Fluid Management: The Challenge of Defining Standards of Care

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In today’s world of big data, metric-driven performance standards, and value-based care, clinicians rely upon a range of quality metrics to support decision-making and promote desirable outcomes. Such metrics are quite common in dialysis care, and standards of urea kinetic modeling, hemoglobin ranges, and infection rates guide clinical decisions, measure quality of care, and even determine reimbursement rates. Quantifiable aspects of dialysis care are plentiful and include laboratory tests, physiologic measurements, and dialysis treatment–related factors. Selecting among candidate metrics and defining standards of care, however, is challenging because we often lack prospective studies confirming the effects of proposed measures on clinical outcomes and patient experience.

Mounting evidence suggests that fluid-related factors are critical contributors to the significant cardiovascular morbidity and mortality experienced by hemodialysis patients. There is growing debate about the best measure(s) of quality fluid management (1). Candidate metrics are plentiful and include interdialytic weight gain (IDWG), ultrafiltration rate, serum–dialysate sodium differential, target weight achievement, and BP. In order for metrics to be meaningful and drive improved outcomes, they must be precise, generalizable, and rooted in the physiologic underpinnings of disease. Developing care standards is difficult and particularly challenging when potential metrics are interrelated and their independent associations with outcomes unclear. Such is the challenge we face as we strive to specify volume-based quality metrics for hemodialysis care.

Greater IDWG, rapid ultrafiltration rates, and chronic volume expansion are all linked to adverse cardiovascular outcomes (2–6). Mechanistic pathways include BP, vascular stiffness, myocardial ischemia and associated cardiac structural changes, systemic inflammation, and other end-organ ischemic damage (7–12). On the surface, thresholds of IDWG, ultrafiltration rates, or target weight achievement represent reasonable metrics for fluid management. However, such factors have complex interrelationships, and their independent causative associations with outcomes are not defined. For example, greater IDWG is associated with cardiovascular morbidity (2,13), and greater weight gain necessitates more rapid fluid removal if target weight is to be achieved in a given treatment time. However, such overly rapid fluid removal is also associated with adverse cardiovascular outcomes (6). In addition, this more aggressive fluid removal may induce hemodynamic instability and ischemic insult, even in a total body volume–expanded patient. Reactive fluid administration or early dialysis termination in such settings may leave the patient above target weight at the end of treatment. Missed target weights are associated with increased cardiovascular morbidity and mortality (5). In these common clinical scenarios, greater IDWG, faster ultrafiltration, and postdialysis fluid overload are all plausible mediators of adverse cardiovascular outcomes. Their relative influence on outcomes is unknown. Such complex dynamics, complicated by the lack of volume status assessment tools and dearth of prospective investigations of the effects of volume management on outcomes, render defining rigorous fluid management standards extremely challenging.

In this issue of CJASN, Stefánsson et al. present data demonstrating an association between intradialytic hypotension (IDH) and cardiovascular outcomes and linking greater IDWG to enhanced IDH risk, further underscoring the complex interrelationships among volume-related factors (14). Using a contemporary cohort of 39,497 incident hemodialysis patients, the authors examined the IDH prevalence according to IDWG strata and estimated the associations between IDH and cardiovascular end points. In adjusted analyses, IDH (compared with no IDH) was associated with an increased risk of all-cause mortality, myocardial infarction, hospitalization for fluid overload, and several composite cardiovascular end points. In addition, incrementally larger IDWG (absolute or relative to body weight) was associated with incrementally greater IDH frequency. The association was unchanged when the authors accounted for dialysis treatment time differences across patients. The authors’ findings extend the existing IDH evidence base by identifying a link between large fluid gains and intradialytic hemodynamic instability and by confirming the oft-reported (15,16) but previously poorly substantiated association of IDH and adverse cardiovascular outcomes.

Strengths of the study include its large sample size, selection of an incident dialysis population for study, and use of US Renal Data System claims data for outcome assessment. Accurate exposure and outcome measurement is a primary challenge in nonexperimental research. Medicare claims data allow for robust outcome

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definitions, which do not depend on data collection or entry by clinical staff or clinical follow-up. Diagnosis codes associated with hospitalization claims for events such as myocardial infarction and heart failure are known to be sensitive and highly specific (17,18). In addition, the authors selected an incident hemodialysis population in efforts to minimize risk from residual kidney function, a factor strongly associated with favorable outcomes and plausibly linked to IDH. Acknowledging the possibility of residual confounding on the basis of urine output, the authors demonstrated stability of the IDH-outcomes associations over time, providing reassurance that residual kidney function did not confound associations between IDH and outcomes. However, concern for confounding on this basis remains, especially given the relatively small associations.

The study by Stefánsson et al. was conducted with scientific rigor, but has some limitations. As the authors point out, defining IDH is complex due to lack of a consensus definition among providers as well as lack of data on symptoms in clinical databases. The authors define IDH as a fall in systolic BP$\geq 20$ mmHg plus at least two responsive measures in at least one exposure period treatment. Thus, patients with as few as a single IDH episode during the 90-day period met the exposure definition, potentially weakening the association with outcomes. In fact, differences in patients with IDH in the cohort by Stefánsson et al. compared with patients with IDH in other cohorts highlight the influence of exposure definition. Stefánsson et al. found patients with IDH to be younger, more likely to be male, and to have similar comorbid cardiovascular disease burdens to patients without IDH. By contrast, other studies found patients with IDH to be older, more likely to be female, and more likely to have cardiovascular comorbid conditions compared with patients without IDH (19,20). In addition, without time sequence data, we cannot exclude the possibility that therapeutic responses like blood flow reduction and early dialysis termination were initiated for reasons other than hemodynamic instability (e.g., faulty vascular access), potentially altering the associations.

Furthermore, the authors did not account for several potential confounding variables including hemoglobin (21), albumin (19,20), and low predialysis BP (20,21). Although multivariable models included a variable for uncontrolled hypertension, defined as mean predialysis BP$\geq 140/90$ or mean postdialysis BP$\geq 130/85$, this dichotomous term does not account for the U-shaped association of BP and outcomes (22). In addition, by selecting a covariate inclusive of both predialysis and postdialysis BPs, the authors confute the confounding influence of these, often disparate, clinical factors. Confounding from these unconsidered or partially considered variables may alter outcome associations.

Despite these issues, the reported associations between IDH and adverse cardiovascular outcomes are plausible. IDH occurs when the rate of fluid removal exceeds the rate of vascular refill. Such circulatory stress can induce myocardial ischemia and end-organ damage to the brain, kidneys, and gut (9,11,23). Emerging evidence suggests that dialysis-associated hemodynamic instability may induce endotoxin translocation from the gut to the circulation, contributing to systemic inflammation and, in turn, to adverse cardiovascular events (11). Another explanation for the IDH-cardiovascular mortality association is that greater weight gain obligates higher ultrafiltration rates that may induce ischemia via myocardial stunning (9). Recurrent stunning, hypoxia, and associated inflammation accelerate cardiac structural changes, predisposing patients to heart failure.

In conclusion, the study by Stefánsson et al. corroborates and extends the existing evidence base supporting associations between IDH and adverse outcomes and underscores the complex nature of fluid dynamics by identifying a link between greater IDWG and IDH risk. These findings highlight the importance of minimizing weight gain and achieving extracellular euvolemia. Although Stefánsson et al. provide valuable observational data regarding fluid-related metrics, we must move beyond nonexperimental studies in order to inform metric selection for fluid management standards of care. Clinical trials evaluating the effects of improved volume control and lower ultrafiltration rates on outcomes like hospitalizations, quality of life, and cardiovascular endpoints are needed.

Existing data and clinical experience strongly suggest that fluid-related factors adversely affect outcomes. Immediate action is warranted. Dialysis organization leaders from 14 of the largest dialysis providers in the United States recently took a step forward in this regard by developing consensus fluid management opinions. They recommended greater attention to extracellular fluid status, gradual fluid removal, goal minimum treatment times of 4 hours, avoidance of intradialytic sodium loading, and dietary sodium avoidance (1). Until more targeted approaches to fluid management are identified through prospective study, nephrologists should heed these recommendations as well as take advantage of the many fluid-related measurements available at every dialysis treatment. By frequently reassessing target weight designation, meticulously tracking and ensuring target weight achievement, following BP trends, and minimizing ultrafiltration rates (possibly by titrating treatment length), we may be able to improve fluid-related outcomes while simultaneously undertaking trials to define patient-centered and outcome-based fluid management care standards.

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