

The Use of a Multidimensional Measure of Dialysis Adequacy—Moving beyond Small Solute Kinetics

Jeffrey Perl, Laura M. Dember, Joanne M. Bargman, Teri Browne, David M. Charytan, Jennifer E. Flythe, LaTonya J. Hickson, Adriana M. Hung, Michel Jadoul, Timmy Chang Lee, Klemens B. Meyer, Hamid Moradi, Tariq Shafi, Isaac Teitelbaum, Leslie P. Wong, and Christopher T. Chan, and on behalf of the American Society of Nephrology Dialysis Advisory Group

Abstract

Urea removal has become a key measure of the intensity of dialysis treatment for kidney failure. Small solute removal, exemplified by Kt/V_{UREA} , has been broadly applied as a means to quantify the dose of thrice weekly hemodialysis. Yet, the reliance on small solute clearances alone as a measure of dialysis adequacy fails fully to quantify the intended clinical effects of dialysis therapy. This review aims to (1) understand the strengths and limitations of small solute kinetics as a surrogate marker of dialysis dose, and (2) present the prospect of a more comprehensive construct for dialysis dose, one that considers more broadly the goals of ESRD care to maximize both quality of life and survival. On behalf of the American Society of Nephrology Dialysis Advisory Group, we propose the need to ascertain the validity and utility of a multidimensional measure that moves beyond small solute kinetics alone to quantify optimal dialysis derived from both patient-reported and comprehensive clinical and dialysis-related measures.

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Introduction

Nephrologists have used Kt/V_{UREA} , removal targets as measures of dialysis treatment intensity for >30 years. Indeed, the US Centers for Medicare & Medicaid Services ESRD Quality Incentive Program includes Kt/V_{UREA} as a Dialysis Adequacy Comprehensive Clinical Measure. However, the dosing of dialysis encompasses more than achieving a certain threshold for the removal of urea, and should include other dosing parameters, such as dialysis duration, frequency, ultrafiltration volume and rate, and proper target weight assessment. The term “dialysis adequacy” has been expressed mostly to achieve the minimally acceptable Kt/V_{UREA} target, and has largely abandoned the importance of additional clinical measures among patients with ESRD. Indeed, the totality of dialysis adequacy should reflect measures that comprehensively aim to maximize the sum of survival, quality of life, cardiovascular outcomes, and other patient-related outcomes. On behalf of the American Society of Nephrology Dialysis Advisory Group, this review aims to explore the origins, available evidence, and limitations of urea removal as a measure of dialysis dose. Moreover, our group would like to advocate and renew the interest for a more multidimensional construct for the quantification and characterization of optimal dialysis.

Small Solute Kinetics: A Historical Perspective

In the 1960s, attempts to measure the effects of dialysis were focused on the function of the hemodialysis

membrane. However, the observation that patients on peritoneal dialysis (PD) had similar clinical results as patients on hemodialysis (HD) despite differences in blood concentrations of small molecules suggested that factors other than small molecule clearance might be important. This thinking was exemplified by the “square meter hour” hypothesis of Babb *et al.*, which may have represented the first attempt to relate the dose of dialysis to its effect on the patient (1). The study suggested that the size of the dialyzing membrane and number of hours on dialysis could influence adequacy of the therapy. Investigators in the 1970s sought alternative biochemical and physiologic measures of the effect of dialysis, exploring the effects of hemofiltration and hemodiafiltration as well as hemodialysis (2). The National Cooperative Dialysis Study (NCDS) attempted to examine the importance of dialysis time (with which larger molecule clearance was presumed to correlate) and small molecule removal on the incidence of nonaccess-related hospitalization (3). Number of hours on dialysis ($P=0.06$) barely missed the $P<0.05$ threshold of statistical significance in the analysis of time to first nonaccess hospitalization, and the importance of treatment time was subsequently glossed over by many clinicians and investigators for the next two decades.

Urea kinetic equations had been used to estimate clearance in the NCDS, and Gotch and Sargent’s mechanistic analysis of this study showed that Kt/V_{UREA} was a powerful predictor of outcome (4). Varieties of Kt/V and its proxy, the urea reduction ratio,

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Dr. Christopher T. Chan, 200 Elizabeth Street, 8N Room 846, University Health Network, Department of Medicine, Toronto General Hospital, Toronto, ON M5G 2C4, Canada. Email: christopher.chan@uhn.ca

dominated thinking about dialysis dose in the 1980s and 1990s. However, the primary analysis of the hemodialysis (HEMO) Study failed to show that increases in small molecule clearances within the confines of conventional (thrice weekly) hemodialysis treatment schedules in the United States had an effect on patient survival (5). This finding resurrected the notion that dialysis frequency and total treatment time might be important determinants of optimal dialysis, and that greater small solute clearances alone did not demonstrably affect patient outcomes on dialysis (6). Subsequently, indices of continuous clearance equivalents were developed to allow comparison of schedules at different frequencies, at least with respect to small molecule clearance (7). A prespecified secondary analysis of the HEMO Study suggested that scaling urea clearance by body surface area rather than by body water might be more informative, perhaps explaining the benefit of higher Kt/V observed among women (7).

Small Solute Kinetics in PD

The consistent demonstration of similar outcomes between patients on PD and conventional hemodialysis despite lower small solute clearances in PD itself suggests that small solute clearance may be an inappropriate metric to quantify the dose of PD. Small solute clearance in PD was adapted largely on the basis of work done in the hemodialysis population. Early studies on the effect of small solute clearance on PD survival suggested better outcomes with higher small solute clearance. A retrospective study of 68 patients on PD found improved survival with weekly Kt/V > 1.96 (8). Similarly, the Canada-USA (CANUSA) study demonstrated progressive improvement in survival as weekly (peritoneal+renal) Kt/V_{UREA} increased from 1.5 to 2.3, or as creatinine clearance (Ccr) (also peritoneal+renal) increased from 40 to 95 L/wk among incident patients on PD (9,10). In this study, each decrease of 0.1 unit Kt/V per week was associated with a 5% increase in the risk of death, and each decrease of 5 L/wk Ccr was associated with a 7% increase in the risk of death. A reanalysis of these data found the association between small solute clearance and survival to be entirely explained by small solute clearance associated with residual kidney function (RKF); once this was taken into account, there was no survival benefit with increase in peritoneal small solute clearance (10). Similarly, two large prospective randomized trials demonstrated no effect of increased peritoneal small solute clearance on mortality. In the ADEquacy of PD in MEXico (ADEMEX) study, increasing weekly peritoneal Kt/V from 1.62 to 2.13 (weekly Ccr from 46.1 to 56.9) had no effect on mortality (relative risk, 1.00 95% confidence interval (CI), 0.8 to 1.24) (11,12). In a study from Hong Kong, patients were randomized to one of three groups for total weekly Kt/V urea: 1.5–1.7, 1.7–2.0, or >2.0. Patients in the group with the lowest Kt/V were more likely to be withdrawn from the study by their physicians on clinical grounds. However, mortality was equivalent in the three groups (12). Thus, no firm “floor” of a minimum Kt/V necessary for survival could be established. In contrast, a retrospective analysis of an administrative database of anuric patients on PD in the United States demonstrated increased mortality in patients with Kt/V < 1.7. Yet, as in the

ADEMEX and Hong Kong studies, there was no effect of increasing weekly Ccr from <50 to >60 L/wk, and there was no survival benefit as Kt/V increased to >2.0 (13). Thus, no clear relationship emerges between small solute clearance and survival in PD.

The Notion of Biochemical Adequacy

Conventional thrice weekly hemodialysis inherently causes fluctuation and shifting of solutes, and intracellular and extracellular fluid. Studies performed over the last three decades have found associations between pre-, intra-, and post-dialysis blood concentrations of multiple solutes and various morbid outcomes, such as mortality and cardiovascular end points. Common to these observational studies, the notions of wide fluctuations in solutes and the inability to remove appropriate amounts of retention toxins are the recurring themes highlighting the inadequacy of intermittent conventional dialysis modalities, which are illustrated herein by potassium (small solute), phosphate (small-to-middle solute), and middle molecular weight uremic toxins.

Potassium

Patients with ESRD depend on dialysis to maintain normal electrolyte concentrations. Structural cardiac changes and ischemic heart disease make them more vulnerable to acute arrhythmogenic triggers. Sudden cardiac death causes about half of all dialysis cardiovascular-related mortality. One of several studies found increased risk of sudden cardiac death during hemodialysis to have a U-shaped association with predialysis serum potassium concentrations: lowest risk at 5 mEq/L and higher risk with both higher and lower serum potassium levels (14,15). The same relationship holds true among patients on PD (16). A larger population-attributable risk is associated with hyperkalemia in hemodialysis, and with hypokalemia in PD, corresponding to the prevalence of these disorders in the two modalities.

CKD-Associated Mineral Bone Disorders

ESRD is associated with bone disease, vascular calcification, and calcific uremic arteriolopathy. Elevated phosphate concentration has been associated with increased mortality, progression of vascular calcification, and hyperparathyroidism (17). No intervention studies show that phosphate control improves survival, in part because placebo-controlled trials are considered inconsistent with the current standard of care (18), and phosphate concentration normalization has become an important surrogate outcome in dialysis patient care. Most phosphate is intracellular, with only a small amount easily removable by dialysis, particularly during shorter hemodialysis treatment times. Early control of secondary hyperparathyroidism is associated with the avoidance of a future parathyroidectomy (19). For CKD stage 5D, current Kidney Disease Improving Global Outcomes guidelines recommend measuring serum calcium and phosphorus every 1–3 months, and parathyroid hormone every 3–6 months. In CKD stages 4–5D, serum alkaline phosphatase should be measured every 12 months, or more frequently in the presence of elevated parathyroid hormone (20).

Middle Molecules

Uremic toxins are solutes that accumulate in kidney failure and have harmful effects. The European Uremic Toxin Working Group now classifies these solutes as small water-soluble or lipid- or protein-bound, or larger solutes (so-called middle molecules) (21). The extent of middle molecule accumulation will also depend on the presence and degree of RKF (21). Middle molecules are solutes with a molecular mass >500 Daltons; several randomized controlled trials have compared renal replacement modalities differing in middle molecule removal, including use of high rather than low flux dialyzers, and hemodialysis rather than hemodiafiltration. Both the HEMO Study (22) and the Membrane Permeability Outcome (MPO) Study (23) compared high to low flux hemodialysis. Neither found a difference between groups in all-cause mortality or cardiovascular events, despite greater middle molecule clearances with high flux hemodialysis. However, in the presence of either longer vintage (>3.7 years) or preexisting cerebrovascular disease, high flux dialysis was associated with a survival benefit for HEMO Study participants. In addition, enhanced β -2 microglobulin (β 2M) clearance (3 ± 7 ml/min [low flux] versus 34 ± 11 ml/min [high flux]) may reduce late amyloid deposition. High flux dialysis was associated with a survival benefit for the subset of MPO Study participants having lower albumin (<4 g/dl). The CONvective TRANsport Study (CONTRAST) Study found better β 2M clearance with hemodiafiltration than with low flux hemodialysis, but no differences in survival (24). The Turkish OL-HDF Study (TURKISH) Study found similar survival with high flux hemodialysis and hemodiafiltration (25). In both the CONTRAST and TURKISH studies, large volumes of hemodiafiltration replacement fluid were associated with longer survival. Despite hypothesis-generating suggestions of benefit in subgroup analyses, the overall results of these trials were neutral. Further prospective studies are required to substantiate a role for measuring middle molecules on a regular basis in clinical practice (5).

The Importance of Time for Solute Clearance

The removal of uremic retention solutes is directly related to the duration of dialysis (26). Dialysis time is of particular importance for large solutes, such as β 2M, and sequestered solutes, such as phosphate (27). With the development of more efficient dialyzers in the 1980s and the increased focus on reduction of urea, a small, readily dialyzable solute, as the indicator of dialysis adequacy, the typical dialysis session length decreased from 6–8 to 2.5–4 hours (28). More recently, several large observational studies have found an association between longer dialysis session duration and lower mortality risk (29–31); however, reduced mortality with longer dialysis time is not evident in all such analyses (32), and an effect of dialysis time on mortality has not yet been established in a sufficiently powered randomized trial. Increased dialysis time may have contributed to the benefit of daily dialysis on the important surrogate outcome, left ventricular mass index (LVMI): in the Frequent Hemodialysis Network (FHN) Trial, the total weekly time was greater with dialysis 6 times/wk than with 3 times/wk, but the relative contributions of increased solute clearance and lower ultrafiltration rate

resulting from increased dialysis time is not known (25). Increased dialysis time is being evaluated by the Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial, an ongoing cluster-randomized pragmatic trial of 4.25 hour hemodialysis sessions (Clinicaltrials.gov identifier: NCT02019225). However, like the FHN intervention, the TiME trial intervention is expected to reduce ultrafiltration rate in addition to increasing solute clearance. Patients on conventional PD remove solutes continuously, and it is the continuous nature of this therapy that has led many to suggest that this may be one reason why patients on PD do comparably well despite maintaining higher serum levels of small retention solutes.

Patient-Reported Outcomes and Measurement of Dialysis Dose

Patient-reported outcomes (PROs) comprise symptoms, health-related quality of life (HRQoL), and experience of care. PROs and consideration of patient preferences are, by definition, important in patient-centered care, may provide important diagnostic information, and may influence patient behavior, thereby affecting morbidity, resource utilization, and survival (33). Moreover, depression is independently associated with survival, and those experiencing acute or chronic pain have alterations in HRQoL (34,35). Current United States regulations require measurement of dialysis patients' HRQoL and experience of care, and most recently, of pain and depression.

Links between hemodialysis dose and PROs have been demonstrated in several studies. The HEMO Study found higher small molecule clearance, but not high flux hemodialysis, to result in a modest improvement in self-reported physical health and pain; mental health scores were not affected (36). The FHN Trial found that 6 d/wk in-center hemodialysis resulted in better physical health, less depression, and shorter recovery time than thrice weekly hemodialysis (37,38). The Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements Study (FREEDOM) Study and other observational data show daily home hemodialysis to be associated with improved patient mental and physical HRQoL (39,40). Assessments of the preferences of patients with CKD and on dialysis show heterogeneity across patients, some of whom are prepared to accept considerable foreshortening of survival to improve HRQoL (41,42). Although these findings suggest a role for PRO measurement in dialysis dose assessment, incorporating this into clinical practice has challenges, including patient fatigue in repeated questionnaire completion as well as comprehensive validation among diverse cultural and sociodemographic patient populations.

The variability in patient preferences and the correlation between dialysis dose and measures of HRQoL supports the use of PROs as measures of dialysis adequacy. Acknowledging this, recently updated Kidney Disease Outcomes Quality Initiative (KDOQI) hemodialysis adequacy guidelines support offering short, frequent in-center dialysis treatments as an alternative to conventional thrice weekly dialysis therapy, to help address individual patient preferences and optimize HRQoL (43). Future research is needed to minimize patient burden and achieve adequate precision to guide individual patient care as well as population assessment. Although duration of survival has

been the principal metric of comparison among dialysis modalities, future research should also address other patient-centered outcomes (44).

Extracellular Volume: A Hazard Hard to Measure

Fluid management is widely thought to be critical to optimal dialysis. Ideally, fluid removal during dialysis maintains euvolemia when urine output no longer matches fluid intake. However, unlike small solute clearance and electrolyte balance, extracellular volume is not easily measured, complicating the assessment of fluid removal needs and rendering adequate fluid management difficult to define objectively.

Extracellular Fluid Overload

Both large interdialytic weight gain (IDWG) and extracellular fluid overload contribute to maintenance hemodialysis morbidity and mortality. Among >30,000 patients in the United States, absolute IDWG of >4 kg (versus 1.5–2 kg) was associated with a 28% increased mortality risk (45). IDWG>3.5% body wt is associated with a comparable increase in hemodialysis (46). Failure to achieve target weight has been associated with mortality (47,48). Chronic volume expansion from incorrect estimates of target weight (with or without concurrent high IDWG) also contributes to fluid-related risk. Bioimpedance and blood volume monitor investigations have revealed volume expansion in the presence of target weight achievement in over a third of studied patients (49,50). Large IDWGs and chronic volume expansion probably contribute to increased morbidity and mortality *via* ventricular remodeling and subsequent heart failure and arrhythmia (51–53).

Although physical examination findings such as hypertension, jugular venous distension, rales, and edema signal extracellular fluid overload in some patients, volume expansion is often not clinically evident. Volume assessment tools exist, such as bioimpedance and blood volume monitors, but lack of regulatory approval as well as validated clinical protocols have resulted in limited uptake. European centers are increasingly relying on bioimpedance for volume assessment and have demonstrated improved cardiovascular outcomes among patients managed with bioimpedance versus clinical volume assessment only (54,55). A randomized controlled clinical trial of blood volume monitors for hemodynamic instability avoidance suggested harm from use (56). However, use of blood volume monitors for identification of volume overload holds promise (57). This alternative use requires further study and protocolization before widespread clinical practice adoption can occur. The absence of standardized volume assessment tools, particularly in the United States, remains a critical unmet need in dialysis care.

The Importance of Ultrafiltration Rate

Both high IDWG and ultrafiltration probing of prescribed target weight obligate faster fluid removal when dialysis treatment times are fixed. Data suggest a strong association between more rapid fluid removal and adverse outcomes. The rate of fluid removal during dialysis is determined by the ultrafiltration volume, often influenced by the IDWG, and the treatment time. Observational

studies have demonstrated associations between higher ultrafiltration rates and adverse outcomes. A prospective Italian cohort found a 22% increase in all-cause mortality for every 1 ml/h per kilogram rise in ultrafiltration rate ($P<0.01$) (58). A *post hoc* analysis of the HEMO Study found a 71% increased risk of cardiovascular mortality among patients with ultrafiltration rates >13 ml/h per kilogram (versus <10 ml/h per kilogram) (59). Associations between higher ultrafiltration rates and adverse outcomes were recently confirmed in a large observational cohort considering ultrafiltration rate normalized to body size (milliliter per hour per kilogram), body mass index (milliliter per hour per kilogram per square meter), and body surface area (milliliter per hour per square meter). Analyses also showed stability of the association of ultrafiltration rate with outcome across subgroups of sex and body size (60). However, these associations have not been confirmed by a randomized controlled clinical trial and questions about the optimal consideration of ultrafiltration rate (normalized to body size versus not) remain.

Despite these unknowns, the association of ultrafiltration rate with outcome is plausible. When ultrafiltration outpaces vascular refill, circulating blood volume falls, and clinically overt or silent end-organ ischemia may occur. Intradialytic transthoracic echocardiography-detected myocardial hypoperfusion, termed “stunning,” has been associated with greater intradialytic BP falls and larger ultrafiltration volumes (61,62). Repeat ischemic episodes, compounded by comorbid microvascular obstructive disease and reduced myocardial capillary density (63), may contribute to ventricular remodeling and its adverse consequences (64,65). Hypoperfusion of other organs, including the gut, brain, and kidney, also probably contribute to ultrafiltration rate–induced harm (66,67). Specifically, intradialytic hypotension is associated with harms, such as vascular access thrombosis and accelerated loss of RKF (68,69), and larger ultrafiltration volumes are associated with prolonged recovery time after dialysis (70). Furthermore, when ultrafiltration rate–induced hemodynamic instability causes hypotension, reactive fluid boluses and upward target weight adjustments may lead to chronic volume expansion and its untoward consequences.

Constructs of dialysis adequacy incorporating fluid management must consider not only extracellular volume status but also fluid removal strategies. Adequate fluid management must balance the risks associated with too much or too fast fluid removal, and associated ischemic complications, with too little or too slow fluid removal, and associated volume expansion complications. Interrelationships among IDWG, volume expansion, and fluid removal practices, lack of objective volume status measurement tools, and absence of randomized controlled clinical trial data complicate the selection of optimal measures of fluid management adequacy.

The Importance of Frequency: Should the Use of Thrice Weekly Hemodialysis Be Reconsidered?

Fiscal constraints in the context of a growing ESRD population set the stage for thrice weekly treatment as a standard of hemodialysis care in the United States. This strategy has been mainly on the basis of the notion that dialysis adequacy is determined by small solute clearance

independent of frequency of treatments. This practice is further entrenched by the financial pressures surrounding more frequent dialysis and a paucity of data from randomized controlled trials. Hence, a one-size-fits-all system has developed, where the majority of patients who initiate and are maintained on hemodialysis receive thrice weekly treatments regardless of their RKF, urine output, clearance requirements, cardiovascular status, quality of life, or preference. Meanwhile, there is some evidence that in incident patients on hemodialysis with significant RKF, less frequent dialysis (twice weekly) can be associated with preservation of residual renal function (71). For example, Obi *et al.* recently reported that patients who initiated hemodialysis therapy on an incremental rather than the conventional thrice weekly regimen had preserved renal urea clearance and urine volume that persisted over time (72). Given that higher RKF is associated with better survival, one can postulate that an incremental dialysis frequency approach can be more favorable in select patients, and that RKF itself should be an important metric to consider in the evaluation of optimal dialysis. Conversely, long interdialytic break has been associated with higher cardiovascular morbidity and mortality in patients on maintenance dialysis. Postulated risk factors may include oscillations in volume and/or solutes coupled with rapid rate of removal. In contrast, frequent hemodialysis sessions were associated with decreased mortality, improved electrolytes, BP control, and quality of life in observational studies (43,73,75,76). Furthermore, the FHN Trial found that more frequent dialysis therapy (5 d/wk) led to reduced left ventricular mass, a surrogate for cardiovascular outcomes (38). Although these findings make a compelling argument for an incremental approach to dialysis frequency, we also need to recognize the limitations of the available research. The studies concerning reduced dialysis frequency were observational in nature. In addition, the randomized controlled trials available (such as the FHN Trial) relied on surrogate outcomes and were not designed to assess an effect on mortality. It is also important to note that more frequent dialysis in the FHN Trial did not result in improvement of anemia or markers of nutritional status. Therefore, the balance between potential benefits of more frequent dialysis and burden to patients also needs to be considered. In regards to patients on PD, the majority of patients who start this modality have significant RKF. Although there is no evidence of its effect on outcome, incremental PD, using partial regimens, offers the patient a less onerous schedule, especially in the first months or years as the patient becomes acclimated to this home therapy.

Optimization of Cardiovascular Health by Dialysis Dosing

The high incidence of cardiovascular mortality and morbidity in maintenance dialysis (76) is likely multifactorial in etiology, but several lines of evidence suggest that the modality or adequacy of solute and fluid removal can alter risk of cardiovascular outcomes in patients on maintenance dialysis (47,60,77,58).

Surrogate measures of cardiovascular risk, such as LVMI, atherosclerosis burden as measured by carotid intimal media thickness (IMT), or measures of heart rate

variability or arrhythmia frequency, may have potential as actionable overall measures of treatment adequacy, with the potential to integrate control of solutes, volume removal, anemia correction, and overall metabolism in the individual patient. For example, a small study of 164 Chinese patients on hemodialysis demonstrated associations between traditional measures of urea removal (single pooled Kt/V) and LVMI (78), whereas the FHN Trials demonstrated convincing reductions in LVMI with frequent compared with standard hemodialysis schedules, particularly in those with limited RKF (25,38). Other studies have demonstrated associations between urea removal and carotid IMT (79), an improvement in heart rate variability with frequent hemodialysis (80), and an increase in risk of sudden death and arrhythmia hospitalization during the long interdialytic interval (81).

These data suggest the possibility of measuring LVMI or IMT, or of monitoring heart rate variability and rhythm to assess dialysis adequacy. These indices can be measured noninvasively and can be repeated at regular intervals to gauge the effect of changes in dialysis prescription. As opposed to hard cardiac events, they also offer the advantage of providing feedback that can be used to prospectively alter dialysis delivery in order to prevent cardiac events. However, studies are needed to confirm the utility of LVMI, IMT, and heart rhythm monitoring as surrogate outcomes measures. On a basic level, broader confirmation of the association of each measure, or the change in those measures, with cardiovascular outcomes is necessary. Furthermore, the degree of change in each measure that should be targeted will require definition. It is unclear, for example, what percentage change in LVMI or IMT is ideal—is it enough to simply stabilize left ventricular hypertrophy or is normalizing LVMI required? Similarly, the optimal measurement frequency is uncertain. In theory, heart rate variability or rhythm can be measured continuously. Conversely, changes in LVMI and IMT are detectable only over periods of months. Lastly, the appropriate response in terms of dialysis prescription to abnormalities in these measures has not been established. Thus, despite their great promise, much work needs to be done before these or other cardiovascular parameters can be advocated as measures of dialysis adequacy.

Does the Meeting of Targets Equate to Clinical Improvement?

Decades of preoccupation with treatment-related laboratory targets as the *sine qua non* for ESRD quality has deeply consumed large dialysis organizations, dialysis facilities, and nephrologists. But despite achievement of these targets, dialysis-related morbidity and mortality remain unacceptably high and HRQoL remains poor relative to the general population. KDOQI recently acknowledged the need to expand the concept of adequacy to include and prioritize improvement in quality of life (82). Others have also expressed the need to redefine the concept and scope of dialysis adequacy (83–85).

Clinical performance measures (CPMs) focusing on biochemical targets and arteriovenous fistula placement were important to establish minimum standards for dialysis treatment (86). Although achieving CPMs has been

associated with improvement over baseline outcomes, lack of further progress reinforces earlier findings that only 15% of variability in dialysis survival can be attributed to them (87).

Targeting Kt/V_{UREA} remains a cultural fixation in ESRD care, despite evidence that urea removal does not reflect clearance of all uremic toxins (6). Treatment of anemia-related morbidity with erythropoiesis-stimulating agents was tainted by issues surrounding utilization driven by reimbursement, and strict policy changes to regulate hemoglobin levels now exist (88). Bone and mineral disorder targets have been controversial and have not affected survival (89). Nonetheless, the regulatory focus seems to be on raising achievement thresholds despite evidence that traditional CPMs may not translate to more meaningful improvements (90).

Physical and emotional symptoms remain prevalent in ESRD, correlating with low quality of life, depression, and reduced patient engagement (35,82). The willingness of patients to participate in their care also depends on the economic concepts of opportunity cost and trade-offs. Patients may have disincentives to taking a more active self-management role. In addition, patient-centric metrics are often hard to measure, and addressing these can be time consuming and frustrating for many dialysis facilities (91).

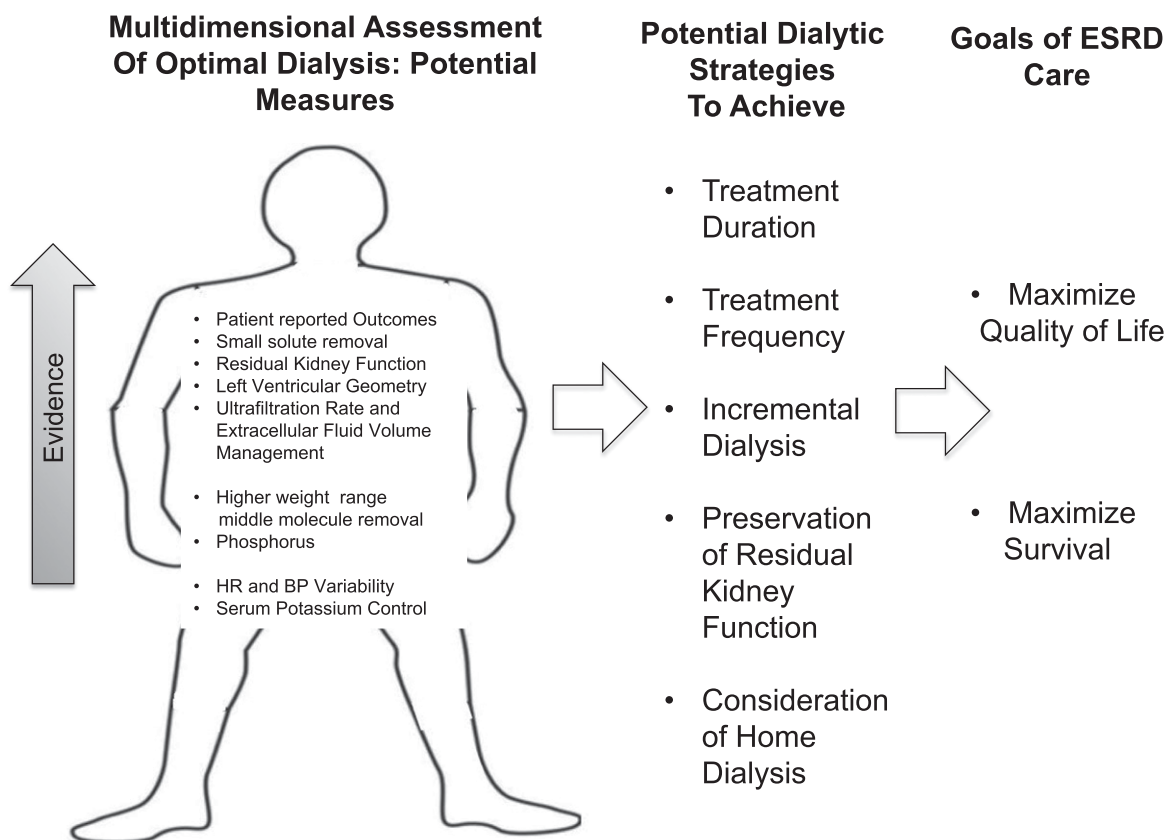
ESRD targets are often mismatched with a patient's life expectancy and wishes (92). Discounting behavior may

show that patients seem to value present life priorities over long-term survival (93). Quality of life is such a uniquely personal perception that is best measured by self-reporting (84). As we shift toward more patient-centric metrics, we will have to consider what outcomes are most meaningful to patients, and become more comfortable with "softer" data as more emphasis is placed on patient-centric outcomes (94).

Call to Action: A Multidimensional Quantification of Dialysis Delivery

Urea kinetics, as exemplified by the NCDS study, have played an important role in defining a minimum small molecule clearance required to avoid unacceptable levels of morbidity and mortality (4), and will be important for quality assurance purposes for the foreseeable future.

However, there is now a general consensus that increases in dialysis dose measurable by small molecule clearance alone are unlikely to yield further major advances in patient health and survival (95). Dialysis schedule, duration, and the management of extracellular volume and hemodynamics seem more productive areas for investigation, as do the removal of a range of solutes larger than urea and creatinine. The lessons learned during four decades of studying small solutes are likely to be important in developing new approaches to dialysis quantification (7).



Abbreviations: HD— hemodialysis, HR— heart rate, BP— Blood Pressure

Figure 1. | Multidimensional Measure of Dialysis. HR, heart rate.

Much of the energy and resources expended over the past two decades has failed to focus on the ultimate end target: how a patient on dialysis feels about life with ESRD. Equally important, our present dosing quantification in conventional hemodialysis does not provide any physiologic titration of our therapy or dosing. Opportunities exist for constructing thoughtful process measures that emphasize physiology and patient experience, better coordination of care, and optimizing overall disease management.

Our group proposes an evolutionary change to optimize dialysis delivery. We suggest that weekly dialysis time (accounting for both frequency and duration of therapy) and basic biochemical indices represent only one important but not sufficient indicator of dialysis delivery. Clinical physiologic parameters (e.g., BP, heart rate, cardiac geometry and function, and nutrition) represent sound outcome measures to quantify the results of our therapy. Our clinical approach must incorporate the dose adjustment and titration to symptoms and physiologic end points. Our group acknowledges that further research is needed to substantiate the use of a multidimensional measure to quantify dialysis dose. Although clearance of small and middle molecules are the basic building blocks of dialysis delivery, it is also critical to ascertain other dimensions of optimizing dialysis delivery, including the balance and effect on survival, end-organ physiology (e.g., cardiovascular health), and quality of life, if we are to shift from merely adequate dialysis to optimal dialysis (Figure 1).

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