Cumulative Exposure to Frequent Intradialytic Hypotension Associates With New-Onset Dementia Among Elderly Hemodialysis Patients

To the Editor: Cognitive impairment, including dementia, affects up to 70% of individuals receiving maintenance hemodialysis,[1] a prevalence that exceeds that of the elderly general population by 3- to 7-fold.[2] Cardiometabolic risk factors for dementia, such as diabetes, hypercholesterolemia, hypertension, and vascular disease, are highly prevalent in end-stage kidney disease.[3] However, the rate of new-onset dementia is higher among hemodialysis patients compared with peritoneal dialysis patients,[4] suggesting that aspects of the hemodialysis procedure may contribute to the development of dementia.

Imaging studies show that hemodialysis can cause significant circulatory stress via ultrafiltration-induced hypoperfusion of vital vascular beds, including the brain.[5] Maintenance of adequate cerebral perfusion during dialysis is dependent on intradialytic blood pressure and the brain's intrinsic ability to preserve relatively constant blood flow despite changes in perfusion pressure. Hemodialysis patients may be particularly susceptible to the neurologic consequences of dialysis-induced blood pressure declines due, in part, to diminished autoregulatory capacity from autonomic and endothelial dysfunction.[6,7] It is thus plausible that repeated exposure to intradialytic hypotension (IDH) and associated cerebral hypoperfusion may increase dementia risk. In fact, general population data indicate that orthostatic hypotension[8] as well as cerebral hypoperfusion[9] are associated with accelerated cognitive decline and a higher risk of new-onset dementia. Although a recent study found an association between IDH and *reversible* cognitive decline in the immediate post-dialysis period,[10] the relationship between long-term, cumulative IDH exposure and the development of dementia in the hemodialysis population has not been established.

The objective of our study was to examine the association between the cumulative exposure to frequent IDH and the 5-year risk of new-onset dementia among elderly individuals initiating maintenance hemodialysis at a large U.S. dialysis organization. After a 30-day lag period following hemodialysis initiation, we determined if patients experienced frequent IDH in successive 90-day exposure intervals (Supplementary Figure S1). Within a given exposure interval, we classified an individual as having frequent IDH if he or she experienced a nadir intradialytic systolic blood pressure <90 mm Hg in at least 30% of hemodialysis treatments. This IDH definition has been associated with all-cause mortality, an important competing event in our analysis.[11] We evaluated the association between the time-updated, cumulative number of exposure intervals with frequent IDH after dialysis initiation and new-onset dementia using marginal structural Fine and Gray proportional subdistribution hazards models. All-cause death was treated as a competing event.

A total of 31,055 individuals initiated maintenance hemodialysis from June 1, 2005, to October 1, 2013, and met study selection criteria (Supplementary Table S1). The study cohort had an average age of 76.0 $\pm$ 6.6 years, 46.2% were women, 19.9% were black, 8.7% were Hispanic, and the most common cause of end-stage kidney disease was diabetes (43.7%). Baseline cardiovascular comorbid conditions were common: 39.9% of the cohort had an arrhythmia or conduction disorder, 59.2% had heart failure, 56.0% had ischemic heart disease, 29.1% had peripheral arterial disease and 18.8% had a history of stroke (Table 1 and Supplementary Table S2).

The cohort was followed for a total of 64,982 person-years and had an average follow-up duration of 2.1 $\pm$ 1.6 years. During the 5-year follow-up period, 4991 individuals developed all-cause dementia (incidence rate = 7.7 cases of new-onset dementia/100 person-years) and 11,037 individuals died (incidence rate = 17.0 deaths/100 person-years). Greater cumulative exposure to frequent IDH after hemodialysis initiation was incrementally associated with a higher 5-year risk of new-onset dementia (Figure 1). Individuals who experienced frequent IDH in $\geq$ 7 (vs. zero) 90-day exposure intervals across time had the highest 5-year risk of new-onset dementia (hazard ratio [95% confidence interval] = 1.36 [1.20–1.48]).

We provide initial evidence linking cumulative IDH exposure to new-onset dementia among individuals receiving maintenance hemodialysis. Prior mechanistic studies have shown that hemodialysis-induced circulatory stress may contribute to the development of cerebral ischemic injury, but these

Table 1. Select characteristics of the study cohort at baseline

Characteristic	Total study population (N = 31,055)
Age at dialysis initiation, yr	76.0 ± 6.6
Female	14,359 (46.2)
Race	
Black	6179 (19.9)
White	23,356 (75.2)
Other	1520 (4.9)
Hispanic	2705 (8.7)
Cause of end-stage kidney disease	
Diabetes	13,565 (43.7)
Hypertension	11,636 (37.5)
Glomerular disease	1742 (5.6)
Other	4112 (13.2)
Current smoker at dialysis initiation	1090 (3.5)
Inpatient dialysis initiation	13,054 (42.0)
Vascular access	
Catheter	22,398 (72.1)
Fistula	6580 (21.2)
Graft	2077 (6.7)
Arrhythmia or conduction disorder	12,393 (39.9)
Diabetes	20,379 (65.6)
Dyslipidemia	9972 (32.1)
Heart failure	18,370 (59.2)
Ischemic heart disease	17,398 (56.0)
Peripheral arterial disease	9046 (29.1)
Stroke	5834 (18.8)
Valvular disease	2464 (7.9)
Pre-dialysis systolic blood pressure, mm Hg	
≤130	8475 (27.3)
131–150	12,240 (39.4)
151–170	7736 (24.9)
≥171	2604 (8.4)

Values are given as number (percent) for categorical variables and as mean ± SD for continuous variables. Baseline covariates, including demographics, comorbid conditions, and health care utilization metrics were obtained in the 365 days preceding dialysis initiation. Baseline laboratory and dialysis treatment-related covariates were obtained in the 30 days immediately after dialysis initiation. The complete list of study cohort baseline characteristics is displayed in Supplementary Table S2.

studies were not powered to consider clinical outcomes. For example, in a cross-sectional study of 12 elderly hemodialysis patients from the Netherlands, Polinder-Bos *et al.*[5] demonstrated that hemodialysis induces a significant reduction in global and regional cerebral blood flow. In a pilot study of 58 prevalent hemodialysis patients from the United Kingdom, MacEwen *et al.*[12] found that more pronounced declines in intradialytic mean arterial pressure associated with a higher incidence of intradialytic cerebral ischemic episodes. Furthermore, in a prospective cohort study of 32 nondiabetic, Japanese hemodialysis patients, Mizumasa *et al.*[13] noted that the number of IDH episodes (defined as a fall in systolic blood pressure >50 mm Hg within 30 minutes of starting hemodialysis plus associated symptoms of hypoperfusion) across time was weakly correlated with greater cerebral frontal lobe atrophy.

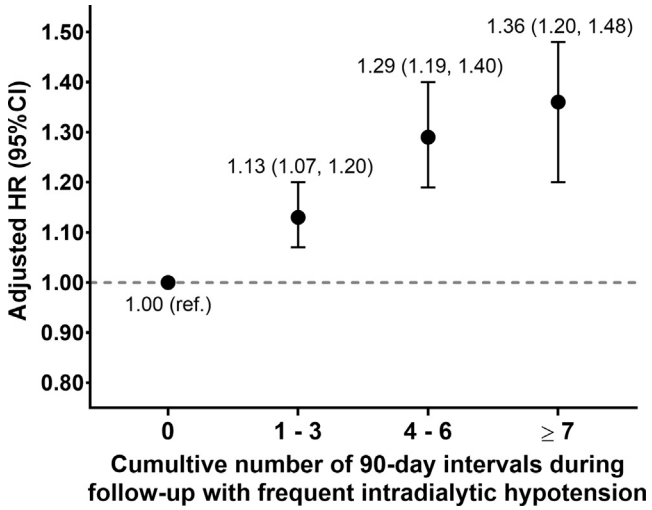

Figure 1. Association between time-updated, cumulative exposure to frequent intradialytic hypotension and the 5-year risk of new-onset dementia. We used marginal structural Fine and Gray proportional subdistribution hazard models, treating death as a competing event, to estimate association between the time-updated, cumulative exposure to frequent intradialytic hypotension and the 5-year risk of new-onset dementia. Within a given 90-day exposure interval, we classified an individual as having frequent intradialytic hypotension if he or she experienced a nadir intradialytic systolic blood pressure <90 mm Hg in at least 30% of hemodialysis treatments. Supplementary Table S3 contains outcome and competing event definitions. We used inverse probability of exposure weighting to adjust for baseline and time-updated covariates listed in Supplementary Table S4. CI, confidence interval; HR, hazard ratio.

Our findings extend this mechanistic evidence by linking frequent IDH to the clinical outcome of new-onset dementia. Dementia is associated with a range of adverse outcomes, including lower quality of life[14] and treatment nonadherence,[15] as well as higher hospitalization and mortality rates.[16,17] Therefore, identification of effective interventions that reduce dementia risk is needed to improve patient outcomes. One promising hemodialysis-based intervention may be the use of cooled dialysate. Cooled dialysate reduces intradialytic hemodynamic instability,[18] likely via cold-induced vasoconstriction and associated improvements in systemic vascular resistance during ultrafiltration. In a randomized controlled trial of 73 incident hemodialysis patients from the United Kingdom, Eldehni *et al.*[19] found that hemodialysis with cooled dialysate (0.5°C below core body temperature) versus standard temperature dialysate (37°C) led to preservation of brain white matter microstructure at 1 year. This relatively low-risk intervention may be a viable, low-cost neuroprotective treatment strategy for individuals initiating hemodialysis. Other potential IDH reduction strategies include treatment time extension, more frequent dialysis, and ultrafiltration profiling, but supporting data, particularly with regard to the latter, are limited.

In conclusion, we found that increased cumulative exposure to frequent IDH after dialysis initiation was incrementally associated with a higher 5-year risk of new-onset dementia in a cohort of more than 30,000 elderly hemodialysis patients. Interventional studies are needed to determine if IDH mitigation reduces dementia risk among individuals receiving maintenance hemodialysis.

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DISCLOSURE

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SUPPLEMENTARY MATERIAL

Study Methods.

Figure S1. Study design.

Table S1. Study inclusion and exclusion criteria.

Table S2. Complete list of study cohort baseline characteristics.

Table S3. Outcome and competing event definitions.

Table S4. Baseline and time-updated covariates.

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis*. 2008;15:123–132.
2. Langa KM, Larson EB, Crimmins EM, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Intern Med*. 2017;177:51–58.
3. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol*. 2002;13:1918–1927.
4. Wolfgram DF, Szabo A, Murray AM, Whittle J. Risk of dementia in peritoneal dialysis patients compared with hemodialysis patients. *Perit Dial Int*. 2015;35:189–198.
5. Polinder-Bos HA, Garcia DV, Kuipers J, et al. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. *J Am Soc Nephrol*. 2018;29:1317–1325.
6. Chesterton LJ, Sigrist MK, Bennett T, et al. Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. *Nephrol Dial Transplant*. 2005;20:1140–1147.
7. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation*. 2007;116:85–97.
8. Wolters FJ, Mattace-Raso FU, Koudstaal PJ, et al. Heart Brain Connection Collaborative Research Group. Orthostatic hypotension and the long-term risk of dementia: a population-based study. *PLoS Med*. 2016;13(10):e1002143.
9. Wolters FJ, Zonneveld HI, Hofman A, et al. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation*. 2017;136:719–728.
10. Costa AS, Tiffin-Richards FE, Holschbach B, et al. Clinical predictors of individual cognitive fluctuations in patients undergoing hemodialysis. *Am J Kidney Dis*. 2014;64:434–442.
11. Flythe JE, Xue H, Lynch KE, et al. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26:724–734.
12. MacEwen C, Sutherland S, Daly J, et al. Relationship between hypotension and cerebral ischemia during hemodialysis. *J Am Soc Nephrol*. 2017;28:2511–2520.
13. Mizumasa T, Hirakata H, Yoshimitsu T, et al. Dialysis-related hypotension as a cause of progressive frontal lobe atrophy in chronic hemodialysis patients: a 3-year prospective study. *Nephron Clin Pract*. 2004;97:c23–c30.
14. Tyrrell J, Paturel L, Cadec B, et al. Older patients undergoing dialysis treatment: cognitive functioning, depressive mood and health-related quality of life. *Aging Ment Health*. 2005;9:374–379.
15. Hain DJ. Cognitive function and adherence of older adults undergoing hemodialysis. *Nephrol Nurs J*. 2008;35:23–29.

16. Mapes DL, Lopes AA, Satayathum S, et al. Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int*. 2003;64:339–349.

17. McAdams-DeMarco MA, Daubresse M, Bae S, et al. Dementia, Alzheimer's disease, and mortality after hemodialysis initiation. *Clin J Am Soc Nephrol*. 2018;13:1339–1347.

18. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. *Nephrol Dial Transplant*. 2006;21:1883–1898.

19. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol*. 2015;26:957–965.

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The Effect of Enlarged Kidneys on Calculated Body Mass Index Categorization in Transplant Recipients With ADPKD

To the Editor: Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of end-stage renal disease and the most common inherited kidney disease.[1] Patients with ADPKD undergo kidney transplantation at high rates, with many undergoing unilateral or bilateral nephrectomy along with transplantation to create space for the kidney allograft or treat symptoms of chronic pain and early satiety, among others.[1–3] Enlarged kidneys may contribute substantially to overall body weight in patients with ADPKD, and body mass index (BMI) selection criteria may exclude patients from either listing or transplantation.[4,5] With an increasing number of obese patients on dialysis, along with an increasing percentage of obese patients with end-stage renal disease being referred for kidney transplantation,[6,7] BMI selection and exclusion criteria are important for transplantation.[4] To date, it is unknown how much weight enlarged organs from ADPKD contribute to BMI except by estimations from imaging studies.[8] In this study, we examined the contribution of kidney nephrectomy specimen weights to BMI categorization in patients with ADPKD who underwent kidney transplantation.

We conducted a retrospective study using the electronic medical record at our center. We identified patients with ADPKD who received kidney transplantation and underwent unilateral or bilateral nephrectomies between 1998 and 2015. We performed a chart review and recorded patients' demographic characteristics, BMI at the time of transplant listing, and dialysis history. Using gross pathology reports, we recorded weights of nephrectomy specimens according to designation as left kidney and right kidney on the reports. We also recorded peri- and postoperative data from operation reports. For the primary analysis, patients were divided into 6 BMI categories designated by our institution's transplantation criteria (we also report categories defined by the Centers for Disease Control and Prevention).[9] Kidney weights by BMI categories were compared using the Kruskal-Wallis test. The association between patients' BMI at transplant listing and total kidney specimen weight was measured by the Pearson correlation coefficient. To estimate the weight that enlarged kidneys contributed to patients' recorded BMI, we generated a "calculated BMI" after nephrectomy by subtracting patients' kidney specimen weights from their body weight and dividing by height. The total weight of both kidneys was subtracted in cases of bilateral nephrectomy. Simple and weighted Cohen's kappa analyses were performed to determine the degree of agreement between patients' BMI at transplant listing and their "calculated BMI." The Committee on Human Research at University of California, San Francisco, approved this study (Institutional Review Board no. 14-15601).

Between 1998 and 2015, 477 patients with ADPKD received kidney transplantation. Seventy patients underwent transplantation and nephrectomy (Supplementary Table S1); 54.3% ($n = 38$) were women and mean ± SD age at the time of transplantation was 49.4 ± 7.92 years; 67.1% ($n = 47$) were white; 74.3% ($n = 52$) of patients had received dialysis before transplantation, with 88.5% ($n = 46$) of this group having had hemodialysis. The median (interquartile range) dialysis vintage was 20 (9, 68) months; 80% ($n = 56$) had simultaneous transplant and nephrectomy, with 82.9% ($n = 58$) and 17.1% ($n = 12$) of patients having had bilateral nephrectomy and unilateral nephrectomy, respectively. Three patients in our study were missing left kidney specimen weights even though they underwent bilateral nephrectomy, and 1 patient did not have a BMI listing. The total mean weight of combined left and right kidney specimens was 4.03 kg (Figure 1) (individual mean weights were 2.38 kg and 2.09 kg for