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

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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^2, the clinical effectiveness of an incremental hemodialysis approach has been re-evaluated in recent studies (Figure 1).[1] 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.[2]

In this issue of *KI Reports,* Chin *et al.*[3] 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_{urea}) 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.*[3] 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.[4] 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.*,[3] many of those 107 patients could have been managed by an incremental

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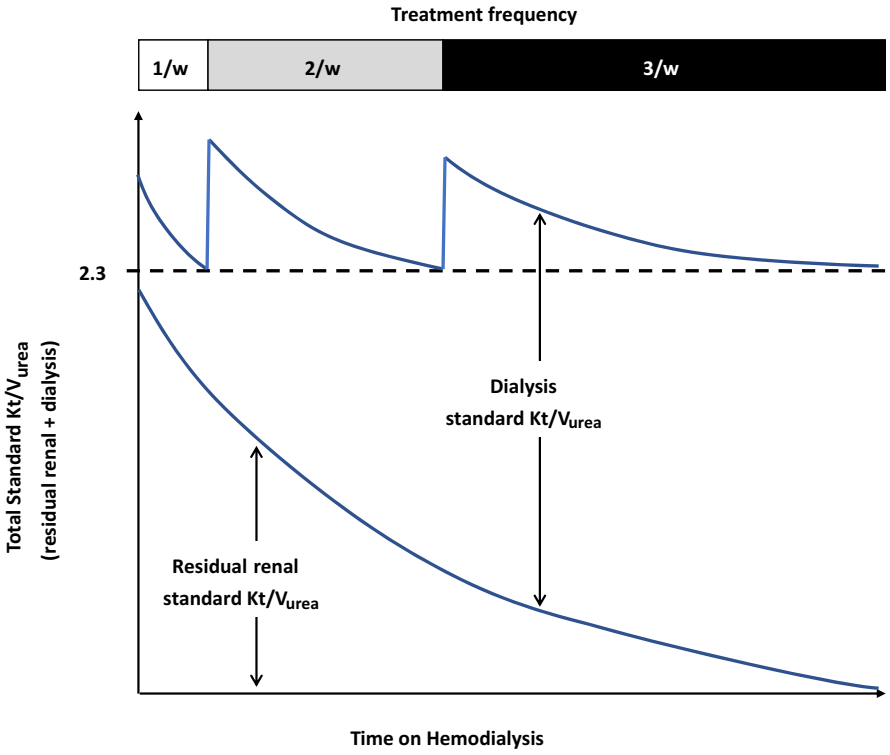

Figure 1. A conceptual scheme for an incremental hemodialysis regimen with adjustment of hemodialysis frequency based on residual renal urea clearance.

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.[5] 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.*[3] 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.[6] 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.[7] 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.*[3] 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[2] 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.*[3] 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