Diuretic use in incident ESKD
Are we out of the loop?

Ke Wang and Nisha Bansal

Clin J Am Soc Nephrol 14: 13–15, 2019. doi: https://doi.org/10.2215/CJN.13361118

Kidney Research Institute, Division of Nephrology, University of Washington, Seattle, Washington

Correspondence: Dr. Nisha Bansal, Kidney Research Institute, Division of Nephrology, University of Washington, 3rd floor, 908 Jefferson Street, Seattle, WA 98104. Email: nbansal@nephrology.washington.edu

In this issue of the *Clinical Journal of American Society of Nephrology*, Sibbel *et al.* (1) examined the association of loop diuretic continuation with clinical outcomes after maintenance hemodialysis initiation among >11,000 patients with incident ESKD. In this large. observational cohort study, the authors utilized US Renal Data System (USRDS) records to ascertain refill of loop diuretic prescriptions after hemodialysis initiation and within 30 days of exhaustion of prior diuretic supply. Patients were studied with an intention-to-treat paradigm for up to 12 months for primary outcomes of death and hospitalizations, as well as for secondary outcomes of interdialytic weight gain, hyperkalemia, intradialytic hypotension, and ultrafiltration rates. Compared with controls who did not refill prescriptions for loop diuretics after dialysis initiation, loop diuretic continuation was associated with lower rates of all-cause hospitalization (adjusted incidence rate ratio, 7% lower; 95% confidence interval, 11% to 2% lower), but not a lower rate of death (adjusted hazard ratio, 8% lower; 95% confidence interval, 16% lower to 1% higher). Loop diuretic use was also associated with lower incidence of intradialytic hypotension and lower intradialytic weight gain, but no differences in monthly ultrafiltration rates between the two groups were observed during follow-up. When the analyses were repeated in the subset of patients who had significant urine output (defined as >200 ml measured by 24-hour urine collections), loop diuretic use was also associated with lower rates of hospitalizations but not a lower risk of death. In contrast to the main analysis, there was a modest but statistically significant association between loop diuretic use and higher rates of intradialytic hypotension (20.1 versus 19.8 episodes per patient-year).

The numerous strengths of the study should be recognized, including the large study population comprising >11,000 patients on incident hemodialysis, reliable ascertainment of diuretic prescription refills through USRDS data, and assessment of longitudinal clinical outcomes. The authors also utilized a novel analytic approach of "treatment decision" study design that corrects for immortal time bias.

The primary limitation of the study is its observational nature, therefore a casual inference regarding loop diuretic use and direct effects on clinical outcomes cannot be established on the basis of these findings. In observational studies of therapies, confounding by indication is an important consideration in the interpretation of the data. More specific to this study, patients with residual kidney function are more likely to be prescribed diuretics, and residual kidney function is linked with lower risk of mortality. To address possible confounding by indication, the authors repeated their analyses among the subset of individuals with residual kidney function only, and found similar associations as those observed in the primary analysis. Even with these analyses, there remains a possibility of residual confounding because the users of loop diuretics differ from nonusers. For one, the mean urine volume was lower in nondiuretic users compared with diuretic users, even when only considering those with residual kidney function. Furthermore, the diuretic users were more likely to receive nephrology care before dialysis initiation, which may have led to differences in decisions around dialysis initiation, peridialytic management, and long-term outcomes.

Other limitations should be acknowledged. Diuretic use was inferred from prescription refills and therefore medication adherence could not be determined, therefore increasing the likelihood of misclassification bias. Exposures and covariates were determined at baseline only, therefore there is a possibility of time-depending confounding. Finally, the detected effect size for lower hospitalization rates and mortality were also relatively modest despite the robust sample size. Therefore, from this observational data alone, the benefit of prescribing diuretics in patients with incident ESKD should be carefully weighed against increased pill burden and medication-related side effects.

Even with these limitations, this study is an important contribution to the literature. Loop diuretics are inexpensive and widely available; thus if effective, more aggressive use of diuretics would be a pragmatic approach to improve outcomes in patients with incident ESKD. However, currently, there are no clinical guidelines to guide diuretic use after initiation of chronic dialysis therapy. Despite the highly prevalent use of diuretics for managing hypertension and volume in patients with nondialysis-dependent CKD, the prescription of diuretics after dialysis initiation remains heterogeneous. A study of USRDS

data reported that diuretic use was approximately 70% in the 3 months before dialysis initiation and dropped off to approximately 30% immediately after (2). Similarly, data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) showed that diuretics were continued in approximately 30% of patients after dialysis initiation; however, after 2 years of chronic dialysis therapy, only approximately 10% of patients remained on diuretics (3). Only a few prior studies have examined the clinical benefit of diuretic use in patients on dialysis. A small, randomized, controlled trial of 61 patients on incident peritoneal dialysis showed that high-dose daily furosemide therapy was associated with higher urine volume and urinary sodium excretion compared with controls at a follow-up of 1 year; however, other clinical outcomes were not examined (4). In a large, observational study, Bragg-Gresham *et al.* utilized data from DOPPS and examined the association of self-reported diuretic use with clinical outcomes among 16,000 patients on hemodialysis across three continents. Diuretic use was associated with lower odds of interdialytic weight gain and hyperkalemia, higher odds of preserving residual kidney function at 1 year, and lower cardiac mortality, with a trend toward lower all-cause mortality (3). In contrast to Sibbel *et al.*, the authors adjusted for the presence of residual kidney function as a potential confounder and further performed stratified analyses among patients with and without residual kidney function. Association of diuretic use with all-cause mortality was similar among patients with and without residual kidney function, whereas diuretic use was associated with lower cardiac mortality among patients without residual kidney function only. In another contrast to the study by Sibbel *et al.*, the classification of residual kidney function was not based on 24-hour urine collections, therefore increasing the likelihood of misclassification bias. The authors also did not limit their study population to patients on incident dialysis, which is another important distinction from the study by Sibbel *et al.*

The study by Sibbel *et al.* also highlights the importance of volume management during the transition from advanced CKD to chronic dialysis, a high-risk period of heightened adverse patient outcomes that has been relatively understudied. Annual mortality rates during the transition from late-stage CKD through the first year of chronic dialysis therapy are >20% (5), and volume overload during this period may predispose patients to further morbidity and mortality. Volume overload is one of the most common causes of hospitalizations and emergency room visits among patients on dialysis. One study reported that patients with late-stage CKD who initiate chronic dialysis for volume overload experience higher mortality rates compared with those who initiate dialysis for uremic symptoms or laboratory abnormalities (6). Although diuretic use has not been shown to increase urea or creatinine clearance (4), the benefit conferred by diuretic use in patients on hemodialysis may be through more consistent volume control, which benefits cardiovascular health. More frequent dialysis leads to lower left ventricular mass compared with conventional thrice weekly hemodialysis resulting from continuous correction of volume overload (7). Continuous fluid removal through diuretic use may also minimize interdialytic weight gain, which is associated with cardiovascular and all-cause mortality among patients on chronic hemodialysis (8).

However, volume management in patients with kidney disease remains challenging because physical examination is highly subjective with low reproducibility, and there are few noninvasive and objective methods to assess volume status. However, prior studies have identified several promising tools that may aid in volume assessment. Bioelectrical impedance analysis is a portable tool that determines the impedance of electric current flow through body tissues. Shorter predialysis bioimpedance vectors, indicating greater tissue hydration, is associated with higher mortality risk in patients on hemodialysis (9). Increased hydration status assessed using bioelectrical impedance analysis may be used as a proxy to guide ultrafiltration. Lung ultrasound is a noninvasive method of estimating lung water in patients with heart disease and respiratory failure treated in intensive care units. An observational study showed subclinical pulmonary congestion detected on lung ultrasound to be an independently associated with cardiovascular events and death in patients on hemodialysis (10). Natriuretic peptides are elevated in states of volume overload as a result of increased myocardial stretch, and may also serve as early markers of abnormal cardiac physiology. Elevation of brain natriuretic peptide has been shown to be associated with higher mortality in patients on dialysis. Future studies assessing noninvasive, objective measures of volume status would provide useful information to help guide diuretic therapy and improve volume management during incident ESKD.

In summary, the study by Sibbel *et al.* underscores the importance of volume management during the transition period between CKD and chronic dialysis initiation. Better volume management may be an important step toward optimizing care in this vulnerable population at high risk for adverse outcomes.

Disclosures

None.

References

1. Sibbel S, Walker AG, Colson C, Tentori F, Brunelli SM, Flythe J: Association of continuation of loop diuretics at hemodialysis initiation with clinical outcomes. *Clin J Am Soc Nephrol* 14: 95–102, 2019
2. Chang TI, Zheng Y, Montez-Rath ME, Winkelmayer WC: Antihypertensive medication use in older patients transitioning from chronic kidney disease to end-stage renal disease on dialysis. *Clin J Am Soc Nephrol* 11: 1401–1412, 2016
3. Bragg-Gresham JL, Fissell RB, Mason NA, Bailie GR, Gillespie BW, Wizemann V, Cruz JM, Akiba T, Kurokawa K, Ramirez S, Young EW: Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). *Am J Kidney Dis* 49: 426–431, 2007
4. Medcalf JF, Harris KP, Walls J: Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. *Kidney Int* 59: 1128–1133, 2001
5. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, Balkrishnan R, Bragg-Gresham J, Cao J, Chen JL, Cope E, Dharmarajan S, Dietrich X, Eckard A, Eggers PW, Gaber C, Gillen D, Gipson D, Gu H, Hailpern SM, Hall YN, Han Y, He K, Hebert H, Helmuth M, Herman W, Heung M, Hutton D, Jacobsen SJ, Ji N, Jin Y, Kalantar-Zadeh K, Kapke A, Katz R, Kovesdy CP, Kurtz V, Lavalee D, Li Y, Lu Y, McCullough K, Molnar MZ, Montez-Rath M,

Morgenstern H, Mu Q, Mukhopadhyay P, Nallamothu B, Nguyen DV, Norris KC, O'Hare AM, Obi Y, Pearson J, Pisoni R, Plattner B, Port FK, Potukuchi P, Rao P, Ratkowiak K, Ravel V, Ray D, Rhee CM, Schaubel DE, Selewski DT, Shaw S, Shi J, Shieu M, Sim JJ, Song P, Soohoo M, Steffick D, Streja E, Tamura MK, Tentori F, Tilea A, Tong L, Turf M, Wang D, Wang M, Woodside K, Wyncott A, Xin X, Zang W, Zepel L, Zhang S, Zho H, Hirth RA, Shahinian V: US renal data system 2016 annual data report: Epidemiology of kidney disease in the United States. *Am J Kidney Dis* 69[Suppl 1]: A7–A8, 2017

6. Rivara MB, Chen CH, Nair A, Cobb D, Himmelfarb J, Mehrotra R: Indication for dialysis initiation and mortality in patients with chronic kidney failure: A retrospective cohort study. *Am J Kidney Dis* 69: 41–50, 2017
7. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Kliger AS; FHN Trial Group: In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 363: 2287–2300, 2010
8. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van Wyck D, Bunnapradist S, Horwich TB, Fonarow GC: Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation* 119: 671–679, 2009
9. Pillon L, Piccoli A, Lowrie EG, Lazarus JM, Chertow GM: Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. *Kidney Int* 66: 1266–1271, 2004
10. Zoccali C, Torino C, Tripepi R, Tripepi G, D'Arrigo G, Postorino M, Gargani L, Sicari R, Picano E, Mallamaci F; Lung US in CKD Working Group: Pulmonary congestion predicts cardiac events and mortality in ESRD. *J Am Soc Nephrol* 24: 639–646, 2013

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Association of Continuation of Loop Diuretics at Hemodialysis Initiation with Clinical Outcomes," on pages 95–102.