (BIS) is a non-invasive method for measuring ECW and total body water. It passes a low-strength alternating current through the body. Because low frequency currents cannot pass the cell membrane, alternating currents of low frequency travel preferentially in the ECW, whereas alternating currents of high frequency traverse both ECW and ICW compartments.[89]

The body composition monitor (BCM®; Fresenius Medical Care, Bad Homburg, Germany) is a whole-body BIS device that has been validated against gold standard methods of volume assessment (bromide and deuterium dilution in a wide range of healthy subjects and patients ranging in age from 2 to 95 years old) and intradialytic weight loss in haemodialysis patients.[90] The BCM measures the resistance and reactance (or the capacitance resistance of the cell membrane) and determines whole-body impedance at 50 frequencies (5–1,000 kHz) via electrodes placed on the wrist and ankle. Measurement can be performed bedside.[15,36,91] When volume overload is determined using BCM, it is calculated in litres, based on a three-compartment physiologic tissue model which differentiates between normohydrated lean tissue mass, adipose tissue mass, and a virtual OH compartment.[91] This model assumes a fixed hydration of lean tissue mass and adipose tissue mass, leading to the calculation of a "normohydration weight". The OH compartment is calculated as the difference between the measured ECW and the ECW which is expected with a working kidney.[90] The 10^{th} to 90^{th} percentile (-1.1 and +1.1 L) of the normal

population is considered to represent a normovolemic state. In the literature, fluid overload is defined as being over > 1.1 L or over > 2.5 L (or a OH:ECW ratio above 7% or 15%, respectively), whereas fluid depletion is usually defined as an OH level below -1.1 L.[92]

BIS devices have been used to guide dry weight assessment in randomised controlled trials, showing regression of left ventricular mass index, decrease in blood pressure, improved arterial stiffness, and reductions in IDH and antihypertensive pill burden.[93–95] The technique provides an objective measurement of hydration and has gained popularity for assessing body composition due to its simplicity and low cost. However, evidence on its impact on survival is still lacking.[69,70,96,97]

There is a lack of guidelines on the clinical implications of BIS, and it is important to keep in mind that the calculation of fluid volumes with BIS depends on various assumptions. The haemodialysis population is a heterogeneous and often fragile group of patients, and as with any technical tool, there is a need for caution when interpreting and applying the results. So far, there is a low number of randomised controlled trials addressing the effect of a BIS-guided fluid strategy compared with conventional fluid management in haemodialysis.[93,94] It should be noted that patients in the existing studies were relatively young, with a mean age of 51 and 52 years, respectively. Body composition changes due to aging and sarcopenia.[26,34] Hence, the results may not be transferrable to an elderly population with extensive comorbidity and systemic inflammation. It cannot be excluded that rapid and overzealous ultrafiltration may put a patient at risk for hypotension and organ ischemia, especially when the refill of plasma volume from the interstitial compartments is hampered by hypoalbuminemia. Attaining euvolemia through BIS-guided strategies may not be feasible or desirable under such circumstances.[42,98] In some subjects, it has been observed that normalisation of fluid status might lead to an undesirable decrease in RRF.[93]

Clinical decision aid

A multidisciplinary approach,[99] dialysis facility practices[46], and frequency of dry weight adjustments[17,46,100] have been shown to have positive implications for fluid status in haemodialysis patients.

In the care of acutely ill patients, it has been recognised that clinical response could be substantially improved by the routine embedding of simple early warning systems, such as the new early warning system (NEWS). NEWS is based on two key requirements: (i) a systematic method to measure and record simple physiological parameters in all patients, to allow early recognition of those presenting with acute illness or who are deteriorating, (ii) a clear definition of the appropriate urgency and scale of the clinical response required, tailored to the level of acute-illness severity.[101]

Theoretical framework

The theoretical framework for this thesis is the implementation model of Grol and Wensing, which proposes that an implementation process may be initiated when new scientific information that indicates patient care can be provided more effectively or efficiently becomes available.[102] In current practice, dry weight estimation predominantly relies on history and physical examination, but accuracy is limited, and 30% of haemodialysis patients remain fluid overloaded at dry weight.[59] Technologies like BIS can be used as aids in dry weight estimation in haemodialysis, but adoption has been limited. It has been suggested that further outcomes and practice-based research to define the utility of BIS and to inform its incorporation into clinical practice is needed, in order to identify the best way to use it in prevention of dialysis-related complications.[17,56,97]

Table 2. *The Grol and Wensing implementation of change model and its application in this thesis.*

Steps of implementation model		**Applications**
1	Development of proposal for change	Overall aim
2	Analysis of actual performance, targets for change	Studies I and III
3	Problem analysis of target group setting	Study II
4	Development and selection of strategies and measures to change practice	Study IV
5	Development and testing and execution of implementation plan	Study V
6	Integration of changes in routine care	Remaining step
7	(Continuous) evaluation and (when necessary) adapting of the plan	Remaining step

The Grol and Wensing implementation model consists of seven steps. As illustrated in Table 2, the overall objective of this thesis covers the first step of the model, involving determination of targets for improvement.[102] The second step of the model explores current practice and analysis of targets for change. This was carried out in Study I and Study III. The third step addresses barriers to and facilitators for the target group and setting. This was considered in Study II, and to a certain extent in Study I. Step four covers development and selection of strategies and measures to change practice, as carried out in Study III and Study IV. Step five of the model concerns development and testing of implementation strategy, which was performed in Study V. What remains, in order to receive sustainable change of practice,[102] are steps six and seven of

the model: integration of changes in routine care and, lastly, evaluation and adapting of the plan.

Planned and systematic interventions, tailored to prospectively identified barriers, are probably more likely to improve professional practice than no intervention or dissemination of guidelines.[103] However, "planned and systematic" does not mean that there is an absolute plan, permitting no deviations. On the contrary, an incremental process is optimal; here, lessons are learned from previous steps and the approach is adapted continuously and when necessary.[102]

Aims

The general aim of the thesis was to investigate current practices and new methods for fluid management in haemodialysis, and to develop a management tool for determination of dry weight, based on multiple complementary methods for assessment of volume status. The purpose is to contribute to reduced prevalence of fluid overload and intradialytic symptoms in haemodialysis patients, by providing the team – the patient, the dialysis nurse, and the nephrologist – with a tool that facilitates communication and enables informed decision-making in dry weight determination.

Specific research objectives of the studies included in the thesis were:

I To investigate clinical practice and local guidelines for dry weight assessment at Swedish and Danish haemodialysis units, and to examine if differences in routines and utilisation of BIS and other assistive technologies have effects on frequency of dry weight adjustments and blood pressure levels.

II To identify renal care professionals' perceived barriers to and facilitators for use of BIS in clinical practice.

III To compare the variation of correlation between BNP and OH within subjects with variation of correlation between subjects in repeated measurements, in haemodialysis patients with elevated BNP.

IV To develop and validate a decision aid combining clinical assessment of fluid status with information from BIS in dry weight determination.

V To evaluate if implementation of Recova®, a tool for recognition and correction of volume alterations, in clinical practice facilitates assessment and improves fluid status in haemodialysis patients.

Material and Methods

Design

The thesis consists of five studies (I–V). In **Study I,** actual performance and targets for change were identified, and a mixed- methods design was used to provide a more complete understanding of the research problem. Qualitative (open- ended) data embedded within cross- sectional quantitative (closed-ended) data were collected in parallel, analysed separately with relevant analysis methods, and finally integrated in a convergent interpretation. In **Study II,** problem analysis of the target group setting was performed. The study had a qualitative explorative design and data were collected through focus group interviews with healthcare professionals. In **Study III,** the correlation between biomarkers, OH, and inflammation was investigated in an additional attempt to identify targets for change. The study had a prospective, observational, single-centre design, and consisted of a cross-sectional part and a longitudinal follow-up. In **Study IV,** a tool for fluid assessment combining systematised clinical assessment with BIS was developed inductively, based on literature review and empirical experience. Development of the tool was followed by a validation process considering item relevance, comprehensiveness, and inter- rater agreement. **Study V** was a prospective implementation intervention, evaluating the effects of the tool developed and validated in Study IV. The impact of the intervention was measured as proportion of study participants at an adequate dry weight at the end of the study, assessed as change in symptoms, hydration status, and NT-proBNP levels. The process of the intervention was measured as frequency of fluid status assessments and change in frequencies of bioimpedance measurements and dry weight adjustments, compared with six months prior to the implementation.

An overview, of the studies' design, study samples and data sources, is presented in Table 3.

Table 3. *Overview of study design, sample and data sources applied in the studies.*

Study	Design	Sample	Data collection
I	Cross-sectional, mixed methods: Descriptive statistics and qualitative content analysis	48 Swedish and Danish HD units Treatment-related data from 99 stratified HD patients at 33 units	Questionnaires, collection of local guidelines, medical records
II	Explorative with a qualitative approach	24 renal care professionals (nurses, dieticians and nephrologists) from 11 HD units	Four focus group interviews. Telemedicine equipment was used to connect the participants to each other and the moderator
III	Prospective, observational, with a cross-sectional part and a longitudinal follow-up.	Part I: 64 HD patients Part II: 11 HD patients with elevated BNP levels	Part I: Blood samples for bedside analysis of BNP and BIS measurement Part II: Echocardiography, HRV, and serial measurements of BNP and BIS
IV	Inductive development and inter-rater reliability analysis	Part I: Interprofessional core development group and multi-professional group of stakeholders Part II: 19 British and Swedish HD nurses	Literature review and empirical experience identifying physiological parameters for fluid status assessment Questionnaires
V	Prospective implementation intervention	49 HD patients from two cohorts	Baseline and end-of-study BIS-measurement, symptom assessment, and NT-proBNP

BIS: bioimpedance spectroscopy; BNP: brain natriuretic peptide; HD: haemodialysis; HRV: heart rate variability; NT-proBNP: N-terminal pro-BNP.

Ethical considerations

All included studies complied with the Declaration of Helsinki, and informed consent was obtained from all study participants. For Studies I and III, ethical approval was obtained from the Regional Ethical Review Board in Uppsala, Sweden (Reg. No. 2014/089 and Reg. No. 2017/006). Study I was also approved by the Danish Data Protection Agency (Reg. No. 2014-41-3063). The Regional Ethical Review Board in Uppsala favourably reviewed the research plan of Study II (Reg. No. 2015/266) and ethical approval to conduct Studies IV and V was obtained from the Swedish Ethical Review Authority (Dnr: 2019-00011).

Subjects and procedures

Study I

In the first study, an online questionnaire was sent to the first- line managers at 68 Swedish and 24 Danish dialysis units. The managers were asked to answer open-ended questions from a questionnaire and to provide their written local guidelines. In addition, 33 units provided treatment- related data from a total of 99 patients. In order to reflect the haemodialysis population, the patient selection was two men for each woman, all with diverse dialytic ages.[6]

Study II

The second study was based on focus group interviews with healthcare professionals who were recruited from a purposive selection of 13 haemodialysis units of different sizes, located in four Swedish regions. All units had access to a BIS device, but had previously reported differing levels of use: frequent (n = 6), occasional (n = 3), or rare (n = 4).[104] Due to unavailability of participants for the interview dates, two units dropped out. Twenty-five individuals volunteered and gave informed consent to participate; one nephrologist was later prevented from attending. A semi-structured questioning route was developed.[105–107] In order to evaluate the questioning route and the technical facilities, two pilot interviews were conducted.

Subsequently, four sessions were conducted, each with four to nine participants. For contrast,[105,108] each focus group included participants from two to four different hospitals. The respondents gathered in conference rooms at their local hospitals and were connected to the other focus group participants and the moderator through equipment for telemedicine. They were informed that the moderator has a medical background, but no experience with haemodialysis care. Audio recording was used, and visual recording was also used in three sessions. Each session lasted approximately 30 min, and the records were transcribed verbatim immediately afterwards.

Study III

In the first part of the third study, 64 haemodialysis patients were enrolled. Criteria for inclusion were dialysis ≥ 3 months, age ≥ 18 years, and ability to give informed consent. Patients with a single pooled pacemaker implant were excluded.

Blood samples were drawn mid-week, pre-dialysis, for analysis of BNP. At the same occasion, blood pressure and body composition were measured, the latter with BIS.

For the second part of the study, 11 individuals with BNP levels above 500 pg/mL[78,109] were enrolled for follow-up. Because dialysis treatment modalities may affect BNP, they were all transferred to treatment with highly permeable membranes – high-flux dialysers – and individuals on dialysis treatment deviating from thrice weekly were not included.[86,110–112]

The included participants had their cardiac function examined using both echocardiography and heart rate variability (HRV). Then, BNP, body composition, and blood pressure were assessed at nine additional visits – at three consecutive sessions during three separate study weeks, with 1–3 weeks between each study week, Table 4.

Table 4. *Study design of the second phase of Study III.*

Timeline	Periods	Number of assessments	
	Baseline	1	(mid-week haemodialysis session)
	26 (23–31) weeks	0	
	Study-week I	3	(consecutive haemodialysis sessions)
	1–3 weeks	0	
	Study-week II	3	(consecutive haemodialysis sessions)
	1–3 weeks	0	
	Study-week III	3	(consecutive haemodialysis sessions)

BNP was assessed bedside; this enabled the use of BNP, rather than NT-proBNP, as a marker of fluid overload. BNP may be difficult to assess due to its short half-life, but its levels in dialysis patients have been reported to differ less than NT-proBNP levels when compared with levels in non-dialysis subjects; they are also less affected by dialysis treatment modalities.[86,113–115]

Hydration status was measured through BIS using the body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany).[36,91,91] In order to clinically assess fluid status, a quantitative score of volume status was used.[116,117] Blood pressure and heart rate were measured with the blood pressure monitor integrated in a Fresenius 5008 haemodialysis machine (Fresenius Medical Care, Bad Homburg, Germany). Information about medical history, treatment modalities, additional biomarkers, and nutritional status was collected from medical records. For analysis of inflammatory markers, blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes and plasma-separated within 5 hours of collection. Plasma was stored at -70 °C until assayed. Also, C-reactive protein (CRP) was used as a marker of inflammation. HRV was measured once between two dialysis sessions with 24–48 h Holter electrocardiography, using a SEER light recorder (GE Medical Systems, Freiburg, Germany).

Study IV

In Study IV, a fluid management decision aid was developed. The decision aid, like the NEWS,[101] aims to standardise the process of recording, scoring, and responding to changes in routinely measured physiological parameters. In addition, it incorporates BIS in fluid management.

A core development group made up of nurses and physicians used empirical experience and a literature review to identify physiological parameters for assessment of fluid status, routinely measured in haemodialysis, and patient-related conditions affecting BIS. Then, in order to evaluate the content and comprehensiveness of the decision aid, the draft tool was circulated for review in a larger group of stakeholders, including clinical scientists, dieticians, physiotherapists, physicians, and patient representatives.

Subsequently, for reliability test of the decision aid, 19 nurses were recruited from three haemodialysis units in Sweden and four haemodialysis units in the United Kingdom. The nurses were instructed to score the symptoms of four fictional patient cases, and to suggest clinical response by choosing one of four options in the decision aid algorithm. All nurses assessed the same four cases individually and responded via a multiple-choice questionnaire.

Study V

In the fifth study, 49 haemodialysis patients from two dialysis units belonging to one renal department were enrolled. Criteria for inclusion were haemodialysis treatment ≥ 3 months, age ≥ 18 years, and ability to give informed consent. The exclusion criterion was RRF preventing the need for ultrafiltration.

The Recova® tool, which is presented in the Study IV results section, was presented to the haemodialysis units' nurses in workshop sessions. The nurses were instructed to use Recova® to systematically assess the study participants' fluid status and score their symptoms of fluid overload/depletion every 14 days. They were also instructed to respond to the Recova® thresholds values as appropriate, and to perform BIS measurements if necessary and alert the responsible nurse or clinician, as recommended in the tool. If appropriate, they were encouraged to initiate dry weight adjustments. Dry weight determination is the responsibility of the nephrologist, but nurses at most Swedish haemodialysis units are authorised to initiate dry weight adjustments of 0.5 to 1 L.[104] In the first cohort, the intervention ran for four months, May–August 2019. In the second cohort, the intervention ran for three months, September–November 2019.

At baseline and at the end of the study, each participating haemodialysis patient's fluid status was assessed with BIS, before a mid-week dialysis session, and blood samples were drawn for analysis of NT-proBNP. Additional laboratory results, dialysis prescriptions, and retrospective data on frequencies

of bioimpedance measurements and dry weight adjustments, were retrieved from medical records. The Recova® symptom scoring system was used for clinical assessment of fluid status.

Analysis

Study I

For correlation analysis between frequency of dry weight adjustments and blood pressure, Spearman's rank correlation for non-parametric variables was used. The phi coefficient for dichotomous variables was used to examine relationship strength in authorisation of nurses to adjust dry weight, presence of local guidelines, and use of BIS.

In order to investigate differences between units using BIS and/or authorising nurses to adjust dry weight or not, an independent samples t-test was used, and analyses were verified using the Mann-Whitney U test for nonparametric analysis. Blood pressure and ultrafiltration were defined as the mean value of measurements at three predefined occasions during 2013, and values were reported as mean and standard deviation or median and interquartile range (25^{th} to 75^{th} percentile), as appropriate. The level of significance was set to $p < 0.05$, and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using version 21.0 of IBM SPSS Statistics for Macintosh (IBM Corp, Armonk, NY, USA).

To analyse written local guidelines and answers to open-ended questions from the questionnaire, qualitative content analysis was performed. Paragraphs containing aspects related to each other through their content and context (meaning units) were sorted into two content areas: (I) routines of dry weight assessment and (II) utilisation of BIS. The meaning units were then condensed into descriptions close to the manifest contents of the text and labelled with codes. Lastly, the codes were compared for differences and similarities and sorted into categories.

Study II

In Study II, a qualitative thematic content analysis process[105,118,119] was performed continuously, in consecutive steps:

Unit of analysis

After each interview, the records were transcribed verbatim. The transcripts were read through several times, while keeping the aim of the study in mind, to obtain a sense of the whole.

Meaning units

Meaning units relating to the aim of the study were highlighted, and all interview data were divided into individual quotations.

Content areas

Quotations relating to the aim of the study were sorted into theoretical domains, used when developing the questioning route.[107]

Codes

Within each theoretical domain, discrete concepts were identified to allow comparisons for similarities and differences of the meaning units. An initial coding scheme was developed to enable connections between concepts.

Categories

After reflection on the identified discrete concepts, and a review of the literature, a multilevel approach for examining barriers to and facilitators for change was found to be applicable to the ideas and categories that arose from the data.[120] The final step of the analysis process involved systematically relating core categories to other categories, to extract barriers and facilitators that could influence use of BIS at multiple levels.

Accuracy of analysis and process of reflection

After the first author of the paper had performed the initial analysis, the co-authors independently reviewed the interview transcripts to identify key words, phrases, and concepts used by the participants. To ensure consistency in the definitions and interpretation, the model codes were compared and contrasted with the codes emerging from the data. A process of reflection and discussion resulted in agreement on how to sort the codes. Finally, in order to ensure trustworthiness of this qualitative inquiry, the credibility, transferability, dependability, and confirmability of the findings were considered.

Study III

To report baseline participants' characteristics, in Study III, descriptive statistics were presented as means with standard deviations, medians with interquartile ranges (IQRs), or frequencies (%), as appropriate. Because BNP values were positively skewed, they were log-transformed to allow for further statistical analysis. To compare differences between two independent groups, the independent samples t-test, the Mann-Whitney U-test, or the chi-squared test was used, as appropriate, depending on the measurement level of the dependent variable. Wilcoxon's signed ranks test was used for analysis of differences between dependent groups.

For analysis of correlations between BNP, OH, and inflammation, Pearson's product or Spearman's rho was used, as appropriate. Then, in order to correct for confounding variables, multiple linear regression analysis was used employing a backward step multivariate analysis, excluding variables that were not significant and did not improve the fit of the model. In analysis of the longitudinal data, the relation between relative OH and log-BNP was analysed with a mixed model, using relative OH as a fixed effect (same slope) and individuals as random effect (different intercepts). Statistical significance was inferred at $p \leq 0.05$. R version 3.3.2 was used for analysis of longitudinal data. For all other statistical analyses, version 25.0 of IBM SPSS Statistics for Macintosh (IBM, Armonk, NY, USA) was used.

Study IV

The draft tool, including measures for fluid alterations and patient-related conditions affecting BIS, was shared with a multi-professional group for review. Empirical consensus was reached through a series of face-to-face meetings, the use of an online questionnaire, telephone conferences, and e-mail communications.

To assess the degree that coders provided consistency in their ratings of symptom score across subjects, nurses' agreement was measured with an inter-rater reliability (IRR) analysis, using a two-way random, consistency, average-measures intraclass correlation coefficient (ICC). For assessment of the nurses' agreement in choice of clinical response, Fleiss' kappa analysis of multiple raters of discrete variables was used. The study participants were asked to rate their perceived confidence in using BIS in fluid management, on a 6-point (0–5) Likert scale, and data from confident raters (rating 5) and less confident raters (rating 0–4) were analysed as separate groups.

For categorisation of agreement, Landis' and Koch's definitions were used: poor (< 0), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.60–0.80), or almost perfect (0.81–1.00).[121] The IBM SPSS Statistics for Macintosh version 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

Study V

The clinically assessed fluid status of each participant in Study V, was categorised as either fluid overload or fluid depletion, depending on whether subtraction of the depletion score from the overload score resulted in a positive or negative number.

In order to measure the urgency of need for dry weight correction, the total symptom score was added up. According to Recova®, if the total sum is 0, no further action is required, but evaluation of dry weight should be performed every second week. If the score is 1–4, dry weight should be questioned, if it

is 5–6, dry weight should be adjusted, and if it is 7 or more, there is an immediate need for evaluation of hydration status and dry weight adjustment.

The study participant's OH post was estimated by subtracting planned ultrafiltration volume from OH, as measured by bioimpedance pre dialysis. Depending on whether the participants' estimated OH post was > 0 L or ≤ 0 L, hydration status was defined as either positive or negative OH.

Based on the predominant symptoms and the hydration status, four fluid status groups were defined: A, symptoms of fluid overload but negative OH; B, symptoms of fluid overload and positive OH; C, symptoms of fluid depletion or absence of symptoms but positive OH; D, symptoms of fluid depletion or absence of symptoms and negative OH. The estimated urgency of need for correction of dry weight and the categorisation of study participants was blinded to the staff of the clinics. An overview of the fluid status groups, the suggested clinical response, and a plausible post-dialysis OH to aim for, as defined by Recova®, is presented in Table 5.

Table 5. *Fluid status groups based on symptoms and bioimpedance-measurement, suggested clinical response, and overhydration target, as defined by Recova®*

	A	B	C	D
Clinically assessed fluid status	Overload	Overload	Depletion	Depletion
OH post (BIS-measured)	≤ 0	> 0	> 0	≤ 0
Suggested clinical response	Decrease DW 0.5–1 kg/week	Decrease DW 0.5–1 kg/week	First treat malnutr. and infl.	Increase DW 0.5–1 kg/week
Plausible OH post target (L)	-2–0	±1	0–2	±1

BIS: bioimpedance spectroscopy; DW: dry weight OH: overhydration.

Due to the low sample size, all data were considered non-parametric. Descriptive data were presented as median and inter-quartile range or as percentage/frequency, as appropriate. Differences at baseline between the four groups were tested for significance with Kruskal-Wallis H for independent groups of non-parametric variables. Within each group, differences between baseline and end-of-study assessments were tested for significance with Wilcoxon's non-parametric test for dependent groups. Correlations between measures of hydration status and intervention-driven response were analysed with Spearman's rank correlation or chi-squared tests, as appropriate. Statistical significance was inferred at $p \leq 0.05$. Statistical analyses were performed using GNU PSPP version 1.2.0, software for statistical analysis (Free Software Foundation, Inc., Boston, MA, USA).

Results

Study I

In Study I the total response rate was 52% (n = 48) of haemodialysis units in Sweden and Denmark. The responding units represented 21 of 26 counties/regions, treating 67% (n = 2,826) of the total haemodialysis populations of the two nations.

Written local guidelines addressing dry weight assessment existed at 54% of the responding units and a device for BIS measurement was available at 52% of the units. Other methods reported for dry weight assessment were chest x-ray (90%), BVM (83%), ultrasound of vena cava (17%), serum N-terminal pro-BNP (15%), cardiothoracic index (one unit), and central venous pressure (one unit).

One prominent difference in routines was that the haemodialysis nurses (henceforth referred to as nurses) were authorised to change dry weight at 60% of the units, but only 48% of the reporting units had this routine regulated in written local guidelines. The authorisation of nurses to change dry weight was associated with frequency of dry weight adjustments ($r = 0.243$; $p = 0.016$) and negatively correlated with systolic blood pressure pre-dialysis ($r = -0.221$; $p = 0.031$). No other significant correlations were found.

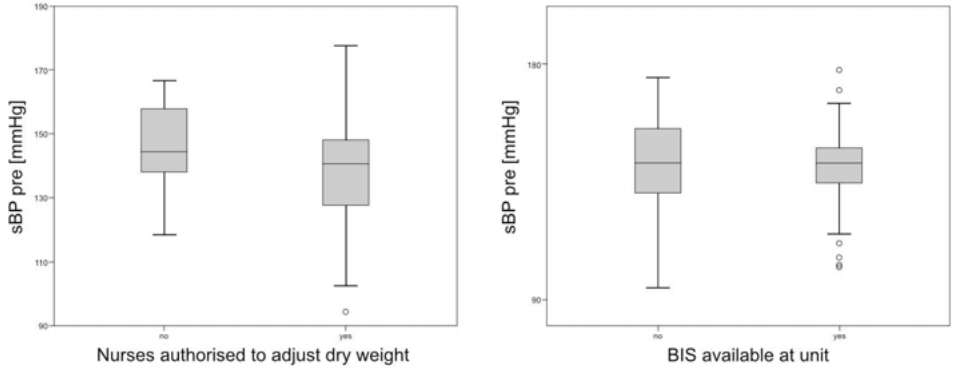

Figure 2. Differences in systolic blood pressure (sBP) between units, by nurses' authorisation to adjust dry weight, and by access to bioimpedance spectroscopy device (BIS).

Where the nurses were authorised to change dry weight, dry weights were adjusted more often (8.1 ± 6.9 versus 5.1 ± 4.5 times/year), and systolic blood pressure pre-dialysis was significantly lower (138 ± 20 mmHg versus 146 ± 12 mmHg). The availability of BIS was not associated with frequency of dry weight adjustments or blood pressure levels, regardless of frequency of use, Figure 2. Nurses were more likely to be authorised to change dry weight at county clinics than at university clinics (66% vs. 44%, p=0.044), but there were no other relevant demographic differences between units.

In the qualitative analysis of open-ended data, two categories related to routines of dry weight assessment, and five categories related to utilisation of BIS emerged, see Table 6.

Table 6. *Content areas and categories identified in qualitative analysis of open-ended data.*

Content areas	**Categories**
Routines of dry weight assessment	Approach to the concept of dry weight
	Authorisation of nurses to adjust dry weight
Utilisation of bioimpedance spectroscopy	Frequency of use
	Initiative
	Indications
	Barriers to utilisation
	Implementation

Routines of dry weight assessment

Approach to the concept of dry weight

Dry weight was evaluated monthly or at up to three-month intervals. Some units had a flexible approach to dry weight; nurses were able to adjust the goal for ultrafiltration from treatment to treatment. One unit aimed for a positive hydration status of 1.0–1.5 L, to retain RRF. Approaches to prevent intra- and/or interdialytic adverse events were, for example, aiming for OH post-dialysis of 0.5–1.0 L in anuric patients or restricting the UFR.

Authorisation of haemodialysis nurses to adjust dry weight

The nurses had a duty to question the plausibility of dry weight. However, whereas some units gave nurses the authority to increase or decrease dry weight by 0.5–1.0 kg, others considered adjustment of dry weight to be solely the nephrologist's responsibility, with nurses only able to propose adjustments.

The main reason for the decision to adjust dry weight falling on nurses was absence of a nephrologist. The nurses would adjust dry weight with the consent of the patient when he/she was identified as being fluid depleted or fluid overloaded, or if the nurse found it impossible or implausible to reach current

dry weight. The nurses would base their judgment on experience, technical aids, such as BVM and blood pressure measurement, and clinical assessment.

Some units regulated the nurses' authorisation via written local guidelines or individual delegation, whereas others advised the nurses to discuss adjustments of dry weight with their colleagues. At some units, the nephrologist was supposed to be alerted immediately to approve nurse-initiated adjustment of dry weight, while at others, the nephrologist was supposed to be alerted before the next treatment or before any further changes of dry weight. At a few units, the adjusted dry weight was evaluated at the next round or "when there was opportunity".

Utilisation of bioimpedance spectroscopy

Frequency of use

Among the units with access to BIS, there were three levels of utilisation: *regular use*, that is every 2–3 months, every month, or more often, either in all patients, or in all incident patients (eleven units), *occasional use* (eight units), and *rare use* (six units).

Initiative

At some units, nurses initiated the use of BIS, whereas other units used it only at a nephrologist's request. At a couple of units, the dieticians were the main initiators of BIS measurements.

Indications

Examples of indications for BIS were for adjustment of dry weight, for assessment of fluid status in patients who could not be weighed on scales, for helping patients lose weight before transplantation, in clinical trials, and in CKD patients not on dialysis.

Barriers to utilisation

The most common reason for not using BIS was a lack of routines. Some units only had the device on loan, and the requirement of a nephrologist's approval for each patient's BIS may also have had an impact. A couple of units reported their physician's questioning of the credibility of the technique as a barrier to use. At some units, the device was mainly used for peritoneal dialysis patients.

Implementation

Most units lacking a routine for use of BIS had an ongoing discussion on what would be best practice. These units aimed for regular use on all prevalent patients or incident patients. The need for serial measurements was mentioned.

Study II

In Study II, barriers to and facilitators for use of BIS in haemodialysis were identified at five levels, see Table 7. Some factors appeared as both barriers and facilitators.

Table 7. *Barriers to and facilitators for use of bioimpedance.*

Levels of determinants	Barriers	Facilitators
Innovation	Credibility	Attractiveness Advantages in practice
Individual professional	Awareness Knowledge Motivation	Motivation
Patient input	Knowledge Preferences	Motivation
Social context	Team process	Team process Inter-professional collaboration
Organisational context	Capacities Care process Structures Regulations	Capacities

Innovation

Barriers

Lack of credibility was considered a barrier to using BIS in assessment of both fluid status and nutritional status. Despite initial enthusiasm about BIS, several users expressed declining confidence in the method. If a result was not supported by clinical assessment or other methods for assessment of fluid status, it would be rejected. This approach was by some individuals considered a strength, reflecting a critical mindset, but other participants saw a risk of arbitrariness. BIS readings from patients who were malnourished, amputees, non-Caucasians, children, body builders, or had chromosomal abnormalities or implants were considered particularly hard to assess.

Facilitators

Facilitators related to the innovation itself were feelings of curiosity and excitement, and perceived advantages in practice. The use of BIS put dry weight determination on the agenda and provided new insights. BIS had been particularly helpful in identifying fluid overload in cases of young, tall patients with severe hypertension but no visible signs of overhydration. Participants also described satisfaction at being able to bring relief to patients by eliminating

symptoms of underhydration through gradually increasing dry weight by several kilograms with support from BIS.

Software for visual imaging of changes in body composition over time in a graph was considered a helpful educational tool in interactions with patients. Some units had a pragmatic approach to using BIS in assessment of nutritional status, as they felt no other objective methods were available.

Individual professional

Barriers

At an individual professional level, lack of awareness, knowledge, and motivation were identified as barriers to use. At several units, BIS had not been introduced systematically or strategically, and the continual education was insufficient, lacking, or dependent on the interest or commitment of certain individuals. Study participants reported differing perceptions of the limitations and restrictions to use.

All professional groups repeatedly emphasised the importance of experience of fluid status assessment, and not to rely solely on BIS. However, some participants reported a lack of pre-existing knowledge about fluid balance, especially when the fluid balance was affected by malnutrition, inflammation, and age. Consequently, some nurses and dieticians expressed limited self-efficacy and feared that incorrect performance due to lack of skill and experience would contribute to misjudgement of fluid status.

Facilitators

Motivation was identified as a facilitator. Study participants were motivated to develop strategies for use of BIS, not the least to assess nutritional status objectively, which was considered impossible otherwise. Nurses saw BIS as particularly helpful for less experienced colleagues.

Patients' input

Barriers

Participants' preferences and lack of knowledge were factors identified as barriers to use. However, it seemed that only a minority of patients were reluctant to have their dry weight determined using BIS, usually because the measurement was not in line with their own preconception. A few respondents reported the patients needing to rest in a supine position for 15 minutes before measurement as a barrier, because patients were unwilling to postpone start of dialysis treatment.

Facilitators

Patients' own motivation to use BIS facilitated its implementation. This applied particularly in limited care settings, where study participants reported that use of BIS could contribute to patients' empowerment.

Social context

Barriers

Team processes could be a barrier to use, and some nurses expressed frustration because physicians did not trust or follow up results. Use of BIS thus felt meaningless.

Facilitators

Team processes, along with inter-professional collaboration, could also be a facilitator for use. Dieticians were acknowledged to have pre-existing knowledge about body composition thanks to their training, and physicians perceived dieticians' contributions in interpreting BIS as highly valuable. Also, physicians appreciated when nurses had performed measurements before discussing dry weight with them.

Organisational context

Barriers

At an organisational level, capacity, care process, structures, and regulations were identified as barriers to use of BIS. There were large variations in routines regarding when to use BIS, how to interpret the readings, and how to follow up the results. Some units had guidelines for utilisation, but due to high workloads and a shortage of trained staff, BIS measurement was not a priority. Also, having to wait for the device if someone else was using it could interrupt workflow. Regulations regarding isolation of patients with multi-drug resistant infections could prevent the use of BIS.

Facilitators

Capacity was also identified as a facilitator, as small units reported higher capacity for organisational change.

Study III

In the 64 haemodialysis patients enrolled in Study III, the median (IQR) BNP value was 365 (178–833) pg/ml. Participants were divided into two groups based on having BNP levels above or below 500 pg/ml, and the groups were analysed for differences.

Twenty-four participants (37.5%) had BNP levels above 500 pg/ml, Md 1,060 (815–2,300) pg/ml. According to BIS, this group had OH = 2.5 (1.8–4.6) L before dialysis, and normohydration weight differed significantly from prescribed dry weight. This group reported more symptoms of fluid overload than participants with low levels of BNP. They also had fewer episodes of symptomatic IDH, but this difference did not reach statistical significance. Ultrafiltration volumes, UFR, and blood pressures did not differ between the groups.

In the 40 participants (62.5%) with BNP levels below 500 pg/ml, the Md value was 208 (117–344) pg/ml, and OH = 1.9 (1.0–2.5) L. Compared with the other group, these participants were younger, had higher body weight, more muscle strength, higher plasma levels of haemoglobin and albumin, and lower plasma levels of CRP. Fifty percent had diabetes type 2. This group had longer dialysis treatment times and 100% were treated with high-flux dialysers (compared with 73.9% in the other group).

Log-BNP correlated positively with relative OH ($Rs = 0.380$, $p < 0.01$), age, CRP, and symptoms of fluid overload, but negatively with handgrip strength, haemoglobin, and albumin. In a multiple linear backward regression analysis, OH, albumin, and age remained significantly associated with log-BNP.

In the second phase of the study, 11 participants were assessed for another nine dialysis sessions each. None of the eleven participants in the longitudinal follow-up had a normal echocardiography, and their cardiac autonomic function was markedly decreased. In analyses of the relationship between relative OH and log-BNP, using a mixed-methods model with the same slope and different intercepts, every percentage point increase of relative OH predicted an increase in log-BNP by five percent. Between-individual variation was larger than within-individual variation, and although the confidence intervals in both BNP and relative OH were wide, the significant correlation between log-BNP and relative OH remained when studied at an individual level in repeated measurements.

Study IV

A decision aid was developed and named Recova® – **Re**cognition and **Co**rrection of **Vo**lume **A**lterations. It consisted of three parts:

1. A symptom scoring system.
2. Thresholds and triggers for action.
3. A decision aid algorithm.

Symptom scoring system

The scoring system for assessment of fluid status (see Figure 3) was based on physiological parameters routinely measured in haemodialysis care. In the content-validation process, consensus was reached upon the inclusion of seven parameters: dyspnoea at rest, pretibial oedema, symptoms of fluid overload between dialysis sessions, blood pressure increase, muscle cramps (calf), symptomatic IDH, and symptoms of fluid depletion between dialysis sessions. The rationale for inclusion and the cut-off values were verified in a review of published literature, detailed in the Discussion section.

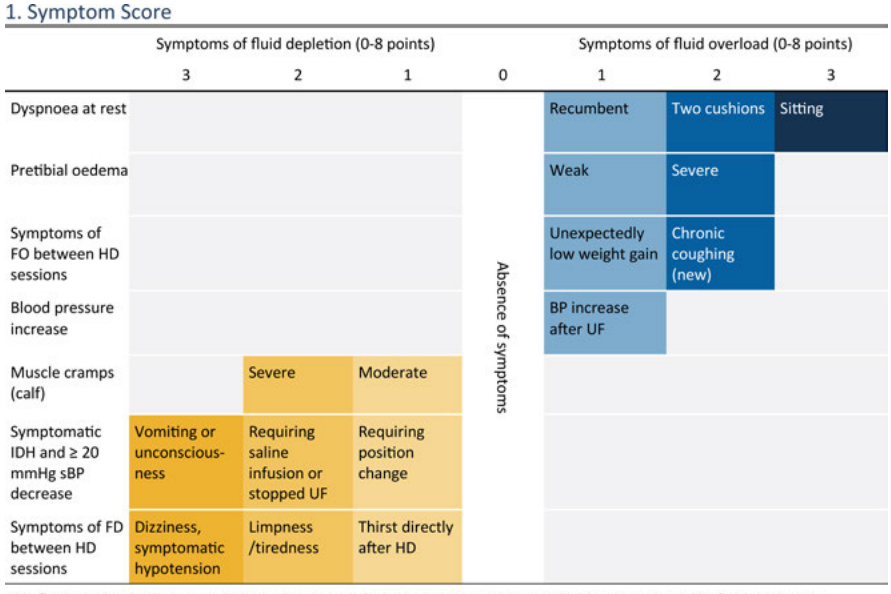

Figure 3. Recova symptom scoring system.

Thresholds and triggers

In order to contribute to improved interprofessional communication, Recova® also defines thresholds and triggers for action, Figure 4. The thresholds are based on a patient's total symptom score, i.e., the total sum of fluid depletion and fluid overload symptom scores. The total score is the grounds for suggestions of a clinical response.

2. Thresholds and triggers

SVS Score	Response	Action
0	Evaluation of target weight (DW) every second week	Bioimpedance measurement 2 – 4 times/year for assessment of hydration status and nutritional status
1 – 4	Target weight should be questioned	Inform registered nurse, who must assess the patient, and decide whether initiation of DW change is required or if symptoms may be explained by other known conditions (such as heart failure or advanced chronic obstructive pulmonary disease). Perform Bioimpedance measurement and evaluate according to decision aid. Repeat measurement at three occasions or until target weight is achieved.
5-6 or 3 in a single parameter	Target weight should be adjusted	Inform clinician for assessment. Perform Bioimpedance measurement without delay and evaluate according to decision aid. Repeat on three occasions or until achievement of target weight goal.
7 or more	Immediate need for evaluation of hydration status and target weight adjustment	Registered nurse to immediately inform the clinician

Figure 4. Recova thresholds and triggers for action.

Decision aid algorithm

The decision aid was constructed as an algorithm based on two primary assessments: the predominant symptoms according to the symptom scoring system (Figure 3) and the hydration status according to BIS. The algorithm is hence based on four possible scenarios, see Figure 5.

Depending on which criteria that are fulfilled, the caregiver is directed along different pathways in the decision aid algorithm, leading to different suggested responses and dry weights to aim for. The caregiver is advised to pay attention to preservation of RRF and to alter the dry weight slowly, by 0.5–1 kg per week. Under some circumstances, the advice is to aim for a dry weight either slightly lower or higher than normohydration according to BIS. In some cases, the advice is to consider possible treatment-related causes of symptoms, e.g., dosing and timing of antihypertensive agents and UFR.

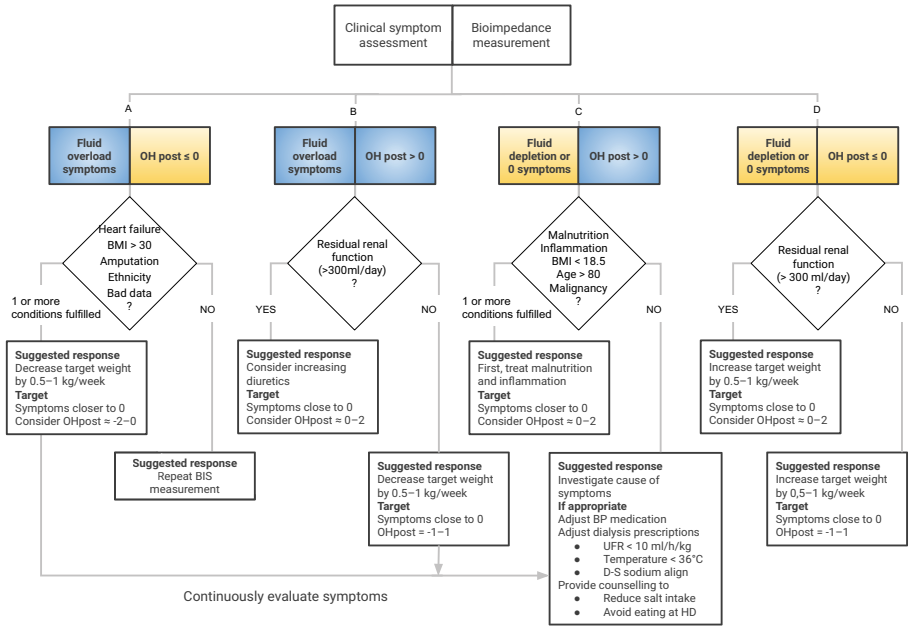

Figure 5. Recova flow chart algorithm.

Validation

Nineteen nurses tested the decision aid. However, one questionnaire was not complete and was therefore excluded from IRR analysis. Ten nurses rated themselves as confident in using the BIS and eight nurses rated themselves as less confident. All confident raters had more than five years' experience from haemodialysis care and had performed more than 20 BIS measurements each.

Confident raters' degree of consistency in ratings of symptoms across subjects was ICC = 0.96 (CI: 0.87–1.0), indicating almost perfect agreement. However, in the choice of clinical response, the kappa value for IRR was k = 0.53 (CI: 0.46–0.61), indicating moderate agreement above chance. The overall percentage agreement was 77.5%. In the patient cases where symptoms and fluid status according to BIS were consistent (directions B and D, Figure 5), the confident raters agreed on the suggested clinical response to 90% and 100%, respectively. However, in cases where symptoms and BIS readings were inconsistent (directions A and C), the overall agreement was only 60%.

The degree to which less confident raters provided consistency in their ratings of symptoms across subjects was ICC = 0.95 (CI: 0.82–1.0), again indicating almost perfect agreement. The overall percentage agreement in suggested clinical response for less confident raters was 56% (range 44–67%), and the overall mean kappa value for IRR was only k = 0.26 (CI: 0.17–0.36), indicating fair agreement above chance.

Study V

Forty-nine haemodialysis patients, including 32 males, with a mean age of 73 (67–80) years, were enrolled in the study. Nine individuals (18.3%) had a clinically assessed volume status score of ≥ 5, indicating an urgent need for dry weight adjustment, and about 50% had a volume status score of 1–4. A third of patients had no symptoms of either fluid overload or fluid depletion. The median OH pre-dialysis in the sample was 1.7 (0.9–3.4) L, OH post was 0.10 (- 0.80–1.3) L and NT-proBNP was 9,270 (2,490–19,600) ng/L. Except for OH, fluid status score, and NT-proBNP, there were no statistical differences in characteristics between the four fluid status groups.

Process measures

In the first cohort the staff were given full responsibility to follow the study protocol, without further support. However, only 67% of the expected assessments were performed. Therefore, in the second cohort, the first author visited the dialysis unit every second week to check if the intervention was carried out as intended and to support the nurses in their response to recognised fluid alterations. Hence, in the second cohort 100% of the expected assessments were performed.

Prior to the intervention, BIS measurements were performed 0.5 times/month, and there was no significant difference in dry weight adjustment frequencies between the cohorts. In cohort 1, the monthly frequencies of both performed BIS measurements and dry weight adjustments increased by 1.5. Whereas, in cohort 2, there was a twofold increase in BIS measurement frequency and close to a twofold increase in dry weight adjustment frequency. There was a correlation between frequency of BIS measurements and frequency of dry weight adjustment, and fluid overload symptoms correlated with OH post and with NT-proBNP.

Outcome measures

Group A – symptoms of fluid overload, but negative OH

In group A (n = 4), OH post was - 1.55 (- 2.6– - 0.35) L at baseline, despite symptoms of fluid overload. In contrast to the suggested clinical response (Table 5), dry weight increased in three cases. Despite this, two participants were relieved from symptoms of fluid overload, and at the end of the study all participants had reached the Recova® defined target of the group, that is OH post below 0 L. At baseline NT-proBNP was 27,150 (10,735–52,400) ng/L. The levels decreased in three cases but increased in one, where the participant had a decrease in lean and adipose tissue. At a group level there was no significant change in NT-proBNP.

Group B – symptoms of fluid overload, and positive OH

At baseline, all participants in group B (n = 10), had symptoms of fluid overload, and OH post was 1.85 (1.4–2.1) L. Dry weights decreased in seven cases, were unchanged in two, and increased in one. At the end of the study, five individuals had reached the target of the group, that is OH post ± 1.1 L. Three participants had remaining symptoms of fluid overload, one was relieved from symptoms, and five had symptoms of fluid depletion. At baseline, this group had the highest NT-proBNP, 33,250 (17,500–41,200) ng/L, but although median pre dialysis OH decreased from 3.8 to 2.9 L, p = 0.047, NT-proBNP was not affected.

Group C – symptoms of fluid depletion or absence of symptoms, but positive OH

In group C (n = 15), OH post was 1.10 (0.2–1.4) L at baseline. The vast majority (12 out of 15 individuals) had no symptoms of either fluid overload or fluid depletion. Dry weights increased in six cases, decreased in six and was unchanged in three. At the end of the study, five individuals had reached the target of the group, that is OH post 0–2 kg. In 10 individuals OH post was between - 1.6 and + 1.6 L. Two of these individuals reported symptoms of fluid depletion. Group C had the lowest NT-proBNP, 4,050 (2,160–10,650) ng/L, and NT-proBNP did not change at a group level.

Group D – symptoms of fluid depletion or absence of symptoms, and negative OH

In group D (n = 20), nine participants had symptoms of fluid depletion. Eleven participants reported no symptoms. At baseline, OH post was -0.85 (- 1.6– - 0.4) L. At the end of the study, dry weight had increased in thirteen cases. Target of the group, that is OH post ± 1.1 L, was reached in 15 cases. The number of individuals reporting symptoms of fluid depletion decreased from 9 to 7. When dry weight increased from 72.8 to 73.4 kg, p = 0.024, OH post increased to - 0.5 (- 1.0–0.5) L. At the end of the study, NT-proBNP had increased from 6,130 to 9,625 ng/L, p = 0.033.

Contextual elements that interacted with the intervention

In cohort 1, the intervention ran for four months, May–August 2019. This coincided with summer holidays and staff vacations, which probably affected process measures.

In both cohorts, changes in participants' body composition were found to interact with outcome measures. Due to changes in adipose and lean tissue mass, dry weight target, as estimated at baseline, was not always adequate at the end of the study.

Discussion

Study I

Our first study revealed wide variation in routines for dry weight determination, as well as differences in approaches to the dry weight concept. The interval for a nephrologist's evaluation of a haemodialysis patient's dry weight varied from once a month to every third month. Instead, the initiative to adjust dry weight was often taken by a nurse. In our sample (especially in many county hospitals), nurses were authorised to adjust dry weight. We found that authorisation of nurses to adjust dry weight was associated with higher frequency of dry weight adjustments and lower blood pressure.

The effects of frequency of dry weight adjustments on patient outcome is scarcely investigated. However, one previous study indicates that increased frequency of dry weight adjustment is associated with improved dry weight achievement and lower mortality.[122] Also, the DOPPS study showed that dialysis facility practices and the frequency of dry weight adjustments had positive implications for fluid status in haemodialysis patients.[46]

Charra et al.[11] state that dry weight is a crucial component of dialysis adequacy, and that achievement of dry weight is feasible on purely clinical grounds. Conversely, Covic and Onofriescu[123] argue that there is a need to re-evaluate the concept of dry weight, and suggest weekly BIS measurements to replace clinical dry weight assessment. Mamat et al.[99] propose that nurses could be trained to use a BIS device to obviate fluid overload in dialysis patients between nephrologist reviews. Prospective trials with regular utilisation of BIS – at least once a month[18,35,93] – indicate that fluid overload and blood pressure can be attenuated, and left ventricular hypertrophy and arterial stiffness can be improved. However, in haemodialysis patients, target blood pressure level is not as clearly defined as in patients with normal renal function. Both high and low blood pressure correlate with increased cardiovascular morbidity and mortality,[90,124] and caution has been called for when implementing technical tools in a fragile population. There is a risk that continual weight loss aimed at a normovolemic hydration status, driven by BIS, will compromise RRF and worsen intradialytic symptoms.[93,125] Remarkably, we found the benefit of preserved RRF was highlighted in only one unit's local guidelines. Loss of RRF is associated with reduced survival, increased left ventricular mass index, increased blood pressure, and reduced removal of uremic tox-

ins.[126] Obtaining the optimal dry weight is thus a delicate treatment task, requiring avoidance of both fluid overload and dehydration. Serial BIS measurements and trends are suggested to be more useful than single determinations, and one should bear in mind that the normal range of hydration varies between -1.1 L and +1.1 L.[90]

Sweden and Denmark, like many other countries,[123,125,127] still have no established guidelines for clinical use of BIS. Fifty percent of the units studied had a BIS device, but only 25% used it regularly, revealing a deficiency in implementation. Our qualitative analysis showed that delay of implementation might be explained, for example, by uncertainty over how to handle the device or how to interpret measurements, or insufficient credibility due to lack of evidence. Reviews suggest not using BIS alone, but instead using multiple complementary methods for assessing dry weight.[21,68] Some units used ultrasound of vena cava and analysis of BNP, and the vast majority used BVM. No guidelines advocated the use of chest x-ray for dry weight assessment; nevertheless, most units reported use of the method. Unfortunately, no data are available on the frequency of use of these methods.

It may be argued that the inference, and thus the generalisability, of our findings is limited by a response rate of 52%. However, the average response rate for studies using data collected from organisations is 35.7%.[128] Moreover, the study provided good geographic and demographic representation of Swedish and Danish haemodialysis units.[129,130] In order to increase the response rate, electronic data collection was used, as it has been shown that electronic data collection produces response rates are higher than the traditional post methodology.[128] The use of a study-specific, not validated questionnaire, may be considered a limitation of the study, raising a risk for bias in responding.[131] However, the use of a study-specific protocol enabled the use of mixed methods. Mixed-methods research builds on the strengths and reduces the weaknesses of both the quantitative and the qualitative approaches.[132] This contributed to a more thorough description of clinical practices, local guidelines, and routines for assessing dry weight than either quantitative or qualitative approaches could provide alone.

Study II

In our first study, we learned that access to BIS devices alone may not have an impact on the practice patterns of clinics.[104,133] In Study II, focus group interviews were used to gain a deeper understanding of determinants acting either as barriers or facilitators, for use of BIS.

Barriers

At several units, BIS had not been introduced strategically, but through passive dissemination of information, which is generally ineffective.[103,134,135] Thus, awareness of the potential benefits of BIS[18,93,94,136,137] was insufficient.

Recommendations for use of BIS have changed over time,[138] but there were diverse opinions on how to use BIS, for example in patients with a pacemaker, in amputees, or for assessing nutritional status. These findings indicate the need for channels to disseminate new and updated research recommendations.[134,139,140]

Users questioning the underlying evidence is a known barrier for implementation, and as evidence often focuses on patients with single diseases and excludes complex patients, practical applicability may be limited.[141–143] Our results show that perception of insufficient credibility was an evident barrier to clinical use of BIS; several participants in the focus groups found the method unreliable, due to inconsistent measurement results. However, all methods for assessment of fluid status perform best when measured serially and in conjunction with other methods of volume assessment.[21,123,125,144,145] Still, not all study participants were aware of the importance of serial BIS measurements.

Although some units had developed routines for use of BIS, many dialysis centres lacked an agreed fluid management policy and BIS measurement would not be a priority in periods of high workload and shortage of trained staff. Some participants perceived patients' preference to start their haemodialysis session without delay as a barrier to using BIS. However, as other participants denied that this was a barrier, professionals may also have misconceptions about patient values.[107]

Lack of inter-professional consensus and collaboration between different types of professionals, and deficient congruency in recommendations, were barriers to use of BIS. At most units, the primary initiators of BIS measurement were nurses, and use of BIS in the clinical setting was dependent on certain individuals' personal interests and dedication. Some nurses reported limited self-efficacy in using BIS and interpreting the results, due to lack of pre-existing knowledge about fluid balance. Inter-professional collaboration may be crucial to the provision of efficient healthcare and has the potential to increase self-efficacy.[146] This was confirmed by our study results; at units where dieticians contributed knowledge, participants expressed a higher degree of self-efficacy.

Facilitators

Several participants in the focus groups, the physicians in particular, found the device attractive, as it had contributed to increased knowledge about fluid status and put the subject of dry weight on the agenda. Participants had experienced advantages in clinical practice and found patients to be motivated, resulting in an increase in the professionals' own motivation to change their practices. Attractiveness and experience of advantages in practice are characteristics considered crucial for successful implementation of an innovation.[102] Thus, implementation of BIS in clinical practice theoretically has a good chance of success.

Contextual factors, such as hospital size, may impact on successful implementation,[147] and in small units, the use of BIS had been implemented successfully without systematic implementation strategies.

Methodological considerations

To increase the dependability of our research findings, we aimed to provide a thorough description of our procedures of data collection and analysis, and study reporting was based on a rich representation of quotations, in order to ensure confirmability.[148–150] In order to prevent inaccuracy and achieve credibility,[148–150] we pilot-tested the questioning route, and used the same moderator in all focus group sessions.[148] The moderator and the assisting moderator debriefed immediately after each session, and were able to identify a tendency to intellectualise in the first focus group.[105] The questioning route could thus be adapted, to make a clearer distinction between participants' intended behaviour and the setting description.

Due to the strategy of purposively recruiting the volunteer participants best able to supply information – renal care professionals with experience of using BIS, but who might also be those with the most favourable opinions – a selection bias might be inherent. That is, professionals with unusual experiences and other perceptions might have been missed. There is also a risk that the study participants' differences in age and years in profession may have biased the results. Furthermore, because input from physicians and dieticians was limited due to the small number of such participants, we cannot be sure that we reached saturation on all themes[105,106] or that all potential perceptions from physicians and dieticians materialised. However, for feasibility reasons, it is an accepted rule of thumb to plan for three or four interviews when using focus groups for data collection.[105] A multidisciplinary perspective, including a wide variety of professionals and different types of clinics, enhances transferability,[148–150] and our aim was not to compare and contrast differences in perceptions between different professionals, but to look for patterns and themes across groups. Moreover, as the relative proportions of dieticians, nephrologists and nurses in the study sample reflected the study population well, the transferability of our findings increases.

Thanks to the qualitative approach, we gained insight into perceived barriers and facilitators, although we cannot appraise the frequency thereof, or their impact on the use of BIS. In developing an implementation strategy at a national level or in other countries, a quantitative study on the frequency and impact of identified themes and concepts in this study could contribute to increased transferability.

Study III

There is an association between OH and BNP,[82,84] and BNP has been proposed as a marker of fluid overload.[81,82,84] Study I showed that few Swedish and Danish haemodialysis units (13%) used BNP in fluid management.[104] However, since BNP is affected not only by fluid overload, but also by a patient's degree of heart failure, dialysis treatment modalities, and adverse events like IDH,[77,86] its use as a marker of fluid overload is controversial.[87] In our sample in Study III, there was a correlation between OH and BNP. BIS measurement revealed 58% more OH in the group of participants with BNP > 500 pg/ml than in participants with low BNP. However, an important finding was that some individuals were severely overhydrated without having increased levels of BNP. Thus, a normal BNP does not rule out OH as defined by BIS in haemodialysis patients.

BNP was also found to correlate with CRP and malnutrition, but not with blood pressure. In the correlation between OH and BNP, the R value was only 0.38, and ROH accounted only for 14% of the variance in log-BNP. When albumin and age were added to a regression model, the model could explain 47% of the variation in log-BNP. The high BNP group consisted of overhydrated, but also elderly and fragile individuals. Compared with the low BNP group, they had less muscle strength, lower BMI, and lower haemoglobin and albumin levels, but higher CRP levels. These findings indicate malnutrition and inflammation, which are associated with fluid overload.[34,42,81,92,151,152] Previously, OH has been associated with other inflammation markers, such as IL-6 and TNF-alpha.[42] However, we were not able to confirm this association.

BNP may vary considerably across the dialysis population.[79] This was confirmed in our findings, as mixed-methods analysis of longitudinal data showed large differences in intercepts. Because difference in BNP levels may depend on dialysis treatment modalities,[79,86] all participants in our longitudinal study phase were transferred to treatment with high-flux dialysers. However, we found that this change did not affect the pre-dialysis BNP levels. Notwithstanding, all 11 participants included in the longitudinal part of the study had echocardiographic anomalies. Thus, the pathologic cardiac function associated with elevated BNP might be an important explanation for the poor prognosis for patients with elevated BNP levels. Furthermore, the decreased cardiac autonomic function (as measured through HRV) that we found in a subset in participants with elevated BNP can contribute to increased cardiovascular mortality, especially sudden death.[111]

Over time, BNP has been found to remain relatively stable within an individual.[88,153] Plasma volume changes very little during dialysis, a change of weight by ultrafiltration may not be immediately sensed as a change in volume by the left ventricle; but some time may be needed to reach a new steady state and change in BNP level. Findings of significant decline in BNP over the course of a week may support this hypothesis.[80] Thus, measurement of BNP

may be better applied in the dialysis population using a relative-change strategy rather than by comparing absolute values to a reference interval or threshold value.[114] Our results from the longitudinal part of Study III support this proposal, as the between-individual variation of BNP in relation to OH was larger than the within-individual variation.

A limitation of this study was that the study sample was relatively small, and the participants were recruited from a haemodialysis centre where RRF, which may affect BNP levels,[154] was not routinely measured. Due to the study design and for reasons of feasibility, cardiac function was examined only in the high BNP group. In order to validate our conclusions, examination of cardiac function in the low BNP group should be added in future research. For assessment of symptoms of fluid overload, we used a scoring system without a validated Swedish translation.[116,117] This might be considered a study limitation. However, there has not been any validated Swedish scoring system for fluid status assessment in the past, and our use of a previous scoring system enables international comparisons.

Study IV

Fluid management has been described as the nephrologist's quest for the holy grail,[155] and new proposals for fluid management are being drafted.[3,156] However, as shown in this thesis, there is still no consensus on how best to assess fluid status in haemodialysis.[104,157] To the best of our knowledge, Recova® is the first validated tool guiding fluid management in haemodialysis by systematising the process of clinical assessment and combining it with BIS.

Symptom scoring system

For a tool to work in diverse haemodialysis care settings, it must be simple to implement. Recova® was therefore based on seven physiological parameters already used in clinical assessment of fluid status (Figure 3). However, clinical assessment of fluid status is not always straightforward. For example, oedema is independently linked to left ventricular hypertrophy and indirectly to systolic hypertension and widened pulse pressure,[63] while dyspnoea is associated with pulmonary congestion and IDWG.[158] Still, many patients with fluid overload do not show obvious signs of oedema or breathing difficulties; on the other hand, chest infections or anaemia can also cause breathlessness. This complicates use of oedema and dyspnoea as markers of fluid overload. Moreover, although there is a causal association between IDWG and fluid overload, unexpectedly low weight gain between dialysis sessions may appear in patients with severe fluid overload, due to inferior nutritional intake.[15,30] Pre- and post-dialysis blood pressure were not included in the scoring system, as they have been shown to be rather poor at predicting fluid status. Patients who are normally hydrated, or even dehydrated, pre-dialysis may have high blood pressure, and patients with fluid overload may have low blood pressure, for

example in heart failure.[61,66] However, intradialytic hypertension (a paradoxical increase in blood pressure during dialysis) has been linked to fluid overload, and was thus included in the symptom scoring system.[159,160]

IDH, which was included as a symptom of fluid depletion, was defined as blood pressure decrease by more than 20 mmHg accompanied by clinical symptoms of hypovolemia requiring nursing intervention.[161,162] Muscle cramps, which affect 25–50% of all dialysis patients during haemodialysis treatment or at home following dialysis,[163] can be related to fluid depletion. However, it is worth noting that muscle cramps – like IDH, increased thirst, and dizziness – may be related to rapid removal of fluid.[62]

The symptoms included in the symptom scoring system as indicators of either fluid overload or fluid depletion, may seem contradictory when assessed in isolation. However, we believe that they have the potential to facilitate recognition of symptoms, when assessed repeatedly and systematically.

Thresholds and triggers

The complexity of fluid management is challenging. For fluid management interventions to be successful, they must be considered in a multidisciplinary team. Although dry weight determination is usually the responsibility of the nephrologist, fluid status is often assessed by nurses.[133] Having a protocol that specifies how often to assess dry weight is associated with lower risk of all-cause and cardiovascular mortality.[46] By providing a systematic approach to fluid assessment, and guidance in deciding when and how to respond to clinical symptoms, as in the Recova ® track-and-trigger system (Figure 4) similar to the NEWS,[101] our aim was not only to facilitate recognitions of symptoms of fluid alterations, but also to contribute to improved interdisciplinary communication, and thereby prevent delay of action.

Decision aid algorithm

Not only BIS-measured overhydration, but also pre-dialysis underhydration, is associated with increased mortality, whereas post-dialysis underhydration is associated with a lower mortality risk.[37] In the decision aid algorithm (Figure 5), four types of fluid status groups are defined: A, B, C, and D.

In direction A, the inverse relationship between OH and obesity in haemodialysis patients is highlighted. For this category of patients – as for patients with heart failure, amputations, or other ethnicity than Caucasian, who experience symptoms of fluid overload despite being underhydrated according to BIS – a dry weight below normohydration according to BIS may be beneficial.[34]

Intra- and post-dialytic complications can make fluid removal difficult even in patients with significant fluid overload.[67] This is reflected in direction B in the decision aid algorithm; it is suggested that dry weight reduction should not be reinforced rapidly. The normohydration range for BIS is between -1.1 L and +1.1 L,[41] but removal of excessive fluid in an attempt to

achieve a euvolemic state can lead to poor patient outcomes by provoking IDH, which may lead to loss of RRF, myocardial stunning, and other organ ischemia.[2] As reflected in directions B and D, many patients would likely benefit from some fluid reserve, for preservation of RRF.[93,164]

As highlighted in direction C, pre-dialysis positive OH is associated with higher levels of CRP, indicating inflammation.[37] Furthermore, positive OH is inversely associated with body mass index and serum albumin, and slightly elevated OH appears to be common in elderly subjects. This may be explained by changes in the composition of adipose tissue and it may not be possible to isolate the effects of malnutrition from those of sarcopenia.[34,165] Thus, there is a general need for caution when reducing the dry weight in elderly and vulnerable patients. In these cases, Recova® advises a dry weight above normohydration – according to BIS – to be considered.

However, although an individual may have symptoms of fluid depletion, such as IDH, this may be related to anti-hypertensive medication use and dialysis prescription rather than fluid depletion per se.[19] When dry weight is decreased, it is usually necessary to gradually and continuously adjust blood pressure medication, alter dialysis prescriptions, and provide dietary counselling, in order to prevent symptoms of fluid depletion. Dietary counselling should emphasise sodium reduction,[3,16,44,45] and high dialysate sodium levels should be avoided. Dialysate to serum sodium alignment has been shown to reduce IDWG, as lowering or individualising dialysate sodium reduces thirst. In order to prevent IDH, reduced dialysate temperature could be considered,[51,52] and UFR is recommended to be kept below 10 mL/h/kg, as higher rates are associated with all-cause mortality.[24]

The choice of BIS device is important, and validation and applicability to patients with CKD should be checked. Some BIS devices are validated in the haemodialysis population, as well as in healthy Caucasian controls.[41] In our opinion, different ethnicities are not barriers to performing BIS measurement. However, in case of bad data, fluid assessment should be guided by clinical assessment until a valid BIS measurement is obtained, and if conflicting results are found in BIS measurement of haemodialysis patients, fluid assessment should be guided by clinical assessment primarily, since evidence on the benefits of BIS is still scarce.[70,166]

Validation

The selection of parameters included in Recova® was supported by a literature review and by empirical consensus, through a face-validity process. However, the challenge in deciding which symptoms to include or exclude and what cut-off values to use in clinical assessment of fluid status may be considered a weakness of the tool. Although we aimed for the decision aid to be simple, we realise that nurses found it difficult to comprehend the algorithm – reflecting the complexity of dry weight determination. In the IRR analysis, raters achieved less agreement when assessing patients in whom clinical

symptoms and BIS conflicted (directions A or C). Poor knowledge of the limitations of BIS may be one explanation for the limited implementation of BIS in clinical practice.[104,133,157]

In the IRR analysis, we considered the symptom scoring system and the adherence to the decision aid algorithm separately. The ICC of the symptom scoring showed almost perfect agreement,[121] suggesting that raters scored clinical symptoms of altered fluid status similarly. The high ICC suggests that a minimal amount of measurement error was introduced by the nurses. However, adherence to the decision aid algorithm showed only fair agreement between raters. One possible explanation for the low IRR may be poorly trained coders.[167] After first conducting a pilot test, we found agreement increased with training, and thus concluded that implementation of the tool would not be successful without education and training of staff. This finding was supported by the results showing that more confident and more experienced users had higher agreement.

There is the potential for bias in this study given the relatively small number and non-random selection of nurses participating in the agreement analysis. However, our selection of raters included a variety of experience and confidence in use of BIS across two countries with different healthcare systems. A selection of only confident raters might have increased IRR, but would have reduced generalisability.

Study V

The final study of the thesis was a prospective implementation intervention evaluating the effect of Recova® in 49 haemodialysis patients at two haemodialysis units. Based on the participants' clinically assessed symptoms and their hydration status as measured using BIS, four groups of fluid status were distinguished. By the end of the study, the frequencies of bioimpedance measurements and of dry weight adjustments had increased, and the number of individuals with a clinically assessed volume status score of ≥ 5, indicating an urgent need for dry weight adjustment, had decreased from 9 to 5. A majority of the participants with both fluid overload symptoms and positive OH had significantly decreased symptoms and pre-dialysis OH. In the group of patients with symptoms of fluid depletion and negative OH post, dry weight had increased in 13 out of 20 cases. In the two groups in which clinical assessments and BIS measurements were in conflict, the intervention had no effect at a group level.

This implementation intervention was introduced similarly in two cohorts, but in the first cohort, only 67% of the expected assessments were performed. In the second cohort, the intervention was more closely monitored and 100% of the expected measurements were performed. This highlights both the importance of having well-established routines for dry weight assessments[46] and the need for tailored implementation strategies. One strength of Recova® is

its multidisciplinary approach. However, this implementation intervention primarily addressed nurses. The physicians at the clinic received only brief information about the tool. It is possible that a multi-professional approach could have improved adherence to the protocol and hence the effect of the implementation.

Only four study participants were included in group A, corresponding to symptoms of fluid overload but negative OH post. For this group, the clinical response, as suggested by Recova®, is decrease of dry weight despite negative OH post, in order to achieve reduced symptoms. However, dry weight did not change significantly in the group. Conversely, median OH post increased, and our results indicate that staff were guided more by the BIS device, trying to get to OH post = 0 in all cases, than by the protocol. However, the low number of participants in the group prevents generalisability, and moreover, the increase in dry weight may be due to contextual elements affecting the outcome, that is individuals' increase in lean and adipose tissue. Still, because our results could be interpreted as indicating that staff members need more training to gain deeper understanding of the relevant applications of BIS, we want to stress the importance of individualised fluid management in haemodialysis. Evidence indicates that fluid depletion post dialysis is associated with a survival benefit.[37] Therefore, a dry weight 1–2 kilograms below normohydration weight may be appropriate in some subjects.

Group B, with symptoms of fluid overload and positive OH post, had the highest NT-proBNP. Interestingly, both group A and group B, with patients who reported fluid overload symptoms, had significantly higher NT-proBNP than groups C and D. This despite group A having negative OH post and group B having positive OH post. The finding underlines the importance of combining BIS with other measures of fluid status for individualised dry weight determination.[92,97] In group B, dry weight had decreased by the end of the study, as recommended by Recova®. As high OH in combination with high NT-proBNP is associated with increased mortality,[168] the improved hydration status in group B may be one of the most important effects of this implementation intervention. However, when pre-dialytic OH decreased, the number of participants reporting symptoms of fluid depletion increased. Intra- and post-dialytic complications can make fluid removal difficult even in patients with significant fluid overload.[67] Symptoms of fluid depletion, as reported in group B, may be related to anti-hypertensive medication use and to dialysis prescription rather than fluid depletion per se.[19] For patients to achieve an adequate dry weight, without experiencing increased intradialytic fluid depletion symptoms, a different dialysis schedule, for example more frequent or longer dialysis sessions, may be required.

According to Recova®, individuals with positive OH but symptoms of fluid depletion or no symptoms, group C, may benefit from a OH post up to 2 L. Correction to a BIS-measured OH = 0 may cause hypotension, if the observed OH is in combination with malnutrition, inflammation, low BMI, high

age, and/or malignancy. There is still no evidence that attaining euvolemia is feasible or desirable under these circumstances.[26,152,169,170] However, none of these conditions applied to our study sample. Still, the relatively low NT-proBNP (significant) and blood pressure (non-significant) confirm that individuals in group C may tolerate an increased dry weight despite positive OH. On the other hand, the vast majority of individuals in group C had no symptoms of either fluid overload or fluid depletion. The observed absence of differences in dry weight adjustments at follow-up may thus be clinically appropriate.

In our study sample, a large proportion of individuals presented with negative OH post and symptoms of fluid depletion, group D. In a recent trial, normalisation of volume status in patients with negative OH resulted in a significant reduction in intradialytic hypotension.[95] In our study, dry weight increased by 0.6 kg this group, as recommended by Recova®, and there was a small decrease in the number of individuals with fluid depletion symptoms. However, NT-proBNP also increased, with 50%. This parameter was not investigated in the study by Patel et al.[95] The increase in NT-proBNP after dry weight increase raises some concern, as elevated NT-proBNP is associated with increased mortality in haemodialysis patients.[171] However, it has been argued that serial NT-proBNP levels need to be doubled or halved in haemodialysis patients to confidently exclude changes due to analytical and biological variation alone.[77]

Both fluid overload and pre-dialysis fluid depletion are associated with increased mortality in haemodialysis patients.[32,172,173] There is a need to individualise haemodialysis treatment. BIS may be a help in fluid assessment, but it cannot provide a simple target applicable to all haemodialysis patients.[97] Recova® contributes to individualised haemodialysis treatment by defining four different types of fluid status. Another of its purposes is to provide the multidisciplinary team with a common language, by defining how and when dry weight should be evaluated.

Recova® emphasises the need for preservation of RRF, but RRF was not routinely measured at the clinic where the trial was conducted. The nurses were encouraged to discuss RRF with the patients, but the parameter was not included in analysis. To correct for this limitation, all patients with RRF large enough to negate the need for ultrafiltration were excluded from the study. Furthermore, in Recova®, it is suggested that dry weight reduction should not be reinforced rapidly.[169] In order to prevent symptoms of fluid depletion when dry weight is decreased, it is usually necessary to gradually and continuously adjust blood pressure medication, alter dialysis prescriptions, and provide dietary counselling on sodium reduction.[16] In further research evaluating the Recova tool, we recommend that these measures are included and taken into consideration.

Conclusions

- There is wide variation in routines for dry weight determination at Swedish and Danish haemodialysis units. Availability of BIS devices is high, but their use in clinical practice is scarce.
- Nurses' authorisation to adjust the dry weight of haemodialysis patients is associated with improved fluid status.
- Barriers to use of BIS among healthcare professionals are insufficient credibility, lack of awareness, insufficient knowledge, limited self-efficacy, lack of structure, and contradictory regulations.
- Facilitators for use of BIS are the attractiveness of the device, users' experiences of advantages in practice, and inter-professional collaboration.
- BNP correlates with OH, but also with CRP and malnutrition.
- In serial measurements, BNP reflects individual variation in hydration status, and the between-individual variation is larger than the within-individual variation.
- A decision aid for early **re**cognition and **co**rrection of **v**olume **a**lterations in haemodialysis patients, Recova®, was developed. It is based on multifactorial symptom assessment and incorporates BIS in dry weight determination.
- Nurses' agreement, measured as inter-rater reliability (IRR), when using Recova® in symptom assessment was almost perfect, but IRR in clinical response was only fair.
- Implementation of Recova® at two haemodialysis units increased the monthly frequency of BIS measurements and dry weight adjustments.
- After implementation, patients with fluid overload symptoms and BIS-measured OH post improved in symptoms and hydration status, and patients with symptoms of fluid depletion and negative OH had increased dry weight.

Clinical implications

This thesis sheds light on the wide variation in routines for dry weight determination across haemodialysis units in Sweden and Denmark. Mortality is high in haemodialysis patients, with fluid overload being one main contributor to poor outcome. BIS may offer an objective measure of fluid status, but although we found the availability of BIS devices was high, their use in clinical practice was limited. The utility of BIS is decreased by several barriers, as identified in Study II. Furthermore, the concept of dry weight has evolved over time, but there is still no consensus on what dry weight to aim for in haemodialysis. In some studies, researchers aim for OH = 0 in the interdialytic interval, with a dry weight below euvolemia at the end of each dialysis session, while other researchers argue for some post-dialysis volume preservation.

Based on the knowledge gained in Study I, Study II, and Study III, we developed (Study IV) and evaluated (Study V) a decision aid for early recognition and correction of volume alterations in haemodialysis patients, the Recova® tool. Recova® defines how and when the dry weight should be evaluated and aims to provide the multidisciplinary team with a common language, helping caregivers not only to recognise, but also to respond to fluid alterations and to individualise dry weights. The tool is based on multifactorial symptom assessment and incorporates BIS in dry weight determination. Because BIS cannot provide a simple target applicable to all haemodialysis patients, Recova® defines four different types of patients based on BIS and clinically assessed fluid status. After the patient has been categorised, and preservation of RRF and possible patient-related conditions have been taken under consideration, the tool suggests whether to aim for OH = 0, or a dry weight 1–2 kilograms either below or above euvolemia.

We believe Recova® has the potential to facilitate fluid management in haemodialysis clinical practice. However, fluid management should be an inter-professional effort, and healthcare professionals need more training in order to gain a deeper understanding of the relevant applications of BIS. In order to contribute to sustainable change of practice, through integration of changes in routine care,[102] we have initiated the development of a digital version of Recova®. The application serves to guide the caregiver through all the steps of the decision aid algorithm, encouraging the user to consider whether various patient-related conditions apply, before determining an individualised dry weight. The digital Recova® application needs testing in further research.

Summary in Swedish

Sammanfattning på svenska

Kronisk övervätskning bidrar till försämrad överlevnad hos hemodialyspatienter. Trettio procent av alla hemodialyspatienter är fortfarande övervätskade när de har nått sin målvikt/torrvikt efter dialys. Användningen av bioimpedansspektroskopi (BIS) för bedömning av vätskestatus kan bidra till förbättrad blodtryckskontroll och bättre kardiovaskulär status, men aktuell forskning har inte kunnat koppla dess användning till förbättrad överlevnad. Däremot har det framkommit att rutiner, för torrviktsbestämning och hantering av dialysrelaterade blodtrycksfall, kan kopplas till förbättrad överlevnad. Således är regelbunden och noggrann klinisk bedömning av dialyspatienters vätskestatus av yttersta vikt.

Avhandlingen bygger på fem artiklar. Den första är en tvärsnittsstudie som undersöker klinisk praxis för torrviktsbedömning i Sverige och Danmark. Vi fann stor variation i rutiner. Trots hög tillgång till BIS-apparater användes tekniken sparsamt. Istället fann vi ett samband mellan att sjuksköterskor hade mandat att justera patienternas torrvikter och förbättrat vätskestatus hos dialyspatienter.

Den andra studien hade en kvalitativ ansats. Fokusgruppsintervjuer med vårdpersonal användes för att ge en djupare förståelse för faktorer som förhindrar eller underlättar användningen av BIS i bedömning av vätskestatus. Faktorer identifierades på fem nivåer: innovationen i sig, den enskilda yrkesverksamma personen, patienten, den sociala kontexten och den organisatoriska kontexten.

I den tredje studien undersöktes möjligheten att använda en biomarkör, brain natriuretic peptide (BNP), för bedömning av hemodialyspatienters vätskestatus. Även om ett samband kunde konstateras mellan BNP och övervätskning såg vi att användningen av ett gränsvärde inte var tillämpbart, och att ett normalt BNP-värde inte kunde utesluta övervätskning. Variation i BNP var större mellan olika individer än inom samma individ vid upprepade mätningar över tid. Om BNP ska kunna användas som markör för övervätskning krävs således upprepade mätningar.

I den fjärde studien utvecklade och validerade vi ett beslutsstöd som integrerar BIS i torrviktsbestämning. Verktyget, som benämnts Recova®, systematiserar klinisk bedömning av vätskestatus och ger vägledning om när och hur personalen ska hantera upptäckta avvikelser. I den femte studien testades

effekten av Recova® på hemodialyspatienters vätskestatus. Vi fann att implementering av Recova® hade effekt både på vätskestatus och på NT-proBNP-koncentrationer.

I vår strävan att bidra till varaktig förbättring av dialyspatienters vätskestatus har vi initierat utvecklingen av en digital version av Recova®. Ytterligare forskning krävs för test av den digitala applikationen i klinisk praxis.

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