

# Incremental and Once- to Twice-Weekly Hemodialysis: From Experience to Evidence



Yoshitsugu Obi<sup>1</sup> and Kamyar Kalantar-Zadeh<sup>1,2,3</sup>

<sup>1</sup>Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, California, USA; <sup>2</sup>Nephrology Section, Tibor Rubin Veterans Affairs Medical Center, Long Beach, California, USA; and <sup>3</sup>Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, USA

*Kidney Int Rep* (2017) 2, 781–784; <http://dx.doi.org/10.1016/j.ekir.2017.07.006>

© 2017 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

See Clinical Research on page 933

In most dialysis centers in North America and Europe, it has been the prevailing dogma to ensure adequate solute clearance by thrice-weekly hemodialysis treatment in the management of dialysis-dependent patients. However, an outright transition from non-dialysis-dependent chronic kidney disease to a thrice-weekly hemodialysis schedule may underappreciate the importance of individualized care among patients with end-stage renal disease. Given that nearly half of incident dialysis patients in the United States may initiate maintenance dialysis therapy at an estimated glomerular filtration rate >10 ml per minute per 1.73 m<sup>2</sup>, the clinical effectiveness of an incremental hemodialysis approach has been re-evaluated in recent studies (Figure 1).<sup>1</sup> Salient benefits of starting with less frequent hemodialysis schedule, for example, once- or twice-weekly hemodialysis and

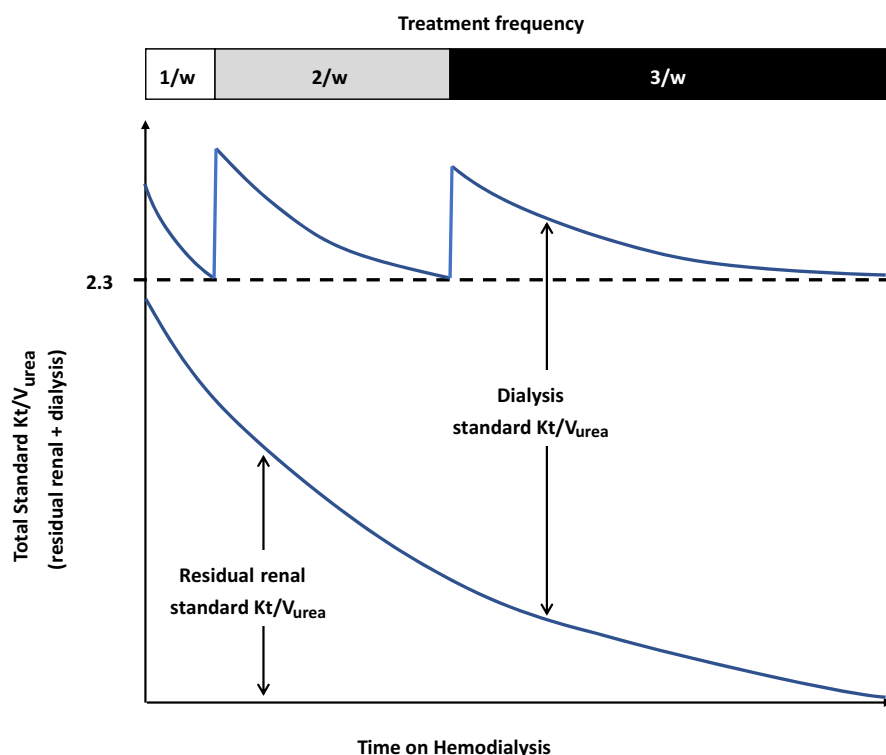
gradually transitioning to a thrice-weekly schedule over time and as needed, includes better quality of life, preservation of residual kidney function (RKF), and longer time of arterio-venous fistula patency. Nevertheless, until very recently, an incremental hemodialysis approach was rarely implemented in the United States, notwithstanding the swiftly heightened interest and enthusiasm since 2014.<sup>2</sup>

In this issue of *KI Reports*, Chin *et al.*<sup>3</sup> reported the feasibility of twice-weekly hemodialysis among incident end-stage renal disease patients in the United States. They assumed twice-weekly hemodialysis with 4-hour treatment time per session as the initial modality, and examined what proportion of their patients could have started maintenance hemodialysis with a twice-weekly schedule (i.e., examining this question as to what if patients had been treated with twice-weekly hemodialysis) based on the following 4 criteria: weekly urea clearance (i.e., standard Kt/V<sub>urea</sub>) delivered by dialysis and RKF; ultrafiltration rate; intradialytic blood pressure; and intradialytic symptoms such as nausea and

vomiting. Their 14-year historical cohort holds a highly unique position because the periodical measurement of RKF has been a part of their standard care for hemodialysis patients. Among 784 incident hemodialysis patients who survived the first 6 months of dialysis, 646 patients (82%) had baseline RKF data including patient-reported “no significant urine output.”

Based on the findings in this simulation study, incremental hemodialysis regimen appeared feasible in many patients. Chin *et al.*<sup>3</sup> selected 410 patients who actually collected 24-hour urine during the first 3 months of dialysis, and reported that 112 patients fulfilled their proposed conditions and were considered “optimal” for twice-weekly hemodialysis. An additional 107 patients had adequate urea clearance, but their interdialytic weight gain was not acceptable to achieve an ultrafiltration rate <13 ml per kilogram per minute because, in theory, the ultrafiltration volume per hemodialysis session and its rate increase as treatment frequency decreases, with a longer interdialytic interval if patients maintain the same amount of fluid intake and urine output. A large ultrafiltration may result in the development of intradialytic hypotension, a risk factor for mortality independent of RKF levels.<sup>4</sup> However, the authors also found that diuretics were underused and that the fluid intake well exceeded the recommended level (i.e., 1.5 L per day). Diuretics can increase urine output among patients with substantial RKF, mitigating the increase in interdialytic weight gain and the need for excessive ultrafiltration volume despite lower treatment frequency. In the study by Chin *et al.*,<sup>3</sup> many of those 107 patients could have been managed by an incremental

**Correspondence:** Kamyar Kalantar-Zadeh, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, 333 City Boulevard West, City Tower, Suite 400, Orange, California 92868, USA. E-mail: [kkz@uci.edu](mailto:kkz@uci.edu)



**Figure 1.** A conceptual scheme for an incremental hemodialysis regimen with adjustment of hemodialysis frequency based on residual renal urea clearance.

hemodialysis regimen if they had received “appropriate” diuretic treatment and dietary counseling. Indeed, a recent case-series report showed that the ultrafiltration volume per hemodialysis session was often lower in the twice-weekly than in the thrice-weekly regimen.<sup>5</sup> These findings suggest that approximately one-third of incident hemodialysis patients (i.e., 219 of 646), rather than “more than half” (i.e., 219 of 410) as reported in the original article, might be good candidates for an incremental hemodialysis approach in the United States.

Chin *et al.*<sup>3</sup> calculated the theoretical probability of achieving the target standard  $Kt/V_{urea}$  of 2.3 with a twice-weekly schedule with standard 4-hour hemodialysis sessions for each patient. The methodology for combining renal and dialysis urea clearance has been scrutinized and upgraded based on formal urea kinetic modeling. Although there is an ongoing debate as to whether  $Kt/V_{urea}$  is the

best index of adequate solute clearance among dialysis patients, it still retains the best available evidence pertaining to patient survival as used in several clinical practice guidelines.<sup>6</sup> Furthermore, standard  $Kt/V_{urea}$  may be a conservative index to ensure adequate solute clearance because it underestimates the contribution of RKF by ignoring the clearance of protein-bound uremic toxins and middle-molecule solutes. RKF also plays additional important physiological roles such as activation of vitamin D, production of endogenous erythropoietin, continuous body fluid control, and amelioration of metabolic derangements, and is strongly associated with patient survival.<sup>7</sup> Therefore, even with the same standard  $Kt/V_{urea}$ , patients with high RKF plus low dialysis  $Kt/V_{urea}$  would have better survival than those with low RKF plus high dialysis  $Kt/V_{urea}$ . However, such benefit attenuates with the inevitable decline in RKF over time in the majority of patients. The rate of RKF

decline has been shown to largely vary among hemodialysis patients, and adverse clinical events may also affect the trajectory of RKF. These uncertainties warrant periodic (at least quarterly) evaluation of RKF and the use of the conservative dialysis adequacy measure (i.e., total standard  $Kt/V_{urea}$ ) among patients on twice-weekly hemodialysis.

Another important finding in the study by Chin *et al.*<sup>3</sup> concerns the use of urine volume as an index to predict the benefit of incremental hemodialysis. Although the correlation between renal urea clearance and urine volume was strong as expected, there was a large variation in renal urea clearance that cannot be explained by urine volume ( $R^2 = 0.47$ ). Indeed, among patients who were not considered appropriate for incremental hemodialysis, only 11% had renal urea clearance of  $>3$  ml per minute, whereas  $>50\%$  of patients had a urine output of  $>500$  ml per day, which have been proposed in a recent consensus article<sup>2</sup> as one of the criteria for initiating and maintaining twice-weekly hemodialysis. The heterogeneity of kidney diseases may cause a variation in the decreased solute clearance and impaired concentrating capacity, depending on the severity of tubular injury in the kidney. Given that the majority of patients who were considered “appropriate” or “ideal” for incremental hemodialysis had urine output  $>500$  ml per day with a low prevalence of diuretic use, this criterion may be used as a minimum requirement for twice-weekly hemodialysis that warrants further evaluation by 24-hour urine collection.

The study by Chin *et al.*<sup>3</sup> has the strength of low missing frequency in data on RKF, thus reducing selection bias that might otherwise have overestimated the prevalence of good candidates for incremental

hemodialysis as done in some other reports. However, several potential limitations of this study are worth noting. First of all, the authors did not have data on patients who actually received incremental hemodialysis. Their judgement on “optimal” or “appropriate” for twice-weekly hemodialysis was made solely by hypothetical simulation based on several assumptions. For example, the authors established hemodynamic criteria using pre- and post-hemodialysis blood pressure among patients on thrice-weekly hemodialysis, but no data on blood pressure were available from patients who actually decreased treatment frequency from thrice to twice weekly. Therefore, it remains unclear as to how many successful cases there would have been among patients in the “optimal” and “appropriate” groups. Second, there was no information as to how long patients remained “optimal” or “appropriate” for twice-weekly hemodialysis. RKF declines over time as a whole, but there are large variations in change in RKF. Factors associated with faster decline in RKF include female sex, nonwhite race, diabetes, and history of congestive heart failure,<sup>7</sup> and patients in the “optimal” and “appropriate” groups might have met the criteria for twice-weekly hemodialysis only for a limited time if they had those risk factors. Longitudinal assessment of patient characteristics including RKF and standard  $Kt/V_{\text{urea}}$  would provide additional insight into this study topic. Third, it is not possible to conclude from these findings whether the authors’ criteria could appropriately guide an incremental hemodialysis approach. When considering twice-weekly hemodialysis, standard  $Kt/V_{\text{urea}}$  has been suggested as an indicator in the Kidney Disease Outcome Quality Initiative (KDOQI) Clinical

Practice Guidelines,<sup>6</sup> and the international consensus paper by Kalantar-Zadeh *et al.* also proposed criteria comprising several conditions including urine volume and interdialytic weight gain.<sup>2</sup> Although a previous study demonstrated equivalent survival between incremental and conventional hemodialysis if patients retained substantial renal urea clearance (i.e.,  $\geq 3.0$  ml/min/1.73 m<sup>2</sup>),<sup>1</sup> there are still scarce data on how to identify patients who would benefit the most from incremental dialysis without compromising their long-term survival and health-related quality of life. Finally, these findings may not be extrapolated to facilities where incident end-stage renal disease patients have different characteristics from those in this study. Indeed, there is large variability in mean estimated glomerular filtration rate at dialysis initiation across geographic regions in the United States,<sup>8</sup> and some countries initiate dialysis at lower estimated glomerular filtration rate levels.

In addition to patients with substantial RKF, patients with severe comorbid conditions may be treated with twice-weekly hemodialysis as a palliative measure. Mortality is exceptionally high during the first 6 months of dialysis among incident hemodialysis patients, and 283 of 1067 patients were excluded from this study because of not being treated on hemodialysis for >6 months. A reliable risk prediction tool, if it were to become available in the future, would help identify patients with a very short life expectancy and aid to implement once to twice-weekly hemodialysis as a palliative measure. A decremental hemodialysis approach, that is, reducing the frequency from thrice- to twice-weekly, could also be considered as an end-of-life adjustment approach for terminally ill dialysis patients.<sup>9</sup>

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Hemodialysis: 2015 Update does not have a specific statement for how to adjust dialysis frequency according to RKF levels, mainly due to a lack of concrete evidence,<sup>6</sup> which suggests that the 2007 KDOQI guidelines<sup>10</sup> are still valid in recommending less-than-thrice-weekly dialysis when KRU is >3 ml per minute per 1.73 m<sup>2</sup> and a switch to thrice-weekly dialysis when KRU falls to <2 ml per minute per 1.73 m<sup>2</sup>. This study by Chin *et al.*<sup>3</sup> is an important step forward toward individualized care for hemodialysis patients. The balance between the benefits and harms of twice-weekly hemodialysis treatment may be influenced not only by RKF but also by several factors such as life expectancy, dietary intake, medication adherence, and access to medical resources.<sup>11</sup> Simple, reliable, and cost-effective criteria for predicting benefit and harm of twice-weekly hemodialysis will help implement an incremental approach in this population. Although an incremental hemodialysis approach may require a labor-intensive process to gain more patient understanding and cooperation than the conventional hemodialysis with the fixed treatment frequency (i.e., 3 times per week), further studies are warranted to develop a safe and practical strategy for incremental hemodialysis as an important part of individualized care in end-stage renal disease.

## DISCLOSURE

KK-Z has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, the American Society of Nephrology, Astra-Zeneca, Aveo, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, the National Institutes of

Health, the National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS-Pharma, outside the submitted work. YO has received honoraria and/or support from Chugai and Ono, outside the submitted work.

### ACKNOWLEDGMENTS

KKZ is supported by the National Institute of Diabetes and Digestive and Kidney Diseases grants R01-DK095668 and K24-DK091419, as well as philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, Dr. Joseph Lee, and AVEO. YO is supported by the Uehara Memorial Foundation Research Fellowship.

### REFERENCES

1. Obi Y, Streja E, Rhee CM, et al. Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. *Am J Kidney Dis.* 2016;68:256–265.
2. Kalantar-Zadeh K, Unruh M, Zager PG, et al. Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. *Am J Kidney Dis.* 2014;64:181–186.
3. Chin AI, Appasamy S, Carey RJ, et al. Feasibility of incremental 2-times weekly hemodialysis in incident patients with residual kidney function. *Kidney Int Rep.* 2017;2:933–942.
4. Chou JA, Streja E, Nguyen DV, et al. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrol Dial Transplant.* 2017.
5. Moghadamyeghaneh Z, Hanna MH, Fazlalizadeh R, et al. A nationwide analysis of kidney autotransplantation. *Am Surg.* 2017;83:162–169.
6. National Kidney Foundation. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis.* 2015;66:884–930.
7. Obi Y, Rhee CM, Mathew AT, et al. Residual kidney function decline and mortality in incident hemodialysis patients. *J Am Soc Nephrol.* 2016;27:3758–3768.
8. Scialla JJ, Liu J, Crews DC, et al. An instrumental variable approach finds no associated harm or benefit with early dialysis initiation in the United States. *Kidney Int.* 2014;86:798–809.
9. Rhee CM, Ghahremani-Ghajar M, Obi Y, et al. Incremental and infrequent hemodialysis: a new paradigm for both dialysis initiation and conservative management. *Panminerva Med.* 2017;59:188–196.
10. National Kidney Foundation. KDOQI clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis.* 2006;48(suppl 1):S2–S90.
11. Obi Y, Eriguchi R, Ou SM, et al. What is known and unknown about twice-weekly hemodialysis. *Blood Purif.* 2015;40:298–305.