10-1-2016

Ultrafiltration Rate Thresholds in Maintenance Hemodialysis: An NKF-KDOQI Controversies Report

Holly Kramer

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

Daniel E. Weiner

Vinod Bansal

Michael J. Choi

See next page for additional authors

Recommended Citation
Kramer H, Yee J, Weiner DE, Bansal V, Choi MJ, Brereton L, Berns JS, Samaniego-Picota M, Scheel P, Jr., and Rocco M. Ultrafiltration rate thresholds in maintenance hemodialysis: An nkf-kdoqi controversies report. Am J Kidney Dis 2016; 68(4):522-532.

Authors

Holly Kramer, Jerry Yee, Daniel E. Weiner, Vinod Bansal, Michael J. Choi, Laura Brereton, Jeffrey S. Berns, Milagros Samaniego-Picota, Paul Scheel, and Michael Rocco

AJKD

Special Report

Ultrafiltration Rate Thresholds in Maintenance Hemodialysis: An NKF-KDOQI Controversies Report

Holly Kramer, MD, MPH,[1,2] Jerry Yee, MD,[3] Daniel E. Weiner, MD, MS,[4] Vinod Bansal, MD,[1] Michael J. Choi, MD,[5] Laura Brereton, MSc,[6] Jeffrey S. Berns, MD,[7] Milagros Samaniego-Picota, MD,[8] Paul Scheel Jr, MD, MBA,[5] and Michael Rocco, MD[9]

High hemodialysis ultrafiltration rate (UFR) is increasingly recognized as an important and modifiable risk factor for mortality among patients receiving maintenance hemodialysis. Recently, the Kidney Care Quality Alliance (KCQA) developed a UFR measure to assess dialysis unit care quality. The UFR measure was defined as UFR $\geq$ 13 mL/kg/h for patients with dialysis session length less than 240 minutes and was endorsed by the National Quality Forum as a quality measure in December 2015. Despite this, implementation of a UFR threshold remains controversial. In this NKF-KDOQI (National Kidney Foundation−Kidney Disease Outcomes Quality Initiative) Controversies Report, we discuss the concept of the UFR, which is governed by patients' interdialytic weight gain, body weight, and dialysis treatment time. We also examine the potential benefits and pitfalls of adopting a UFR threshold as a clinical performance measure and outline several aspects of UFR thresholds that require further research.

Am J Kidney Dis. 68(4):522-532. © *2016 by the National Kidney Foundation, Inc.*

INDEX WORDS: Hemodialysis (HD); dialysis; ultrafiltration rate (UFR); quality of care; performance measure; interdialytic weight gain (IDW); sodium; volume management; dialysis dose; treatment time; fluid removal; end-stage renal disease (ESRD); NKF-KDOQI; controversies.

In 1995, the National Kidney Foundation (NKF) launched the Dialysis Outcomes Quality Initiative (DOQI) to improve outcomes for patients with end-stage renal disease receiving maintenance dialysis, resulting in the publication of clinical practice guidelines that addressed dialysis treatment adequacy in 1997.[1] Twenty years and 2 guideline updates later, many of the clinical questions posed in the guidelines remain unanswered. To date, only 2 large-scale randomized clinical trials have assessed the effect of different hemodialysis doses on clinical outcomes: the National Cooperative Dialysis Study (NCDS)[2] and the Hemodialysis (HEMO) Study,[3] published approximately 35 and 14 years ago, respectively. Notably, participants in these trials are not representative of the current US hemodialysis population; the NCDS excluded patients with diabetes, whereas the HEMO Study generally excluded obese patients. Consequently, much of the updated 2015 NKF-KDOQI (NKF−Kidney Disease Outcomes Quality Initiative) guideline for optimizing dialysis therapy represents suggestions based on the clinical experiences of the writing group, anecdote grounded in physiology, and lower-level data.[4]

Throughout the past decade, high hemodialysis ultrafiltration rates (UFRs) have been increasingly recognized as an important and modifiable risk factor for morbidity and mortality among patients receiving maintenance hemodialysis, but to date, no clinical trial has assessed clinical outcomes associated with a given UFR limitation. Recently, both the Kidney Care Quality Alliance (KCQA) and the Centers for Medicare & Medicaid Services (CMS) developed similar measures addressing UFR in hemodialysis patients. The KCQA metric development process used a modified Delphi survey of stakeholders across the

From the [1]Division of Nephrology, Department of Medicine and [2]Department of Public Health Sciences, Loyola University Chicago, Maywood, IL; [3]Division of Nephrology, Department of Medicine, Henry Ford Medical Center, Detroit, MI; [4]Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA; [5]Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; [6]National Kidney Foundation, New York, NY; [7]Renal, Electrolyte, and Hypertension Division, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [8]Division of Nephrology, Department of Medicine, University of Michigan, Ann Arbor, MI; and [9]Division of Nephrology, Department of Medicine, Wake Forest University, Winston-Salem, NC.

Received February 8, 2016. Accepted in revised form June 2, 2016. Originally published online July 19, 2016. Corrected online July 30, 2016 to correct the affiliations of the first and fourth authors. The errors have been corrected in the print, PDF, and HTML versions of this article.

Because an author of this article is an editor for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Sankar Navaneethan, MD, MPH) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Journal Policies.

Address correspondence to Holly Kramer, MD, MPH, Loyola University Chicago, 2160 First Ave, Maywood, IL 60153. E-mail: hkramer@luc.edu

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2016.06.010

dialysis community to determine what aspect of dialysis care should be targeted for measure development and identified volume management as the area of greatest need. There are modest differences between the KCQA and CMS measures, with the measure stewarded by KCQA receiving National Quality Forum endorsement in November 2015 (see Table 1). Although the CMS-stewarded measure was included in the 2016 calendar year End-Stage Renal Disease Quality Incentive Program proposed rule, CMS did not include a UFR reporting or performance measure in the 2016 Final Rule.

Although widely acknowledged as important, developing a UFR measure with a specific target is not without controversy. For example, in a recent survey administered by NKF-KDOQI on their website (https://www.kidney.org/professionals/guidelines), 54% of 1,090 respondents answered "No" to the following question: "Should hemodialysis units limit ultrafiltration rates for chronic dialysis patients to <10 ml/kg/hr?" In this NKF-KDOQI Controversies Report, we review the history of dialysis treatment time, one of the main components that define the UFR, and discuss the existing controversies regarding the potential implementation of UFR as a clinical performance measure. We also identify areas of research in which clinical evidence is urgently needed to guide clinical decision making regarding UFR limitations.

ULTRAFILTRATION RATE

The UFR is determined by the predialysis weight and the desired postdialysis weight and is a function of the total fluid removed and the time devoted to removing that fluid, adjusted for patient weight. When ultrafiltration is performed, volume is removed from the vascular space. Maintenance of effective circulating volume therefore depends on the ability of fluid from the interstitial space to refill the vascular space; this refill varies from patient to patient.[5] If fluid is removed too rapidly, patients may have symptomatic intradialytic hypotension and/or cramping, both of which may cause patients to terminate the dialysis session prematurely.[1] In extreme cases, patients may have loss of consciousness. To treat intradialytic hypotension, patients may receive isotonic or hypertonic saline solution; this fluid bolus then impedes the ability to reach the prescribed ultrafiltration goal and postdialysis "dry weight." Recurrent episodes of intradialytic hypotension are associated with higher rates of hospitalizations and mortality.[6] Excessive interdialytic weight gain (IDWG), independent of UFR, is recognized as an important predictor of morbidity and mortality, and methods for mitigating fluid intake between treatments have been discussed in all NKF-KDOQI dialysis guidelines.[1,4,7,8] High IDWG may lead to volume overload and clinical

Table 1. Description of the KCQA and CMS Measures for UFR Limits

	KCQA Measure	CMS Measure
Numerator	No. of patients from denominator with average UFR ≥ 13 mL/kg/h who receive an average of <240 minutes per treatment session during calculation period[a]	No. of patient-months for adult ESRD patients at a dialysis facility with UFR > 13 mL/kg/h
Denominator	No. of adult in-center HD patients at reporting facility undergoing maintenance HD during calculation period	No. of adult in-center HD patients at reporting facility undergoing maintenance HD during calculation period
Calculation period	The same week the monthly Kt/V is drawn; the annual performance on the metric is mean of performance scores for each month over performance year	The last HD session of the month; the annual performance on the metric is number of months with UFR above threshold divided by total facility patient-month
Denominator exclusions	(1) Patients aged < 18 y; (2) home dialysis patients; (3) patients in a facility <30 d; 4) patients with ≥4 HD treatment sessions during calculation period; (5) patients with <7 HD sessions in facility during reporting month; (6) patients without a completed CMS Medical Evidence Form in reporting month; (7) kidney transplant recipients with functioning transplant; (8) facilities treating ≤25 adult in-center HD patients during reporting month	(1) Pediatric patients; (2) peritoneal dialysis patients; (3) patients new to ESRD (<90 d on maintenance dialysis); (4) patients who have not been with same facility for entire reporting month (transient patients)

Note: UFR is defined as total amount of fluid removed for a given dialysis session divided by dialysis session length and by the patient's body weight in kilograms.

Abbreviations: CMS, Centers for Medicare & Medicaid Services; ESRD, end-stage renal disease; HD, hemodialysis; KCQA, Kidney Care Quality Alliance; UFR, ultrafiltration rate.

[a]If more than 1 Kt/V is drawn in a given month, the last draw for the month will be used to define the data collection period (ie, these data elements will be collected during the week that the final Kt/V value of the month is drawn).

symptoms of volume overload if fluid is not removed in a timely fashion. If no changes are made in the frequency or duration of dialysis sessions, high IDWG will require a high UFR during a given hemodialysis session. For example, IDWG of 3.5 L in a 60-kg patient removed over a 4-hour dialysis session results in a UFR of 14.6 mL/kg/h. Thus, the UFR and IDWG are interdependent.

HISTORICAL CONTEXT OF DIALYSIS TREATMENT TIME DETERMINATION

Dialysis treatment time is a critical factor in determining the rate of fluid removal, but has varied dramatically over the history of dialysis. In the 1960s, patients generally dialyzed once a week after the onset of uremia.[9] During the ensuing decade, dialysis time gradually lengthened from 12 hours per session twice weekly to more than 20 hours per session twice weekly, with the goal of controlling hypertension and reducing the progression of peripheral neuropathy. In the early 1970s, the nephrology community suggested that patients weighing at least 60 kg required a minimum of 18 hours per week of dialysis using coil dialyzers and that dialysis thrice weekly led to less neuropathy.[9,10] Of note, these practices were based entirely upon observation, anecdote, and opinion, with no clinical trial data to support them.

The conflict between dialysis treatment time and efficiency was examined in the NCDS. The NCDS evaluated the effect of both dialysis treatment time and efficiency, defined by small-molecule clearance, using a 2×2 factorial randomized trial design in 151 participants with 12 months' planned follow-up. A total of 151 patients from 9 dialysis units were randomly assigned to 2 average urea concentration arms (achieved by varying dialyzer sizes and flow rates) and either 3-times-per-week short (2.5-3.5 hours) or long (4.5-5 hours) dialysis sessions.[2] The study was brought to an end early because of a higher rate of hospitalizations in the group randomly assigned to higher average urea concentrations. Overall mortality was low, with no difference in mortality rates noted between the 2 urea concentration groups. The association between allocation to a longer dialysis treatment time and morbidity did not reach statistical significance ($P = 0.06$), potentially reflecting limited statistical power.

After completion of the NCDS, the concept of Kt/V emerged as the primary measure of hemodialysis adequacy.[11] The definition of Kt/V is clearance of urea multiplied by dialysis session duration divided by volume of distribution of urea in the body, with correction factors introduced for urea generation during dialysis and for volume and urea lost through ultrafiltration. With the assumption that uremia reflects the accumulation of organic waste products, mostly small molecules that are normally cleared by the kidneys, this easily quantifiable measure of dialysis small-molecule clearance supplanted clinical symptoms such as hypertension and peripheral neuropathy as the principal determinant of dialysis session duration. Instead, hemodialysis adequacy was now predicated on achieving a specified Kt/V or the simpler urea reduction ratio.[11] With the development of larger, more efficient, and less expensive hemodialysis membranes, target Kt/Vs became readily achievable, even in the setting of relatively short session lengths. The HEMO Study evaluated whether higher target Kt/V would be associated with better outcomes, randomly assigning 1,846 patients receiving maintenance hemodialysis to either high- or standard-dose dialysis and to a high- or low-flux dialyzer using a 2×2 factorial design.[3] The HEMO Study did not specifically examine dialysis treatment time. Overall, no significant difference in mortality was noted between the high-dose versus standard-dose group (single-pool Kt/Vs of 1.65 and 1.25, respectively; hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.84-1.10) or in the high-flux versus low-flux group (HR, 0.92; 95% CI, 0.81-1.05).[3]

Shorter session length has advantages. For patients, less time is required to be spent in the hemodialysis facility; and for providers, more patients can be treated in a fixed time. Given that hemodialysis in the United States is reimbursed based on the number of treatment sessions without regard to duration of these sessions, shorter session lengths may have substantial economic benefits for providers. Nevertheless, some experts have recommended that hemodialysis session duration should continue as a measurement of treatment adequacy.[12]

INITIAL CLINICAL GUIDELINES AND TREATMENT TRENDS

The debate of hemodialysis time versus adequacy assessed using urea nitrogen clearance (Kt/V or urea reduction ratio) was discussed in the first NKF-DOQI guideline ("Hemodialysis and Peritoneal Dialysis Adequacy and Vascular Access") published in 1997.[1] This initial guideline established the necessity of measuring the dose (small-molecule clearance) of dialysis in all long-term dialysis patients, but consensus was not reached regarding the minimum time for a dialysis treatment session.[1] The 2006 NKF-KDOQI guideline on dialysis adequacy suggested a minimum of 3 hours of treatment time per session or 9 hours per week for patients with low (<2 mL/min) residual kidney function, but also acknowledged the lack of clinical trial data supporting any minimum standard for dialysis session length.[7] In contrast, the European Best Practice Guidelines for Hemodialysis published in 2002 stated that the standard minimum

hemodialysis dose should be delivered as three 4-hour sessions per week and that session length and/or frequency should be extended in patients with hemodynamic instability.[13] This statement was supported by B level evidence, reflecting the limited clinical trial data for hemodialysis session duration and patient outcomes.

Potentially reflecting economic factors, patient preferences, improved dialysis membranes, and the clinical guidelines, the percentage of US patients with session lengths less than 3 hours initially trended downward from 37.2% in 1997 to 28.4% in 2006. Interestingly, since 2006, the proportion of patients with session lengths less than 3 hours has trended upward, although overall average session length remains less than 4 hours (Fig 1).[14] Although practice patterns vary widely within the United States, clinical data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) through 2011 reveal that average US dialysis session lengths are lower than in all other industrialized countries participating in the DOPPS (Fig 1), with these lower session lengths posited as one cause for higher mortality rates among US dialysis patients.[15-17]

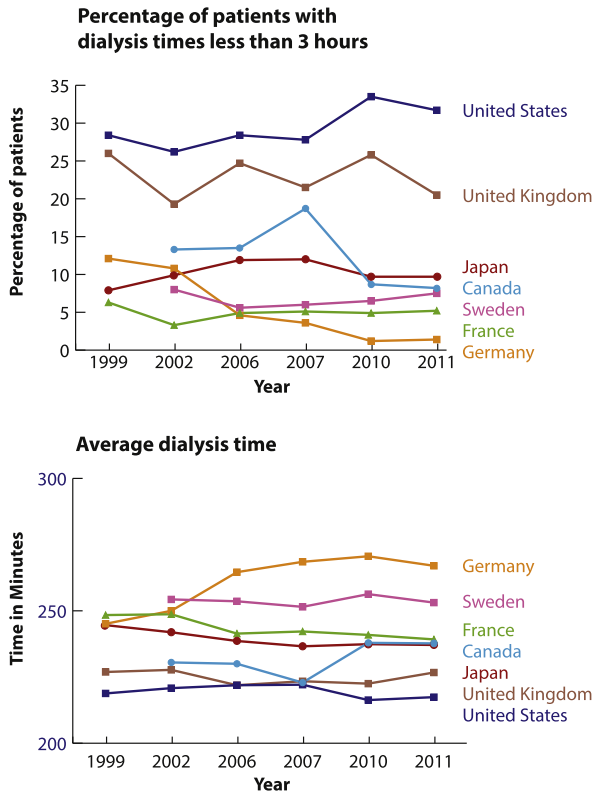

Figure 1. (Top) Percentage of patients with session length less than 3 hours and (bottom) average dialysis session length, by year and by nation. Data for Sweden and Canada are not available for 1999. Data from the Dialysis Outcomes and Practice Patterns Survey (www.dopps.org).

SESSION DURATION

By definition, higher IDWG and shorter dialysis session length require higher UFRs to achieve any desired postdialysis weight. Notably, higher UFRs have been associated with increased mortality.[17-19] In a secondary analysis of the HEMO Study, the risk for cardiovascular and all-cause mortality increased sharply with UFRs between 10 and 14 mL/kg/h as compared to UFRs < 10 mL/kg/h.[18] Consequently, in this analysis, UFR was stratified into $\leq$10, 10 to 13, and $>$13 mL/kg/h groups. Individuals with UFRs > 13 mL/kg/h had a mean UFR of 16.8 ± 3.6 (standard deviation) mL/kg/h and mean IDWG of 3.6 ± 1.0 L, whereas individuals with UFRs ≤ 10 mL/kg/h gained a mean of 2.1 ± 10.9 L between dialysis sessions. Average session length differed significantly among UFR groups: the $>$13-mL/kg/h group, 209 minutes; 10- to 13-mL/kg/h group, 220 minutes; and $<$10-mL/kg/h group, 226 minutes ($P < 0.001$).

The highest UFR group in the HEMO Study had a higher percentage of participants with heart failure (44% vs 37% in the other groups). The presence of heart failure at baseline in the HEMO Study modified the association between UFR and mortality, such that UFRs of 10 to 13 mL/kg/h were associated with increased all-cause mortality and almost associated with increased cardiovascular mortality in patients with heart failure, but were not associated with mortality in patients without heart failure. UFR $>$ 13 mL/kg/h was associated with heightened mortality regardless of heart failure status. Notably, the greater risk for mortality associated with higher UFRs in the HEMO Study was independent of IDWG, residual urine output, and dialysis vintage. Although residual kidney function could confound these results, only one-third of HEMO Study participants had residual urea clearance above zero, and mean dialysis vintage among HEMO Study participants was 3.7 ± 4.4 years.

These findings from the HEMO Study data are supported by observations in an Italian cohort of adult maintenance hemodialysis patients followed up for approximately 4 years, in which mortality increased linearly at UFRs > 12.4 mL/kg/h.[19] Notably, all observational studies showing an association between higher UFRs and increased mortality risk are susceptible to residual confounding due to unmeasured variables. For example, patients with high IDWGs and high UFRs may also have poor adherence to medications and dietary advice and/or poor social support, factors that are difficult to measure and may influence mortality risk. In addition, the few studies showing an association between UFRs and mortality risk relied on observed UFR and not prescribed UFR.[18,19]

The heightened mortality risk noted with higher UFRs may be due to reductions in myocardial blood flow during hemodialysis sessions with large volume removal.[20,21] Repeated episodes of regional cardiac ischemia can lead to myocardial fibrosis, diastolic dysfunction, and clinical heart failure[22] and theoretically can heighten risk for arrhythmias and sudden death.[20,23-26] Serial echocardiograms in 30 patients with a history of hemodialysis-induced myocardial ischemia were performed to assess fixed changes in systolic dysfunction over time. After 12 months, 19 patients showed fixed systolic function declines $> 60\%$.[23] Assa et al[27] completed echocardiograms before a dialysis session, after 60 and 180 minutes of a dialysis session, and then again at 30 minutes postdialysis in 105 patients receiving maintenance hemodialysis. Regional left ventricular systolic dysfunction, defined as an escalation in wall motion scores in 2 or more segments, occurred in 27% of patients, with most events occurring within 1 hour of a dialysis session. However, in these observational studies, UFRs did not differ among patients with and without fixed systolic function decline[23] or regional wall motion changes.[27] Increasing the frequency or duration of dialysis sessions and reducing the dialysate temperature along with biofeedback dialysis have been shown to reduce the frequency of myocardial stunning among patients receiving maintenance dialysis,[28-30] but no study to date has demonstrated that UFR limits mitigate reductions in myocardial perfusion or other cardiovascular outcomes during hemodialysis.

UFR LIMITS AS A CLINICAL PERFORMANCE MEASURE

The observation that high UFR may represent a risk factor for patient mortality prompted the initial 2010 CMS Technical Expert Panel charged with establishing metrics for the ESRD Quality Improvement Program (QIP) to explore volume management measures as a potential metric of dialysis quality.[31] One proposed metric emerging from this panel assessed the proportion of patients with UFRs $\geq$ 15 mL/kg/h at the treatment session when Kt/V was measured for the reporting month, whereas others included documented periodic assessment of dry weight and other process measures. Although consensus was reached among panel members, initial efforts to include fluid management metrics in the QIP were unsuccessful due to the lack of community-wide consensus regarding the definition of fluid overload, limited enthusiasm for potential process measures such as updating the estimated dry weight, and concerns that the proposed measure could not be readily manipulated.

In March 2013, the Chief Medical Officer Initiative convened the chief medical officers of the 14 largest US dialysis providers to meet and discuss ways to improve clinical outcomes for dialysis patients. The leaders participating in that meeting uniformly agreed that despite its absence in any existing quality metric at that time, optimizing extracellular fluid status was a critical element of dialysis care and that in many ways, optimal volume control was equally important to solute clearance in determining adequate dialysis.[32] One key concordance from this initiative was that fluid removal should be gradual. Similarly, following a modified Delphi process in which the kidney community was surveyed regarding the most important element of dialysis care that remained unincorporated in the QIP, Kidney Care Partners, a coalition of care providers, nephrology professionals and professional societies, manufacturers, and patient and patient advocate groups that include the NKF,[33] charged the KCQA with developing a metric that addressed volume management in hemodialysis. Following review of existing data and specification testing using data from 3 of the largest US dialysis providers, KCQA developed and validated an ultrafiltration metric that assessed the percentage of patients receiving thrice-weekly in-center hemodialysis with an average UFR $\geq$ 13 mL/kg/h and session duration less than 240 minutes. This proposed measure incorporates UFR and dialysis session duration for all 3 treatments completed during the week of the monthly clearance assessment. The KCQA-developed UFR measure was endorsed by the National Quality Forum in 2015, but to date has not been recommended by CMS as a clinical performance measure for dialysis facilities.[34]

The potential use of UFR thresholds as a quality metric recounts the 1997 NKF-DOQI hemodialysis adequacy guideline that recommended avoidance of excessive UFR and use of low UFRs for patients who incur intradialytic hypotension and/or cramps. However, in that guideline, no ideal UFR was identified or specified. Ultrafiltration and IDWG were addressed again in the 2006 NKF-KDOQI clinical practice guideline for dialysis adequacy, with emphasis on the importance of fluid removal and treatment time. Guideline 5 stated that the "ultrafiltration component of the hemodialysis prescription should be optimized with a goal to render the patient euvolemic and normotensive."[7] Poor volume control was recognized as a major contributor to morbidity and mortality, but no upper threshold for optimal UFR was identified. This guideline discussed the variability in ultrafiltration tolerance among patients and stated that a slow approach to achieving dry weight was suitable for most patients. However, the 2006 guideline also suggested that patients with heart failure or severe hypertension might require more aggressive ultrafiltration and pointed out the lack of standards for monitoring extracellular volume.[7]

The 2015 NKF-KDOQI guideline for dialysis adequacy emphasized a need to look beyond standard measures of dialysis adequacy such as Kt/V in order to determine whether dialysis was meeting the needs of an individual patient. This guideline supported previous recommendations for a 3-hour minimum session length for patients with residual kidney function <2 mL/min, again without delineating a specific UFR limit.[4] It stated that the UFR for each dialysis session should allow an optimal balance for attaining euvolemia, blood pressure control, and solute clearance while also minimizing hemodynamic instability and patient symptoms.[4] The Renal Association, a professional society of nephrologists and renal scientists in the United Kingdom, suggested limiting UFR to 10 mL/kg/h based on the observation that UFRs exceeding this threshold are associated with higher morbidity and mortality.[18] The Renal Association also endorsed using the percentage of patients with UFRs > 10 mL/kg/h as an audit measure for dialysis units.[35]

IMPLICATIONS OF A DIALYSIS FACILITY UFR QUALITY MEASURE

Implementation of UFR limits will require increased efforts for patients, clinicians, and staff, with strong emphasis placed on reducing IDWG in patients with high UFRs. A common practice for controlling IDWG not supported by randomized clinical trial data is instructing patients to limit fluid intake to < 1 L/d regardless of body weight. Given the distribution of body water and the fact that high sodium intake stimulates thirst, sodium restriction is likely much more effective for limiting IDWG and preventing volume overload.[36,37] Unfortunately, many patients receiving maintenance hemodialysis live in poor communities with limited access to nonprocessed healthy foods.

Dialysate sodium exposure may also be an area to target for patients with volume overload and/or high IDWG.[36] The average dialysate sodium concentration has increased from an approximate average of 135 mEq/L during the 1970s to 140 mEq/L today.[38] Although higher dialysate sodium exposure minimizes changes in plasma osmolality during dialysis, it may also increase IDWG.[38-41] Intradialytic hypotension and cramping is sometimes addressed with sodium profiling, whereby the nephrologist prescribes a supraphysiologic dialysate sodium concentration with a gradual or stepwise decline in the dialysate sodium concentration over the treatment session. Although sodium modeling may improve plasma refilling and reduce risk for intradialytic hypotension and cramping, sodium profiling that leads to an overall net sodium gain may exacerbate thirst during the intradialytic period and increase IDWG.[42] Sodium profiling may also be structured to achieve a neutral sodium balance, with the postdialysis plasma sodium level being equivalent to the predialysis plasma sodium level.[42,43] When combined with ultrafiltration that decreases over the dialysis session length (ultrafiltration profiling), sodium balance–neutral sodium profiling decreases the risk for intradialytic hypotension while increasing the ability to achieve an ultrafiltration goal in patients prone to intradialytic hypotension.[41,44,45] A personalized approach to sodium modeling may also be useful to reduce IDWG by individualizing the dialysate sodium concentration to the patient's plasma sodium level.[46,47] Although existing trials addressing sodium-neutral sodium modeling with and without ultrafiltration modeling and personalized sodium profiling demonstrate beneficial effects on IDWG, ultrafiltration goals, and blood pressure, [41,42,44-47] more and larger studies representing the diverse demographics of the US population are needed to determine optimal approaches for the dialysate composition to curtail IDWG and help patients achieve a euvolemic state. Additionally, more reliable measures of delivered dialysate composition may be necessary to optimally tailor dialysate sodium concentration to individual patients.[48] More studies are also needed to determine best strategies for not only reducing sodium intake but also for maintaining a reduced sodium intake. Such studies should include a diverse dialysis population, including patients with limited access to healthy foods.

When strategies for mitigating high IDWG fail, hemodialysis treatment time must be extended to prevent a high UFR, and this may be accomplished by increasing the duration or frequency of treatment sessions. In a survey of 588 patients receiving maintenance hemodialysis in 18 dialysis units across the United States, 44.6% of respondents were willing to extend their session lengths by 15 minutes. However, willingness to extend treatment time was dependent on the liberalization of fluid intake. Only 12.2% of patients were willing to add a fourth treatment per week, and only 13.5% were willing to accept nocturnal dialysis.[49] Increasing hemodialysis treatment time may also be constrained by the number of hemodialysis shifts within an individual facility and the number of available staff. Thus, the costs of implementing UFR as a clinical performance measure could include additional hemodialysis staff, reduction in the total number of patients treated per day, and additional use of water and other utilities. However, the potential costs associated with UFR limitations as a clinical performance measure remain unquantified.

Whether extending dialysis time affects outcomes and quality of life is currently being addressed in the Cluster-Randomized, Pragmatic Trial of Hemodialysis

Session Duration (TiME; ClinicalTrials.gov study number NCT02019225). TiME is evaluating whether a minimum session length of 4.25 hours thrice weekly versus usual care is associated with lower mortality, fewer hospitalizations, and improved health-related quality of life among incident hemodialysis patients. This trial is a collaborative research effort between the National Institutes of Health and 2 large dialysis organizations in the United States: DaVita and Fresenius Medical Care North America. The ACTIVE (A Clinical Trial of Intensive) Dialysis Study (ClinicalTrials.gov study number NCT00649298) is a multicenter randomized trial of extending maintenance hemodialysis treatment time to 24 hours per week or longer versus the standard of 12 to 18 hours per week for 12 months.[50] Overall, 200 patients receiving maintenance dialysis in Australia (29.0%), China (62.0%), Canada (5.5%), and New Zealand (3.5%) were enrolled, with the primary outcome being patient quality of life. Secondary outcomes comprise change in left ventricular mass index assessed by magnetic resonance imaging and dialysis access events. The ACTIVE Dialysis Study has been completed, but the full results have not yet been published. Information from TiME and the ACTIVE Dialysis Study may help determine whether increasing dialysis treatment time improves outcomes for patients receiving maintenance hemodialysis.

DRY WEIGHT

Achieving a euvolemic state remains a primary goal of hemodialysis treatments and is equated with the achievement of a person's dry weight. The definition of dry weight has changed over time. In 1967, Thomson et al[51] defined dry weight as the weight at which further fluid removal leads to hypotension. The 1997 NKF-DOQI guideline strongly discouraged using hypotension at end of dialysis as an indicator of estimated dry weight and discussed the impact of intradialytic hypotension and cramps on an individual's ability to complete hemodialysis treatments.[1] However, more recent definitions state that dry weight should be defined as the lowest tolerated postdialysis weight, with minimal hypovolemia symptoms that can be achieved by a gradual change in postdialysis weight.[36,52] Although more studies are needed, the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) Study elegantly demonstrated the importance of volume control to achieve blood pressure control, including blood pressure assessed outside of dialysis. The DRIP trial also showed that quality of life did not differ between patients with and without their dry weight probed.[53] Focusing on UFR rates solely, rather than achievement of a euvolemic state, ignores the fact that some patients who are volume overloaded do not have high IDWG.[36,38,54] In this regard, the lack of a gold standard to reliably assess dry weight remains a major impediment to achieving a euvolemic state in patients receiving maintenance hemodialysis.[32]

Table 2 lists potential methods for assessing extracellular volume to manage ultrafiltration needs. No current method can accurately pinpoint an individual patient's dry weight, and the majority of clinicians rely on physical examination findings, which are highly insensitive for detection of a volume-overloaded state.[55-57] Existing studies suggest that bioimpedance, lung ultrasonography, and relative plasma volume monitoring can help guide ultrafiltration goals and improve overall volume status and blood pressure.[58-62] Inferior vena cava diameter measures show measurable and consistent change in response to probing dry weight among patients receiving maintenance dialysis. However, the change in inferior vena cava diameter does not correlate with blood pressure responses to reductions in postdialysis

Table 2. Current Methods for Assessing Extracellular Volume in Patients Receiving Maintenance Hemodialysis

Indicator	Pros	Cons	References
Physical examination	No equipment needed	Low sensitivity	55-57
Postdialysis hypotension	No equipment needed	Increased mortality risks, cramping, early dialysis termination	76-78
Bioimpedance	Available, validated in many different patient populations	Requires equipment, cost, training	58-60, 79, 80
Vena cava diameter	Available	Requires equipment, cost, training; may be operator dependent; lack of normative data for patient size	63, 81, 82
Brain natriuretic peptide	High plasma levels associated with volume overload	Influenced by cardiac disease, intradialytic removal, and fistula blood flow	83, 84
Blood volume monitoring	Low intraindividual variability	Lack of standards to predict hypotension, not widely available	62, 85
Lung ultrasound	Detection of pulmonary congestion predicts mortality	Requires equipment and training; clinical trials ongoing; mainly sensitive for volume overload and not for determining dry weight	58, 74

weight.[63] Larger studies of diverse populations are needed to determine the optimal measure of extracellular fluid status and the best method for implementing extracellular fluid status measures in clinical practice for the prevention of high UFRs and achieving euvolemic states in patients receiving maintenance dialysis.

VOLUME OVERLOAD, HYPERTENSION, AND HEART FAILURE

Although controversy surrounds the optimal blood pressure targets for patients receiving maintenance hemodialysis,[64,65] maintaining interdialytic blood pressure at <140/90 mm Hg has been suggested as a reasonable goal for patients receiving maintenance hemodialysis.[66] Because blood pressure control among most patients receiving maintenance hemodialysis is largely volume dependent,[67,68] achieving this blood pressure goal requires more aggressive ultrafiltration for many patients.[69] However, if a short-term UFR threshold impedes the ability to obtain a euvolemic state in patients with high IDWG, fluid overload and blood pressure increase, requiring a higher number of antihypertension medications. This polypharmacy may have important consequences, including cost and drug-drug interactions.

Long-term volume overload also increases the risk for heart failure and mortality.[70-72] Heart failure and fluid overload are among the most common reasons for hospitalization among maintenance hemodialysis patients. Arneson et al[73] analyzed the total cost of hospitalization care for volume overload in 176,790 patients receiving maintenance hemodialysis over an average of 2 years. Among the 25,291 patients with claims data meeting criteria for volume overload, the total cost for hospitalizations and emergency department care during this period exceeded US $260 million.[73] Volume overload is also associated with heightened risk for mortality. Among 269 hemodialysis patients with an average dialysis vintage of 41.2 months, a 2.5-L extracellular water excess assessed by body composition monitor was associated with a 2-fold higher mortality rate over a 3.5-year follow-up.[71] Similarly, using lung ultrasound, Zoccali et al[74] showed that very severe pulmonary congestion was associated with a 4.2-fold higher (95% CI, 2.45-7.23) risk for death among 392 patients receiving maintenance hemodialysis in Italy. Aside from heart failure and hypertension, long-term volume overload may also impair pulmonary function and increase the risk for pulmonary hypertension, a condition that may go unrecognized in many patients and that is associated with high mortality risk.[75]

Critically, an ultrafiltration metric cannot exist in isolation, but rather would be considered as one metric among many that are applied to dialysis facilities, and the interplay among these metrics could provide important information. For example, if in striving to meet an ultrafiltration threshold, patients have more cramping or are compelled to undergo longer hemodialysis sessions, their satisfaction with the dialysis facility may decrease, resulting in lower In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) scores. In contrast, if facilities increase the estimated dry weight to meet an ultrafiltration threshold, volume overload may occur more often, resulting in increased deaths, hospitalizations, and hospital readmissions.

Nonclinical issues should also be considered before implementing a UFR limitation as a clinical performance measure. First, the current UFR measure suggested by the KCQA indexes UFR to body weight. Patients with lower body weight will have a higher UFR for a given IDWG compared with larger patients. Use of one UFR threshold for all patients regardless of body size will differentially affect hemodialysis units. Units with a large percentage of patients with low body weight, such as older women, frail and elderly patients, and patients with Asian or Hispanic background, will likely have a higher percentage of UFRs > 13 mL/kg/h and session lengths less than 240 minutes compared with units with a high percentage of young and male patients. Second, UFR depends on IDWG, which is highly variable across time. For example, UFRs are typically highest at the first dialysis session of the week due to the long weekend; IDWG is also affected by season, holiday, and other family celebrations that occur throughout a year. Averaging the UFR over the week that Kt/V is reported may not allow flexibility for the inherent variability in patient IDWG. It also remains unknown whether UFR limits should be based on ideal, actual, or dry body weight. Tolerance of a given UFR in a lean and muscular 90-kg individual is likely to be different from one of the same weight with a much higher percentage of body fat and/or edema.

In summary, the unique payment structure for dialysis treatment in the United States has led to shorter dialysis session lengths requiring high UFRs in patients with large IDWGs. High UFRs are associated with increased mortality, and limiting UFRs has been proposed as a way to improve patient outcomes. If not properly implemented, it is also possible that a policy establishing a UFR limit could increase the risk for unintended consequences, including complications related to long-term volume overload such as increased blood pressure and heart failure. For many patients, increasing hemodialysis session length or adding additional sessions will be required to avoid high UFRs, an unpalatable prospect for many patients. Box 1 lists the research recommendations to enhance support for use of a UFR limitation as a

Box 1. Research Recommendations for UFR Thresholds as a Clinical Performance Measure

1. Identify optimal measures for assessing extracellular volume in patients receiving maintenance hemodialysis.
2. Develop effective methods to modify behaviors for reducing intradialytic weight gain and salt intake.
3. Determine the impact of implementing UFR limits (eg, ≥13 mL/kg/h) on hospital admissions, readmissions, and mortality.
4. Quantify the impact of UFR limits (eg, ≥13 mL/kg/h) on blood pressure, blood pressure control, and number of antihypertension medications prescribed for patients receiving maintenance hemodialysis.
5. Determine whether indexing the UFR for measures such as body surface area or body mass index influences the association between UFR and patient outcomes.
6. Establish whether patients are willing to extend dialysis time to maintain UFRs < 13 mL/kg/h.
7. Examine whether the association between UFR and patient outcome differs by residual kidney function and whether UFR limits (eg, ≥13 mL/kg/h) affect loss of residual kidney function over time.
8. Quantify the financial impact of implementing UFR thresholds on hemodialysis units.
9. Determine appropriate risk adjusters and performance thresholds consistent with high-quality care based on a metric defining UFR limits (eg, ≥13 mL/kg/h).
10. Examine use of sodium profiling with and without ultrafiltration profiling for prevention of intradialytic hypotension, interdialytic weight gain, and patient outcomes.
11. Investigate the role of extracellular fluid status measures for determining UFR goals and achievement of dry weight and blood pressure goals.
12. Determine the optimal dialysate concentrations that minimize interdialytic weight gain, hospitalization rates, and mortality.

Abbreviation: UFR, ultrafiltration rate.

clinical performance measure. Currently, few studies have examined the effectiveness of behavioral modification programs and dialysate concentrations to minimize IDWG. With thrice-weekly hemodialysis, achievement and maintenance of a near-euvolemic state remains one of the most important and challenging goals. More studies are also needed to identify accurate and reliable methods to determine the extracellular volume status of a patient receiving maintenance hemodialysis and how these measures can be implemented into practice to optimize patient quality of life and overall survival. Identifying these gaps in knowledge may greatly improve the care of patients receiving maintenance hemodialysis and will help delineate the clinical implications of a UFR limitation as a clinical performance measure.

ACKNOWLEDGEMENTS

Dr Rocco is NKF-KDOQI Chair; Dr Kramer is NKF-KDOQI Vice Chair, Research and Commentaries; and Drs Scheel and Samaniego are Co-chairs, NKF-KDOQI Public Policy. Dr Berns is NKF President.

The authors thank Thomas Mattix for assistance with graphics.

Support: No institutional funding has been provided for this work.

Financial Disclosure: Dr Weiner was a member of the work group that developed the KCQA ultrafiltration measure and of the guideline work group for the 2015 updated NKF-KDOQI clinical practice guideline for hemodialysis adequacy. He receives research funding from Dialysis Clinic Inc, Boston, where he serves as Medical Director. Dr Berns has provided consultancy to Bayer and Amgen on the subject of anemia. Dr Choi acknowledges consultancy to the Glaxo Smith Kline-Data Monitoring Safety Board and Genentech Advisory Board. Dr Bansal is Medical Director at Loyola University Outpatient Dialysis Center. Dr Yee is Chief Medical Director at Greenfield Health Systems, Bingham Farms, MI. Dr Samaniego acknowledges research and speakers bureau grants from Alexion Pharmaceuticals and consultancy for Sanofi and Thermo-Fisher Corporation. The other authors declare that they have no relevant financial interests.

Peer Review: Evaluated by 3 external peer reviewers and an Acting Editor-in-Chief.

REFERENCES

1. National Kidney Foundation. DOQI clinical practice guidelines for hemodialysis adequacy. *Am J Kidney Dis*. 1997;30(3)(suppl 2):S15-S66.

2. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. *N Engl J Med*. 1981;305(20):1176-1181.

3. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*. 2002;347(25):2010-2019.

4. National Kidney Foundation. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis*. 2015;66(5):884-930.

5. Agar JW. Personal viewpoint: limiting maximum ultrafiltration rate as a potential new measure of dialysis adequacy [published online ahead of print March 16, 2015]. *Hemodialysis Int*. 2016;20:15-21.

6. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724-734.

7. NKF-KDOQI Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis*. 2006;48(suppl 1):S33.

8. National Kidney Foundation. I. K/DOQI clinical practice guidelines for hemodialysis adequacy: update 2000. *Am J Kidney Dis*. 2001;37(1)(suppl 1):S7-S64.

9. Blagg CR. The early history of dialysis for chronic renal failure in the United States: a view from Seattle. *Am J Kidney Dis*. 2007;49(3):482-496.

10. De Palma JR, Bolton CF, Baltzan MA, Baltzan RB. Adequate hemodialysis schedule. *N Engl J Med*. 1971;285(6):353-354.

11. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int*. 1985;28(3):526-534.

12. Capelli JP, Kushner H, Camiscioli T, Chen SM, Stuccio-White NM. Factors affecting survival of hemodialysis patients utilizing urea kinetic modeling. A critical appraisal of shortening dialysis times. *Am J Nephrol*. 1992;12(4):212-223.

13. European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section II. Haemodialysis adequacy. *Nephrol Dial Transplant*. 2002;17(suppl 7):16-31.

14. Arbor Research Collaborative for Health. Dialysis Outcomes and Practice Patterns Study annual report 2012.

http://www.dopps.org/annualreport/html/qdialduration_US2011.htm. Accessed December 9, 2015.

15. Tentori F, Zhang J, Li Y, et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2012;27(11):4180-4188.

16. Brunelli SM, Chertow GM, Ankers ED, Lowrie EG, Thadhani R. Shorter dialysis times are associated with higher mortality among incident hemodialysis patients. *Kidney Int*. 2010;77(7):630-636.

17. Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int*. 2006;69(7):1222-1228.

18. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int*. 2011;79(2):250-257.

19. Movilli E, Gaggia P, Zubani R, et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. *Nephrol Dial Transplant*. 2007;22(12):3547-3552.

20. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol*. 2008;3(1):19-26.

21. Dasselaar JJ, Slart RH, Knip M, et al. Haemodialysis is associated with a pronounced fall in myocardial perfusion. *Nephrol Dial Transplant*. 2009;24(2):604-610.

22. Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev*. 1999;79(2):609-634.

23. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4(12):1925-1931.

24. Burton JO, Korsheed S, Grundy BJ, McIntyre CW. Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmias. *Ren Fail*. 2008;30(7):701-709.

25. Narula AS, Jha V, Bali HK, Sakhuja V, Sapru RP. Cardiac arrhythmias and silent myocardial ischemia during hemodialysis. *Ren Fail*. 2000;22(3):355-368.

26. Mohi-ud-din K, Bali HK, Banerjee S, Sakhuja V, Jha V. Silent myocardial ischemia and high-grade ventricular arrhythmias in patients on maintenance hemodialysis. *Ren Fail*. 2005;27(2):171-175.

27. Assa S, Hummel YM, Voors AA, et al. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. *Clin J Am Soc Nephrol*. 2012;7(10):1615-1623.

28. Selby NM, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. *Clin J Am Soc Nephrol*. 2006;1(6):1216-1225.

29. Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol*. 2011;6(6):1326-1332.

30. Selby NM, Lambie SH, Camici PG, Baker CS, McIntyre CW. Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. *Am J Kidney Dis*. 2006;47(5):830-841.

31. [No author given]. Arbor Research Collaborative for Health and University of Michigan Kidney Epidemiology and Cost Center. *Clinical and Data Technical Expert Panel Meetings Synthesis Report*. Bethesda, MD: Department of Health and Human Services, Centers for Medicare and Medicaid Services; 2010. https://www.cms.gov/Medicare/End-stage-renal-Disease/CPMProject/downloads/ESRD2010TechnicalExpertPanelReport.pdf. Accessed November 13, 2015.

32. Weiner DE, Brunelli SM, Hunt A, et al. Improving clinical outcomes among hemodialysis patients: a proposal for a "volume first" approach from the chief medical officers of US dialysis providers. *Am J Kidney Dis*. 2014;64(5):685-695.

33. [No author given]. Kidney Care Partners. http://kidneycarepartners.com/about-kcp/. Accessed December 1, 2015.

34. Zumoff R. National Quality Forum endorses ultrafiltration measure for dialysis patients. Nephrology News and Issues. December 8, 2015. http://www.nephrologynews.com/national-quality-forum-endorses-ultrafiltration-measure-for-dialysis-patients/. Accessed December 8, 2015.

35. Mactier R, Hoenich N, Breen C. Renal Association guidelines-haemodialysis, 2009. http://www.renal.org/guidelines/modules/haemodialysis#s8. Accessed December 1, 2015.

36. Agarwal R, Weir MR. Dry-weight: a concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010;5(7):1255-1260.

37. Kayikcioglu M, Tumuklu M, Ozkahya M, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant*. 2009;24(3):956-962.

38. Munoz Mendoza J, Arramreddy R, Schiller B. Dialysate sodium: choosing the optimal hemodialysis bath. *Am J Kidney Dis*. 2015;66(4):710-720.

39. Davenport A, Cox C, Thuraisingham R; PanThames Renal Audit Group. The importance of dialysate sodium concentration in determining interdialytic weight gains in chronic hemodialysis patients: the PanThames renal audit. *Int J Artif Organs*. 2008;31(5):411-417.

40. Arramreddy R, Sun SJ, Munoz Mendoza J, Chertow GM, Schiller B. Individualized reduction in dialysate sodium in conventional in-center hemodialysis. *Hemodial Int*. 2012;16(4):473-480.

41. Song JH, Park GH, Lee SY, Lee SW, Lee SW, Kim MJ. Effect of sodium balance and the combination of ultrafiltration profile during sodium profiling hemodialysis on the maintenance of the quality of dialysis and sodium and fluid balances. *J Am Soc Nephrol*. 2005;16(1):237-246.

42. Stiller S, Bonnie-Schorn E, Grassmann A, Uhlenbusch-Korwer I, Mann H. A critical review of sodium profiling for hemodialysis. *Semin Dial*. 2001;14(5):337-347.

43. Sang GL, Kovithavongs C, Ulan R, Kjellstrand CM. Sodium ramping in hemodialysis: a study of beneficial and adverse effects. *Am J Kidney Dis*. 1997;29(5):669-677.

44. Zhou YL, Liu HL, Duan XF, Yao Y, Sun Y, Liu Q. Impact of sodium and ultrafiltration profiling on haemodialysis-related hypotension. *Nephrol Dial Transplant*. 2006;21(11):3231-3237.

45. de Vries PM, Olthof CG, Solf A, et al. Fluid balance during haemodialysis and haemofiltration: the effect of dialysate sodium and a variable ultrafiltration rate. *Nephrol Dial Transplant*. 1991;6(4):257-263.

46. Santos SF, Peixoto AJ. Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. *Clin J Am Soc Nephrol*. 2008;3(2):522-530.

47. de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. *Kidney Int*. 2004;66(3):1232-1238.

48. Gul A, Miskulin DC, Paine SS, et al. Comparison of prescribed and measured dialysate sodium: a quality improvement project. *Am J Kidney Dis*. 2016;67(3):439-445.

49. Flythe JE, Mangione TW, Brunelli SM, Curhan GC. Patient-stated preferences regarding volume-related risk mitigation strategies for hemodialysis. *Clin J Am Soc Nephrol*. 2014;9(8):1418-1425.

50. Jardine MJ, Zuo LI, Gray NA, et al. Design and participant baseline characteristics of 'A clinical trial of IntensiVE dialysis': the ACTIVE dialysis study. *Nephrology (Carlton)*. 2015;20(4):257-265.

51. Thomson GE, Waterhouse K, McDonald HP Jr, Friedman EA. Hemodialysis for chronic renal failure. Clinical observations. *Arch Intern Med*. 1967;120(2):153-167.

52. Sinha AD, Agarwal R. Can chronic volume overload be recognized and prevented in hemodialysis patients? The pitfalls of the clinical examination in assessing volume status. *Semin Dial*. 2009;22(5):480-482.

53. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension*. 2009;53(3):500-507.

54. Hecking M, Karaboyas A, Antlanger M, et al. Significance of interdialytic weight gain versus chronic volume overload: consensus opinion. *Am J Nephrol*. 2013;38(1):78-90.

55. Frank Peacock W, Soto KM. Current technique of fluid status assessment. *Congest Heart Fail*. 2010;16(suppl 1):S45-S51.

56. Wizemann V, Schilling M. Dilemma of assessing volume state–the use and the limitations of a clinical score. *Nephrol Dial Transplant*. 1995;10(11):2114-2117.

57. Agarwal R, Andersen MJ, Pratt JH. On the importance of pedal edema in hemodialysis patients. *Clin J Am Soc Nephrol*. 2008;3(1):153-158.

58. Siriopol D, Hogas S, Voroneanu L, et al. Predicting mortality in haemodialysis patients: a comparison between lung ultrasonography, bioimpedance data and echocardiography parameters. *Nephrol Dial Transplant*. 2013;28(11):2851-2859.

59. Moissl U, Arias-Guillen M, Wabel P, et al. Bioimpedance-guided fluid management in hemodialysis patients. *Clin J Am Soc Nephrol*. 2013;8(9):1575-1582.

60. Onofriescu M, Hogas S, Voroneanu L, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am J Kidney Dis*. 2014;64(1):111-118.

61. Weir MR. Relative plasma volume monitoring and blood pressure control: an overlooked opportunity to achieve dry weight in the hemodialysis patient. *Hypertension*. 2010;55(2):226-227.

62. Sinha AD, Light RP, Agarwal R. Relative plasma volume monitoring during hemodialysis aids the assessment of dry weight. *Hypertension*. 2010;55(2):305-311.

63. Agarwal R, Bouldin JM, Light RP, Garg A. Inferior vena cava diameter and left atrial diameter measure volume but not dry weight. *Clin J Am Soc Nephrol*. 2011;6(5):1066-1072.

64. Zager PG, Nikolic J, Brown RH, et al. "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int*. 1998;54(2):561-569.

65. Zoccali C. Arterial pressure components and cardiovascular risk in end-stage renal disease. *Nephrol Dial Transplant*. 2003;18(2):249-252.

66. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and management of hypertension in patients on dialysis. *J Am Soc Nephrol*. 2014;25(8):1630-1646.

67. Charra B, Chazot C. Volume control, blood pressure and cardiovascular function. Lessons from hemodialysis treatment. *Nephron Physiol*. 2003;93(4):94-101.

68. Vertes V, Cangiano JL, Berman LB, Gould A. Hypertension in end-stage renal disease. *N Engl J Med*. 1969;280(18):978-981.

69. Davenport A, Cox C, Thuraisingham R. Achieving blood pressure targets during dialysis improves control but increases intradialytic hypotension. *Kidney Int*. 2008;73(6):759-764.

70. Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. *Hypertension*. 2010;56(3):512-517.

71. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(5):1574-1579.

72. Fagugli RM, Pasini P, Quintaliani G, et al. Association between extracellular water, left ventricular mass and hypertension in haemodialysis patients. *Nephrol Dial Transplant*. 2003;18(11):2332-2338.

73. Arneson TJ, Liu J, Qiu Y, Gilbertson DT, Foley RN, Collins AJ. Hospital treatment for fluid overload in the Medicare hemodialysis population. *Clin J Am Soc Nephrol*. 2010;5(6):1054-1063.

74. Zoccali C, Torino C, Tripepi R, et al. Pulmonary congestion predicts cardiac events and mortality in ESRD. *J Am Soc Nephrol*. 2013;24(4):639-646.

75. Elsayed ME, Stack AG. What are the consequences of volume expansion in chronic dialysis patients? Pulmonary manifestations of volume expansion. *Semin Dial*. 2015;28(3):235-239.

76. Charra B, Laurent G, Chazot C, et al. Clinical assessment of dry weight. *Nephrol Dial Transplant*. 1996;11(suppl 2):16-19.

77. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int*. 2004;66(3):1212-1220.

78. Henderson G, Fahey T, McGuire W. Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge. *Cochrane Database Syst Rev*. 2007;4:CD004696.

79. Zhu F, Kuhlmann MK, Kotanko P, Seibert E, Leonard EF, Levin NW. A method for the estimation of hydration state during hemodialysis using a calf bioimpedance technique. *Physiol Meas*. 2008;29(6):S503-S516.

80. Kuhlmann MK, Zhu F, Seibert E, Levin NW. Bioimpedance, dry weight and blood pressure control: new methods and consequences. *Curr Opin Nephrol Hypertens*. 2005;14(6):543-549.

81. Brennan JM, Ronan A, Goonewardena S, et al. Handcarried ultrasound measurement of the inferior vena cava for assessment of intravascular volume status in the outpatient hemodialysis clinic. *Clin J Am Soc Nephrol*. 2006;1(4):749-753.

82. Chang ST, Chen CL, Chen CC, Lin FC, Wu D. Enhancement of quality of life with adjustment of dry weight by echocardiographic measurement of inferior vena cava diameter in patients undergoing chronic hemodialysis. *Nephron Clin Pract*. 2004;97(3):c90-c97.

83. Roueff S, Martin E, Chauffert ML, et al. Brain natriuretic peptide variations are linked to volume status in hemodialysis patients. *Clin Nephrol*. 2008;70(6):508-513.

84. Levin NW, Kotanko P, Eckardt KU, et al. Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes Controversies Conference. *Kidney Int*. 2010;77(4):273-284.

85. Javed F, Savkin AV, Chan GS, Mackie JD, Lovell NH. Recent advances in the monitoring and control of haemodynamic variables during haemodialysis: a review. *Physiol Meas*. 2012;33(1):R1-R31.