Title

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Journal

Seminars in Nephrology, 38(4)

ISSN

0270-9295

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Publication Date

2018-07-01

DOI

10.1016/j.semnephrol.2018.05.003

Precision Medicine in the Transition to Dialysis and Personalized Renal Replacement Therapy

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Summary: Launched in 2016, the overarching goal of the Precision Medicine Initiative is to promote a personalized approach to disease management that takes into account an individual's unique underlying biology and genetics, lifestyle, and environment, in lieu of a one-size-fits-all model. The concept of precision medicine is pervasive across many areas of nephrology and has been particularly relevant to the care of advanced chronic kidney disease patients transitioning to end-stage kidney disease (ESKD). Given many uncertainties surrounding the optimal transition of incident ESKD patients to dialysis and transplantation, as well as the high mortality rates observed during this delicate transition period, there is a pressing urgency for implementing precision medicine in the management of this population. Although the traditional paradigm has been to commence incident hemodialysis patients on a 3 times/week treatment regimen, largely driven by adequacy targets, there has been growing recognition that alternative treatment regimens (ie, incremental hemodialysis) may be preferred among certain subpopulations when taking into consideration factors such as patients' residual kidney function, volume status fluctuations, symptoms, and preferences. In this review, we examine the origins of current practices in how dialysis is initiated among incident ESKD patients; incremental dialysis therapy as a dynamic and patient-centric approach that is tailored to patients' unique characteristics; recent data on the incremental hemodialysis regimen and outcomes; and future research directions using a precision nephrology approach to ESKD management with the potential to develop novel approaches, tools, and collaborative efforts to improve the health, well-being, and survival of this population.
Semin Nephrol 38:325−335
Keywords: Incremental dialysis, twice-weekly hemodialysis, residual kidney function, individualized dialysis

In 2016, the Precision Medicine Initiative was launched by the Office of the US President, National Institutes of Health, Food and Drug Administration, Office of the National Coordinator for Health Information Technology, and other stakeholders as a revolutionary approach that takes into account individuals' variability in their underlying biology and genetics, lifestyle, and environment in the treatment and prevention of disease.[1−4] In lieu of a one-size-fits-all model developed for the average person, the overarching goal of precision medicine is to pursue a personalized approach that identifies interventions that are most effective for patients according to their unique characteristics.

Although the Initiative is in its early stages, the concept of precision medicine has been pervasive in nephrology for many years, and is particularly relevant to the care of advanced chronic kidney disease patients transitioning to end-stage kidney disease (ESKD). Indeed, using a personalized approach that comprehensively considers a patient's medical history, lifestyle factors (eg, diet, physical activity, health behaviors), environment (eg, geographic location, social support), and personal beliefs and preferences is essential in determining which treatment strategy (eg, hemodialysis versus peritoneal dialysis, kidney transplantation, conservative management) is most ideal for the individual (Fig. 1).

The framework used in the transition of patients to ESKD is a prime example of how a personalized approach is used to guide clinical practice in nephrology (Fig. 2). However, there is further need for a more expanded role of precision medicine in the management of incident ESKD patients who are transitioning to dialysis. For example, the traditional paradigm has been to commence incident hemodialysis patients on a 3 times/week treatment regimen, which largely has been driven by adequacy targets.[5−7] However, there has been growing recognition that alternative treatment regimens (ie, more-frequent, less-frequent treatment schedules)

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Financial support: Supported by research grants from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases K23-DK102903 (C.M.R.), K24-DK091419 (K.K.-Z.), R01-DK096920 (K.K.-Z.), U01-DK102163 (K.K.-Z.); National Kidney Foundation (C.M.R.); American Thyroid Association (C.M.R.); and philanthropist grants from Mr. Harold Simmons (K.K.-Z.), Mr. Louis Chang (K.K.-Z.), and Dr. Joseph Lee (C.M.R, K.K.-Z.).

Conflict of interest statement: none.

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0270-9295/ - see front matter

https://doi.org/10.1016/j.semnephrol.2018.05.003

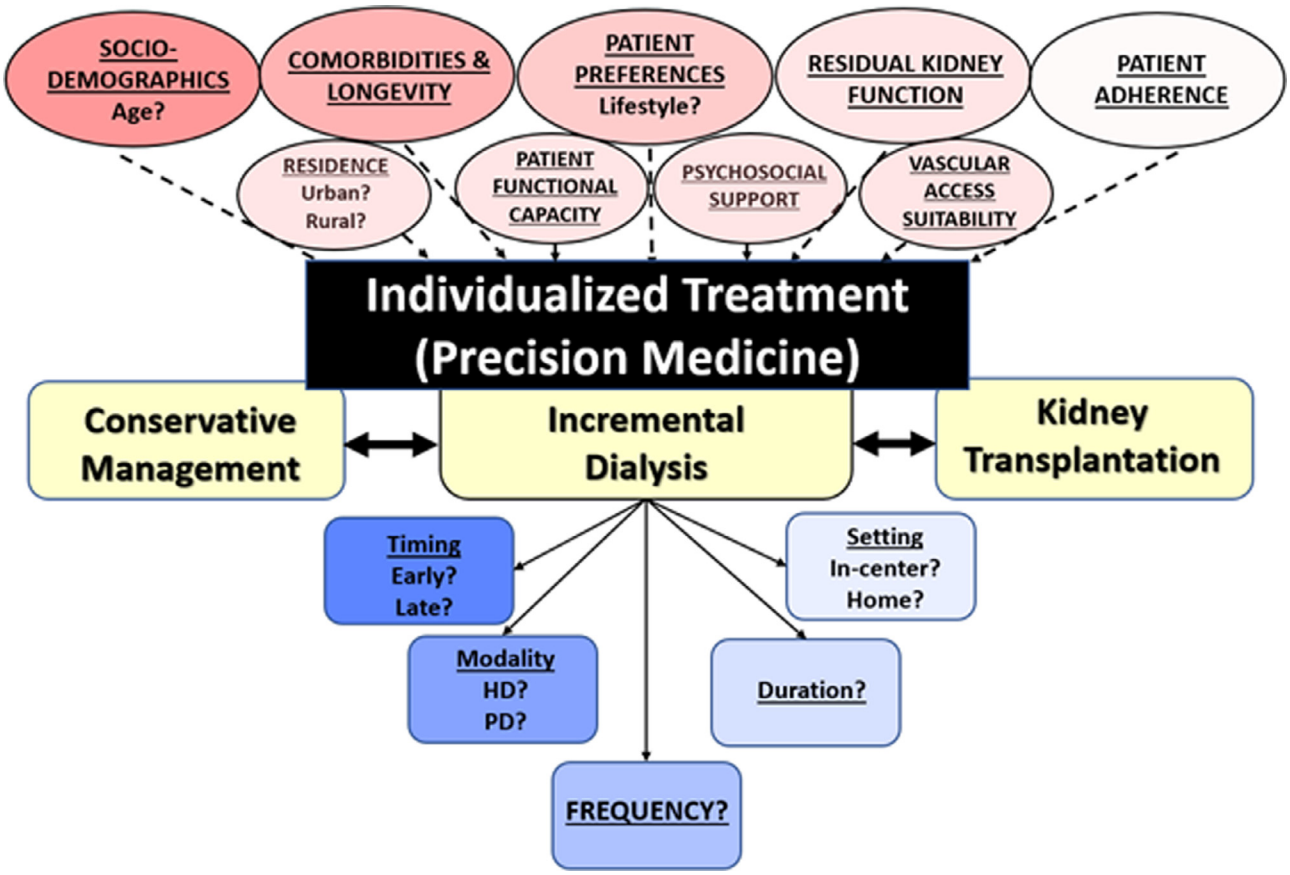


Figure 1. Personalized approach in the transition to renal replacement therapy.

may be preferred among certain subpopulations when taking into consideration additional factors such as patients' residual kidney function, volume status fluctuations, symptoms, and preferences. Indeed, the optimal regimen in the first few months after dialysis initiation is not known,[5–8] and adding further complexity to this uncertainty is the heightened mortality risk of this early transition period.[9–11] In this article, we examine current

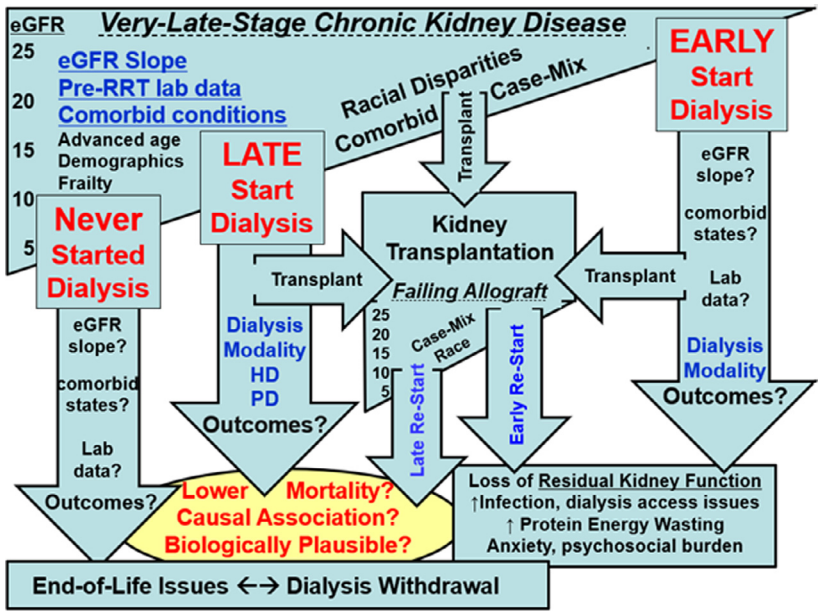


Figure 2. Framework used in the transition of patients to end-stage kidney disease. eGFR, estimated GFR; RRT, renal replacement therapy.

practices in how dialysis is administered among incident ESKD patients transitioning to dialysis, as well as novel approaches tailored to patients' unique characteristics.

CURRENT PARADIGMS IN THE TRANSITION TO DIALYSIS

Origins of Thrice-Weekly Hemodialysis

Historical narratives have indicated that the 3 times/week hemodialysis schedule was first established as a means to provide adequate dialysis therapy while also treating the greatest number of ESKD patients using constrained resources.[5–8] After Dr Belding Scribner's creation of the first permanent vascular access device at the University of Washington in the 1960s, maintenance hemodialysis treatment was administered every 5 to 7 days until symptoms of uremia recurred, and later was escalated to twice-weekly treatments because of complications of malignant hypertension resulting from hypervolemia and uremia-associated peripheral neuropathy from inadequate clearance.[12,13] Because this twice-weekly treatment schedule with session lengths of 12 to 20 hours was onerous on patients' lifestyles, prescribing hemodialysis regimens 3 times/week with session lengths of 6 to 10 hours[14] were the usual practice when the Medicare End Stage Renal Disease Program came into being in 1973.[5–8]

Focus on Dialysis Adequacy: Landmark Trials

In contemporary practice, most hemodialysis patients are prescribed fixed-dose, hemodialysis regimens 3 times/week irrespective of incident versus prevalent ESKD status, underlying residual kidney function, and other factors.[5–8] Indeed, in a seminal trial that established an individualized quantitative approach to the hemodialysis prescription, the US National Cooperative Dialysis Study (NCDS), frequency of treatment was fixed as a 3 times per week schedule during the protocol development to avoid variability across centers.[15] By using a two-by-two factorial design in which patients were randomized to two time-averaged blood urea nitrogen level (50 versus 100 mg/dL) and two dialysis session length (2.5-3.5 versus 4.5-5.0 h) targets, the NCDS study showed that patients in the lower blood urea nitrogen group had fewer withdrawals because of death or medical illness. This trial also led to the development of Kt/V_{urea} as the standard metric of dialysis adequacy. However, it should be noted that the study was restricted to prevalent hemodialysis patients with a creatinine clearance of 3 mL/min or less, and hence may not be generalizable to incident ESKD patients with substantial residual kidney function.[7,16] The Hemodialysis trial subsequently randomized patients in a two-by-two factorial design to receipt of standard versus a higher dialysis dose (equilibrated Kt/V, 1.05 versus 1.45) and low-flux versus high-flux dialyzer membranes, which showed no difference in survival across groups.[17] Similar to the NCDS study, the Hemodialysis trial was restricted to prevalent hemodialysis patients with minimal residual kidney function (urea clearance, ≤1.5 mL/min per 35 L body water).

Clinical Practice Guidelines

The optimal adequacy targets among incident ESKD patients transitioning to hemodialysis have not yet been established. However, early recommendations from the 1997 Kidney Disease Outcomes Quality Initiative (KDOQI) Hemodialysis Adequacy Group supported dialysis initiation at a glomerular filtration rate (GFR) of approximately 10 mL/min/1.73 m^2,[18] whereas updated 2006 KDOQI guidelines have indicated that dialysis initiation may be warranted at higher levels of GFR (<15 mL/min/1.73 m^2) in the setting of symptoms or decompensation in health status related to a decline in kidney function.[19]

The 2006 KDOQI guidelines advise that, among patients lacking substantial residual kidney function (defined as a residual urea clearance of <2 mL/min/1.73 m^2), the minimally adequate and target dialysis doses are a single-pool Kt/V of 1.2 to 1.4 per session, respectively.[19] Among patients whose residual urea clearance is less than 2 mL/min/1.73 m^2, a treatment schedule of fewer than 3 times/week is not recommended, which likely is based on the estimation of the minimum weekly standardized Kt/V of more than 2.2 defined by observational studies of Kt/V and survival.[19–21] Among patients with a residual urea clearance of >3 mL/min/1.73 m^2, allowances are made for a dose reduction to 60% of the minimum target of those lacking residual kidney function,[19] and this may be a population in whom an incremental hemodialysis regimen can be initiated and maintained until residual urea clearance falls below 2 mL/min/1.73 m^2 (see later in the *Practical Implementation of Incremental Hemodialysis* section).

USING A PERSONALIZED APPROACH IN THE TRANSITION TO DIALYSIS

Tailoring Dialysis to Residual Kidney Function

Data from the US Renal Data System data show that approximately 120,000 incident ESKD patients transition to dialysis each year, among whom 27% and 12% of patients commence therapy with an estimated GFR of 10 to less than 15 mL/min/1.73 m^2 and greater than 15 mL/min/1.73 m^2, respectively.[9] Hence, a large proportion of incident ESKD patients may transition to hemodialysis with substantial residual kidney function. Compared with peritoneal dialysis, hemodialysis has been shown to result in a more accelerated decrease in residual kidney function[22] owing to intradialytic hypotension, renal

ischemia, and exposure to nephrotoxic inflammatory mediators during dialysis.[5–7] However, some data suggest that hemodialysis patients experience greater preservation of kidney function than previously estimated, with as many as 70% and 14% to 20% of patients retaining residual kidney function after 1 and 3 to 5 years, respectively, after the transition to dialysis.[23]

Residual Kidney Function and Outcomes in Dialysis

Given its continuous nature, residual kidney function may have considerable impact on both uremic toxin clearance (particularly middle and large molecules), as well as greater solute and fluid removal with subsequent attenuation of large interdialytic weight gains, high ultrafiltration requirements, left ventricular hypertrophy, intradialytic hypotension, myocardial stunning, and cardiovascular morbidity and mortality.[5–7,21,24] Residual kidney function in dialysis patients also may be linked with greater phosphorous excretion, endogenous vitamin D production, and erythropoietin production, resulting in improved mineral bone disease and anemia indices. Furthermore, rigorous studies have shown that preservation of residual kidney function is associated with reduced inflammation, improved nutritional parameters, and greater health-related quality of life (HRQOL).[16,24] Among peritoneal dialysis and hemodialysis patients, a growing body of evidence has shown a graded association between the presence of residual kidney function and greater survival (Table 1).[16,23,25–30] Given these numerous benefits, incident ESKD patients' residual kidney function should be measured at the time of transition to dialysis, and reassessed frequently over time.[6,7,21,31] Although oftentimes overlooked as a determinant of an individual's dialysis prescription, there is now increasing interest in alternative dialysis treatment strategies, such as an incremental dialysis approach, as a means to preserve existing residual kidney function.

INCREMENTAL APPROACH IN THE TRANSITION TO DIALYSIS

Historical Precedents: Example of Peritoneal Dialysis

Peritoneal dialysis has been the archetype of applying an incremental approach that is tailored to a patient's residual kidney function.[32,33] In patients newly initiating peritoneal dialysis, both native kidney function and dialysis clearance are incorporated into the total weekly clearance target calculations. Upon loss of residual kidney function, the dialysis prescription is intensified to maintain total renal and dialytic clearance above a certain minimum. Among incident ESKD patients transitioning to hemodialysis, the initial prescription (including dose and frequency) ideally should take into consideration of patients' residual kidney function, and undergo frequent adjustment as function declines over time.[34]

Rationale for Incremental Hemodialysis

The rationale for using an incremental and less frequent (ie, twice-weekly) approach among incident hemodialysis patients is based largely on observations that more frequent hemodialysis leads to faster loss of residual kidney function over time, presumably owing to ischemic kidney damage resulting from intradialytic hypotension and postdialytic hypovolemia, release of nephrotoxic mediators during hemodialysis, greater reduction in blood urea nitrogen concentrations resulting from more frequent hemodialysis, and deactivation of remaining nephrons.[5–7]

Global data suggest that twice-weekly hemodialysis is a prevalent practice pattern in non-Western countries. For example, limited observational studies have indicated that 9% of prevalent and 25% of incident hemodialysis patients in Japan,[35] 43% of prevalent hemodialysis patients in Iran,[36] and 75% of prevalent patients in Sudan[37] are prescribed a less-frequent regimen. In an analysis of 1,737 outpatient dialysis facilities from a large US dialysis organization, the prevalence of dialysis units with 0%, greater than 0% to 3%, and greater than 3% of patients who were prescribed an incremental hemodialysis regimen was 74%, 17%, and 9%, respectively.[20]

Incremental Hemodialysis and Outcomes

In the past 2 decades, an increasing number of observational studies have shown that incremental or less-frequent hemodialysis regimens are associated with greater preservation of residual kidney function,[38–40] similar to lower mortality risk,[20,39,41,42] and improved HRQOL[43,44] in dialysis patients (Table 2).

Residual kidney function

Several studies have shown that incremental or less-frequent hemodialysis is linked to better preservation of native kidney function, whereas more frequent hemodialysis may be associated with accelerated residual kidney function decline over time (Table 2). In a study of 74 prevalent hemodialysis patients in Taiwan by Lin et al,[38] the rate of residual kidney function decline was compared among those who received twice-weekly versus 3 times/week hemodialysis and had similar creatinine clearance and urine output levels at baseline. Patients maintained the same hemodialysis frequency over the study period, and after a mean follow-up of 18 months, those who received twice-weekly treatment had higher creatinine clearance, higher urine output, and a slower

Table 1. Residual Kidney Function, Residual Urine Output, and Mortality in Dialysis Patients

Study	Study Population	Findings
Bargman et al,[25] 2001	PD patients (re-analysis of CANUSA study)	Each 5 L/wk/1.73 m^2 increase in RKF was associated with a decrease in mortality Each 250-mL increase in UOP was associated with a decrease in mortality Peritoneal clearance was not associated with survival
Shemin et al,[28] 2001	HD patients	Each 1 mL/min/1.73 m^2 increase in baseline RKF (defined as renal urea and creatinine clearance) was associated with a decrease in mortality
Paniagua et al,[27] 2002	PD patients (ADEMEX trial)	Each 10 L/wk/1.73 m^2 increase in RKF was associated with a decrease in mortality Peritoneal clearance was not associated with survival
Termorshuizen et al,[29] 2004	Incident HD patients (NECOSAD cohort)	Each 1 L/wk increase in RKF (defined as renal Kt/V urea) was associated with a decrease in mortality RKF was a stronger predictor of survival than dialytic clearance
Vilar et al,[23] 2009	Incident HD patients	RKF (defined as renal urea clearance) was associated with a decrease in mortality at 6, 12, and 24 months of follow-up evaluation
Shafi et al,[16] 2010	Incident HD patients (CHOICE cohort)	Preserved UOP after 1 year was associated with a decrease in all-cause mortality and a trend toward a decrease in CV mortality Baseline UOP was associated with an increase in HRQOL, improved cognition, dietary liberalization, decreased ESA use, and decreased inflammation
van der Wal et al,[30] 2011	Incident HD and PD patients (NECOSAD cohort)	Full loss of RKF (defined as a mean of renal urea and creatinine clearance) was associated with increased mortality
Obi et al,[26] 2016	Incident HD patients	Graded association between lower RKF (defined as renal urea clearance) and urine volume 1 year after HD initiation and increased mortality Graded association between a decrease in RKF (defined as renal urea clearance) and urine volume 1 year after HD initiation and increased mortality

ADEMEX, Adequacy of Peritoneal Dialysis in Mexico; CANUSA, Canada-USA Peritoneal Dialysis Study Group; CHOICE, Choices for Healthy Outcomes in Caring for End-Stage Renal Disease; CV, cardiovascular; ESA, erythropoietin-stimulating agent; HD, hemodialysis; NECOSAD, Netherlands Cooperative Study on Adequacy of Dialysis; PD, peritoneal dialysis; RKF, residual kidney function; UOP, urine output.

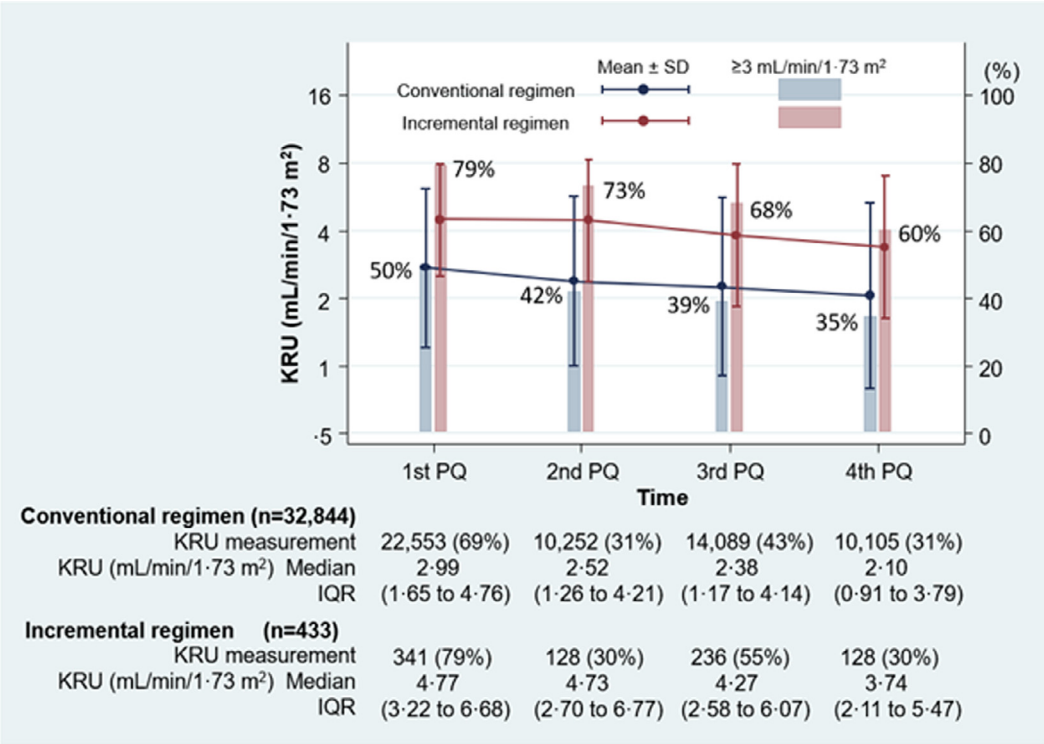
Table 2. Incremental (or Less-Frequent), Conventional, and More-Frequent Hemodialysis Regimens and Outcomes

Study	Study Population	Findings
Residual Kidney Function		
Lin et al,[38] 2009	74 prevalent HD patients (Taiwan)	Twice-weekly HD was associated with better preservation of RKF (defined by creatinine clearance and UOP)
Zhang et al,[40] 2014	85 incident HD patients (Shanghai)	Twice-weekly HD was associated with better preservation of RKF (defined by urine volume)
Daugirdas et al,[45] 2013	63 HD patients (FHN Nocturnal trial subcohort; United States and Canada)	More frequent HD was associated with a faster decline in RKF (defined by urea clearance, creatinine clearance, and urine volume)
Obi et al,[39] 2016	8,419 incident HD patients (United States)	Twice-weekly HD was associated with better preservation of RKF (defined by renal urea clearance and urine volume)
Mortality		
Hanson et al,[41] 1999	15,067 incident and prevalent HD patients (United States)	Incident patients: twice-weekly HD was associated with similar mortality versus HD 3 times/wk Prevalent patients: twice-weekly HD associated with decreased mortality versus HD 3 times/wk
Lin et al,[42] 2012	1,288 incident and prevalent HD patients (Shanghai)	All patients (adjusted): twice-weekly HD was associated with similar mortality versus HD 3 times/wk Incident patients (unadjusted): twice-weekly HD was associated with decreased mortality Prevalent patients (unadjusted): twice-weekly HD was associated with decreased mortality
Obi et al,[39] 2016	8,419 incident HD patients (United States)	All patients: twice-weekly HD was associated with similar mortality Analyses stratified by KRU: KRU $\leq$3 mL/min/1.73 m^2: twice-weekly HD was associated with increased mortality KRU $>$3 mL/min/1.73 m^2: twice-weekly HD was associated with similar mortality
Mathew et al, 2016[20]	50,756 incident HD patients (United States)	Incremental HD was associated with similar mortality versus conventional HD Frequent HD was associated with increased mortality versus conventional HD
Health-related quality of life		
Bieber et al, 2014[43]	1,379 HD patients (China)	Twice-weekly versus HD 3 times/wk was associated with similar HRQOL scores

FHN, Frequent Hemodialysis Network; HD, hemodialysis; KRU, renal urea clearance; RKF, residual kidney function; UOP, urine output; wk, week.

rate of residual kidney function decline versus those who received treatment 3 times/week. Notably, only crude results were presented, and analyses did not take into consideration differences in case-mix characteristics using multivariable regression. In a subsequent study of 85 maintenance hemodialysis patients from Shanghai by Zhang et al,[40] among 30 patients who were initiated and maintained on twice-weekly hemodialysis for at least 6 months versus 55 patients who were initiated and maintained on a 3 times/week schedule, those in the twice-weekly group experienced better preservation of residual kidney function as defined by urine volume. In a subcohort of 48 incident hemodialysis patients (ie, period of time on dialysis $<$12 mo) who had a baseline urine output of greater than 500 mL/d, each additional treatment per week was associated with a seven-fold higher risk of residual kidney function loss (defined as urine output $<$200 mL/d). Most recently, in a study by Obi et al[39] of incident hemodialysis patients from a large US dialysis organization who had residual kidney function data in the first 91 days of dialysis and survived the first year of dialysis, 8,068 patients receiving conventional (3 times/week) hemodialysis patients were matched to 351 incremental (twice-weekly) hemodialysis patients. In adjusted analyses, patients receiving incremental hemodialysis had greater preservation of residual kidney function (defined as renal urea clearance) as well as urine volume over the course of 1 year (Fig. 3).

With respect to more frequent hemodialysis regimens, a corollary study from the Frequent Hemodialysis Network Daily and Nocturnal trials compared the association of more frequent versus conventional treatment regimens with residual kidney function trajectory.[45] Among a subcohort of nonanuric patients in the Nocturnal trial, patients who received frequent hemodialysis had a faster decline in residual kidney function (defined by urea and creatinine clearance) and urine volume at the 4- and 12-month follow-up evaluations compared with those who received conventional hemodialysis. It should be highlighted that patients in the frequent hemodialysis group also experienced a lower nadir in intradialytic blood pressure versus the conventional group, suggesting hemodynamic instability may have been an underlying pathway to decline in residual kidney



Conventional regimen (n=32,844)				
KRU measurement	22,553 (69%)	10,252 (31%)	14,089 (43%)	10,105 (31%)
KRU (mL/min/1·73 m²) Median	2·99	2·52	2·38	2·10
IQR	(1·65 to 4·76)	(1·26 to 4·21)	(1·17 to 4·14)	(0·91 to 3·79)
Incremental regimen (n=433)				
KRU measurement	341 (79%)	128 (30%)	236 (55%)	128 (30%)
KRU (mL/min/1·73 m²) Median	4·77	4·73	4·27	3·74
IQR	(3·22 to 6·68)	(2·70 to 6·77)	(2·58 to 6·07)	(2·11 to 5·47)

Figure 3. Incremental hemodialysis and preservation of residual kidney function and urine output. IQR, interquartile range; KRU, renal urea clearance; PQ, patient-quarter.

function. Although the Daily trial subanalyses did not show a significant difference in the residual kidney function trajectory among the frequent versus conventional hemodialysis groups, it should be noted that the Daily trial excluded patients with higher levels of residual kidney function compared with those in the Nocturnal trial arm (urea clearance thresholds, <3 mL/min/35 L body water versus 10 mL/min/35 L body water, respectively).

Mortality

Multiple observational studies also have suggested that incremental or less-frequent hemodialysis is associated with similar survival compared with conventional treatment (Table 2).[20,39,41,42] In one of the early studies conducted, Hanson et al[41] compared mortality risk among 15,067 incident and prevalent hemodialysis patients receiving twice-weekly versus 3 times/week treatment from the US Dialysis Morbidity and Mortality cohort. Among incident hemodialysis patients, twice-weekly treatment was associated with decreased mortality compared with treatment 3 times/week in analyses adjusted for case-mix covariates, but this was attenuated to the null after adjustment for residual kidney function. Analyses restricted to prevalent hemodialysis patients showed that twice-weekly treatment was associated with decreased mortality as compared with treatment 3 times per week; however, interpretation of these findings is limited by the lack of residual kidney function data, as well as the more favorable patient characteristics observed in the twice-weekly group. In a subsequent study of 1,288 incident and prevalent hemodialysis patients from the Shanghai Renal Registry by Lin et al,[42] although unadjusted analyses showed that twice-weekly treatment was associated with a lower mortality risk compared with treatment 3 times/week, equivalent survival was observed in analyses accounting for case-mix differences. It should be noted that these analyses also did not account for differences in residual kidney function across groups.

More recently, Obi et al[39] re-examined the mortality risk of a matched cohort of incident hemodialysis patients receiving incremental (twice-weekly) versus conventional (3 times/week) therapy, this time taking into consideration underlying residual kidney function. In the overall cohort, there was no difference in survival across the two groups. However, in analyses stratified by renal urea clearance and urine volume, incremental versus conventional hemodialysis was associated with higher mortality among patients with inadequate residual kidney function (renal urea clearance, ≤3 mL/min/1.73 m^2) and low urine volume (≤600 mL/d), but showed similar mortality risk among those with higher levels of renal urea clearance and urine volume, suggesting that an incremental hemodialysis regimen is more suitable for patients with substantial residual kidney function. Notably, a significant trend between incremental

hemodialysis and better survival was observed across higher increments of renal urea clearance, but not across higher levels of urine volume. This study was followed by an analysis by Mathew et al[20] comparing survival in patients receiving incremental, conventional, and frequent hemodialysis regimens among patients from a large US dialysis organization. After matching 434 incremental, 50,162 conventional, and 160 frequent hemodialysis patients and accounting for differences in residual kidney function, patients in the incremental hemodialysis group had similar survival compared with that of the conventional hemodialysis reference group, whereas the frequent hemodialysis group had a higher mortality risk. In subgroup analyses stratified by comorbidity burden defined by the Charlson Comorbidity Index score, among patients with a higher comorbidity burden (Charlson Comorbidity Index score, ≥5), incremental hemodialysis was associated with a higher risk of death. Among patients with a low or moderate comorbidity burden, incremental versus conventional hemodialysis showed a similar mortality risk, and among patients with a low comorbidity burden frequent versus conventional hemodialysis showed similar survival.

Health-related quality of life

In recent years, there has been substantial progress in recognizing the importance of patients' mental and physical well being. Thus, there has been considerable interest in understanding how more tailored hemodialysis regimens such as incremental hemodialysis influences patients' HRQOL, as well as patient satisfaction and experience. Theoretically, gradual transition to hemodialysis using an incremental regimen may attenuate the potential psychological, emotional, and physical strain experienced in the early stages of treatment, while also minimizing interruptions in patients' lifestyles (eg, employment status, social activities). However, the impact of less-frequent hemodialysis on patients' symptoms (eg, fatigue, pain, etc) has not yet been defined, which also could have downstream effects on patients' mental and physical states. In a study led by Bieber et al[43] examining a subcohort of Dialysis Outcomes and Practice Patterns Study patients from China, it was found that 26% of the sampled population received twice-weekly hemodialysis, and that HRQOL scores were similar among patients receiving twice-weekly versus treatment 3 times/week (Table 2).

Other benefits

Incremental hemodialysis also may have potential benefits on nutrition, vascular access preservation, and anemia indices, although further research in this area is needed.[5–7] With respect to nutrition, it is possible that frequent hemodialysis could worsen nutritional status by promoting dialytic losses of key nutrients. Conversely, it is unclear if incremental and less-frequent hemodialysis could aggravate malnutrition because prior studies have shown that patients converted from conventional to daily hemodialysis experienced greater appetite and protein intake. However, in a small study of hemodialysis patients from Taiwan, patients receiving twice-weekly treatment had similar nutritional indices, defined by serum albumin and normalized protein catabolic rate, compared with patients receiving treatment 3 times per week.[38] In another cross-sectional study of prevalent hemodialysis patients in Thailand receiving twice-weekly versus treatment 3 times per week, there were no differences in self-reported dietary protein intake across the two groups, and patients receiving twice-weekly treatment reported greater dietary energy intake than patients receiving treatment 3 times per week.[46] Given the paramount importance of vascular access as the life-line of dialysis, future research also is needed to determine the impact of incremental hemodialysis on access preservation. Indeed, prior research comparing more frequent versus conventional treatment regimens has shown that the former is associated with greater vascular access complications, likely owing to more frequent access cannulation and dialysis-associated inflammation.[47] Because less-frequent hemodialysis may reduce erythropoietin-stimulating agent resistance and cumulative dosage over time owing to reduced dialytic blood loss, iron deficiency, and inflammation associated with the dialysis procedure, future research examining the potential benefits of a less-frequent regimen on anemia indices, HRQOL, and cardiovascular status are needed.[5–7] Finally, individualizing hemodialysis prescriptions according to patients' residual kidney function and health status using a precision medicine approach may allow for reductions in excess dialysis treatment time and frequency, with subsequent improvement in patients' satisfaction and experience, as well as savings in medical costs.[5–7,10]

PRACTICAL IMPLEMENTATION OF INCREMENTAL HEMODIALYSIS

Criteria

It should be highlighted that beyond residual kidney function, there are additional factors that warrant consideration in tailoring incident ESKD patients' dialysis regimens using a precision medicine approach. For example, even in the presence of substantial residual kidney function, among patients with large fluctuations in volume status, active cardiovascular/pulmonary symptoms, higher comorbidity burden, large body habitus, uncontrolled potassium and phosphate levels, poor nutritional or hypercatabolic status, and suboptimal anemia indices, a more frequent (ie, conventional or frequent hemodialysis) treatment regimen may be preferred. Among experts

Table 3. Proposed Criteria for Incremental or Twice-Weekly Hemodialysis

Required criteria	Renal urea clearance >3 mL/min/1.73 m^2 and urine output >600 mL/d
Additional criteria (≥five required)	Limited fluid retention between two consecutive hemodialysis sessions Interdialytic weight gain <2.5 kg or <5% of ideal dry weight without hemodialysis for 3-4 days Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant volume overload Suitable body size relative to residual kidney function Patients with large body habitus may not be suitable for twice-weekly hemodialysis if not hypercatabolic Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant volume overload Infrequent or readily manageable hyperkalemia Infrequent or readily manageable hyperphosphatemia Adequate nutritional status without hypercatabolism Absence of profound anemia and appropriate responsiveness to erythropoietin-stimulating agents Infrequent hospitalization and readily manageable comorbidities Optimal HRQOL

in the field, 10 clinical criteria adapted from the 1997 KDOQI Peritoneal Dialysis Work Group and the European Best Practice Guidelines Expert Group on Hemodialysis guidelines have been proposed in identifying patients who may be suitable for incremental hemodialysis (Table 3).[31] It has been suggested that these criteria be reassessed routinely among patients receiving incremental hemodialysis, and that further refinement is needed to guide clinical practice and future research studies owing to a lack of supportive evidence.

Transition to More Frequent Hemodialysis Over Time

With respect to practical implementation, it is critical to emphasize that incremental hemodialysis is a dynamic treatment strategy that should be adjusted and tailored to changes in patients' residual kidney function and overall health status over time. Given prior rigorous research studies showing that incremental hemodialysis was associated with higher mortality risk among patients with minimal residual kidney function and higher comorbidity burden, the frequency of hemodialysis must be escalated promptly among patients on an incremental schedule who experience change in these characteristics.[6,7,31] Indeed, in a report documenting the experiences with 13 ambulatory incident hemodialysis patients enrolled in the University of California Irvine's Incremental Hemodialysis Program, five patients maintained a twice-weekly hemodialysis schedule whereas eight patients transitioned to a 3 times/week schedule over a 24-month period.[48] In addition, frequent hemodialysis also may benefit long-term survival among prevalent hemodialysis patients without residual kidney function.[49] Hence, there should be mutual understanding among patients and clinicians that dialysis frequency inevitably will increase over time.

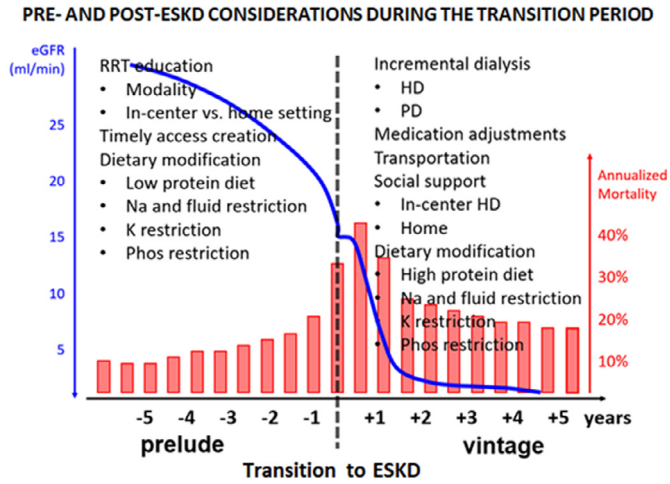


Figure 4. Pre- and post-end stage kidney disease considerations among patients transitioning to dialysis. eGFR, estimated GFR; HD, hemodialysis; PD, peritoneal dialysis; Phos, phosphorus; RRT, renal replacement therapy.

FUTURE DIRECTIONS

At this time, there are a number of areas requiring further research before the broad implementation of incremental hemodialysis. First, although observational studies have suggested that incremental hemodialysis may be an acceptable treatment strategy among incident ESKD patients transitioning to dialysis with substantial residual kidney function and low-to-moderate comorbidity burden, further studies including randomized controlled trials are needed to define its safety and effectiveness on patient-centric, intermediate, and hard outcomes, including HRQOL, patient symptoms, metabolic status, and cardiovascular status.[5–8,10,24] Second, determining which clinical characteristics are best suited for incremental dialysis and developing precision medicine tools that can identify which patients will maximally benefit from this treatment regimen that can be readily applied in the clinical setting are needed. Third, future research is needed to identify effective adjunctive therapies that promote patients' health on an incremental dialysis regimen in both the pre-transition and post-transition periods (Fig. 4), such as pharmacotherapies (ie, use of renin-angiotensin-aldosterone system inhibitors), social support, educational tools, and dietary interventions (ie, modulation of dietary protein and fluid intake, and amino acid or keto-analogue supplements). Finally, greater study of optimal thresholds for transitioning from incremental to conventional and more-frequent hemodialysis regimens are needed.

In conclusion, expanding the role of precision medicine in the field of nephrology can lead to paradigm shifts and improvements in the way that incident ESKD patients are transitioned to dialysis. The use of a precision nephrology approach has the potential to lead to new approaches and tools in the management of ESKD patients; forge new collaborations among clinicians, scientists, patients, patient advocacy groups, dialysis providers, and industry partners; and, most importantly, improve the health, well being, and survival of this population.[1–4]

REFERENCES

1. Centers for Disease Control and Prevention. Precision medicine: what does it mean for your health? [cited 2018 February 2]. Available from: https://www.cdc.gov/features/precision-medicine/index.html.
2. The White House Office of the Secretary. Fact sheet: President Obama's precision medicine initiative. [cited February 1, 2018]. Available from: https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative.
3. US National Library of Medicine, National Institutes of Health, Department of Health and Human Services. Precision Medicine. Lister Hill National Center for Biomedical Communications. [cited February 15, 2018]. Available from: https://ghr.nlm.nih.gov/primer#precisionmedicine.
4. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–5.
5. Obi Y, Eriguchi R, Ou SM, Rhee CM, Kalantar-Zadeh K. What Is known and unknown about twice-weekly hemodialysis. Blood Purif. 2015;40:298–305.
6. Rhee CM, Ghahremani-Ghajar M, Obi Y, Kalantar-Zadeh K. Incremental and infrequent hemodialysis: a new paradigm for both dialysis initiation and conservative management. Panminerva Med. 2017;59:188–96.
7. Rhee CM, Unruh M, Chen J, Kovesdy CP, Zager P, Kalantar-Zadeh K. Infrequent dialysis: a new paradigm for hemodialysis initiation. Semin Dial. 2013;26:720–7.
8. Toth-Manikowski SM, Shafi T. Hemodialysis prescription for incident patients: twice seems nice, but is it incremental. Am J Kidney Dis. 2016;68:180–3.
9. US Renal Data System. USRDS 2017 annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD:2017.
10. Kalantar-Zadeh K, Crowley ST, Beddhu S, et al. Renal replacement therapy and incremental hemodialysis for veterans with advanced chronic kidney disease. Semin Dial. 2017;30:251–61.
11. Kalantar-Zadeh K, Kovesdy CP, Streja E, et al. Transition of care from pre-dialysis prelude to renal replacement therapy: the blueprints of emerging research in advanced chronic kidney disease. Nephrol Dial Transplant. 2017;32(Suppl 2):ii91–8.
12. Blagg CR. The early history of dialysis for chronic renal failure in the United States: a view from Seattle. Am J Kidney Dis. 2007;49:482–96.
13. Scribner BH, Cole JJ, Ahmad S, Blagg CR. Why thrice weekly dialysis? Hemodial Int. 2004;8:188–92.
14. Shaldon S. Experience to date with home hemodialysis. In: Scribner BH, editor. Proceedings of the working conference on chronic dialysis. Seattle, WA. University of Washington; 1964. p. 66–9.
15. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. N Engl J Med. 1981;305:1176–81.
16. Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study. Am J Kidney Dis. 2010;56:348–58.
17. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010–9.
18. National Kidney Foundation. NKF-DOQI clinical practice guidelines for hemodialysis adequacy.. Am J Kidney Dis. 1997;30(Suppl 2):S15–66.
19. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. Am J Kidney Dis. 2006;48(Suppl 1):S2–90.
20. Mathew A, Obi Y, Rhee CM, et al. Treatment frequency and mortality among incident hemodialysis patients in the United States comparing incremental with standard and more frequent dialysis. Kidney Int. 2016;90:1071–9.
21. Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K. Preservation of residual kidney function in hemodialysis patients: reviving an old concept. Kidney Int. 2016;90:262–71.
22. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002;62:1046–53.
23. Vilar E, Wellsted D, Chandna SM, Greenwood RN, Farrington K. Residual renal function improves outcome in incremental haemodialysis despite reduced dialysis dose. Nephrol Dial Transplant. 2009;24:2502–10.

24. Wang AY. Preserving residual kidney function in hemodialysis patients-back in the spotlight. J Am Soc Nephrol. 2016;27:3504–7.
25. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001;12:2158–62.
26. Obi Y, Rhee CM, Mathew AT, et al. Residual kidney function decline and mortality in incident hemodialysis patients. J Am Soc Nephrol. 2016;27:3758–68.
27. Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13:1307–20.
28. Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis. 2001;38:85–90.
29. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004;15:1061–70.
30. van der Wal WM, Noordzij M, Dekker FW, et al. Full loss of residual renal function causes higher mortality in dialysis patients; findings from a marginal structural model. Nephrol Dial Transplant. 2011;26:2978–83.
31. 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;64:181–6.
32. Agrawal A, Saran R, Nolph KD. Continuum and integration of pre-dialysis care and dialysis modalities. Perit Dial Int. 1999;19 (Suppl 2):S276–80.
33. Mehrotra R, Nolph KD, Gotch F. Early initiation of chronic dialysis: role of incremental dialysis. Perit Dial Int. 1997;17:426–30.
34. Keshaviah PR, Emerson PF, Nolph KD. Timely initiation of dialysis: a urea kinetic approach. Am J Kidney Dis. 1999;33: 344–8.
35. Japanese Society for Dialysis Therapy. An overview of regular dialysis treatment in Japan as of December 31, 1997. Tokyo: Bunkyo-ku; 1997. p. 266.
36. Haghighi AN, Broumand B, D'Amico M, Locatelli F, Ritz E. The epidemiology of end-stage renal disease in Iran in an international perspective. Nephrol Dial Transplant. 2002;17:28–32.
37. Elamin S, Abu-Aisha H. Reaching target hemoglobin level and having a functioning arteriovenous fistula significantly improve one year survival in twice weekly hemodialysis. Arab J Nephrol Transplant. 2012;5:81–6.
38. Lin YF, Huang JW, Wu MS, et al. Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. Nephrology (Carlton). 2009;14:59–64.
39. 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;68:256–65.
40. Zhang M, Wang M, Li H, et al. Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. Am J Nephrol. 2014;40:140–50.
41. Hanson JA, Hulbert-Shearon TE, Ojo AO, et al. Prescription of twice-weekly hemodialysis in the USA. Am J Nephrol. 1999;19:625–33.
42. Lin X, Yan Y, Ni Z, et al. Clinical outcome of twice-weekly hemodialysis patients in Shanghai. Blood Purif. 2012;33:66–72.
43. Bieber B, Qian J, Anand S, et al. Two-times weekly hemodialysis in China: frequency, associated patient and treatment characteristics and Quality of Life in the China Dialysis Outcomes and Practice Patterns study. Nephrol Dial Transplant. 2014;29:1770–7.
44. Kalantar-Zadeh K, Casino FG. Let us give twice-weekly hemodialysis a chance: revisiting the taboo. Nephrol Dial Transplant. 2014;29:1618–20.
45. Daugirdas JT, Greene T, Rocco MV, et al. Effect of frequent hemodialysis on residual kidney function. Kidney Int. 2013;83: 949–58.
46. Supasyndh O, Satirapoj B, Seenamngoen S, Yongsiri S, Choovichian P, Vanichakarn S. Nutritional status of twice and thrice-weekly hemodialysis patients with weekly Kt/V >3.6. J Med Assoc Thai. 2009;92:624–31.
47. Group FHNT, Chertow GM, Levin NW, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363:2287–300.
48. Ghahremani-Ghajar M, Rojas-Bautista V, Lau WL, et al. Incremental hemodialysis: the University of California Irvine experience. Semin Dial. 2017;30:262–9.
49. Chertow GM, Levin NW, Beck GJ, et al. Long-term effects of frequent in-center hemodialysis. J Am Soc Nephrol. 2016;27: 1830–6.