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Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Dialysis Patients: A Cohort Study

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Background: Maintenance hemodialysis is typically prescribed thrice weekly irrespective of a patient's residual kidney function (RKF). We hypothesized that a less frequent schedule at hemodialysis therapy initiation is associated with greater preservation of RKF without compromising survival among patients with substantial RKF.

Study Design: A longitudinal cohort.

Setting & Participants: 23,645 patients who initiated maintenance hemodialysis therapy in a large dialysis organization in the United States (January 2007 to December 2010), had available RKF data during the first 91 days (or quarter) of dialysis, and survived the first year.

Predictor: Incremental (routine twice weekly for >6 continuous weeks during the first 91 days upon transition to dialysis) versus conventional (thrice weekly) hemodialysis regimens during the same time.

Outcomes: Changes in renal urea clearance and urine volume during 1 year after the first quarter and survival after the first year.

Results: Among 23,645 included patients, 51% had substantial renal urea clearance (≥ 3.0 mL/min/1.73 m²) at baseline. Compared with 8,068 patients with conventional hemodialysis regimens matched based on baseline renal urea clearance, urine volume, age, sex, diabetes, and central venous catheter use, 351 patients with incremental regimens exhibited 16% (95% CI, 5%-28%) and 15% (95% CI, 2%-30%) more preserved renal urea clearance and urine volume at the second quarter, respectively, which persisted across the following quarters. Incremental regimens showed higher mortality risk in patients with inadequate baseline renal urea clearance (≤ 3.0 mL/min/1.73 m²; HR, 1.61; 95% CI, 1.07-2.44), but not in those with higher baseline renal urea clearance (HR, 0.99; 95% CI, 0.76-1.28). Results were similar in a subgroup defined by baseline urine volume of 600 mL/d.

Limitations: Potential selection bias and wide CIs.

Conclusions: Among incident hemodialysis patients with substantial RKF, incremental hemodialysis may be a safe treatment regimen and is associated with greater preservation of RKF, whereas higher mortality is observed after the first year of dialysis in those with the lowest RKF. Clinical trials are needed to examine the safety and effectiveness of twice-weekly hemodialysis.

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INDEX WORDS: Incremental hemodialysis; twice-weekly hemodialysis; frequent hemodialysis; treatment regimen; residual kidney function (RKF); renal urea clearance; interdialytic weight gain; standard Kt/V; mortality; dialysis initiation.

Editorial, p. 180

Residual kidney function (RKF) in patients with end-stage renal disease plays a critical role in dialysis adequacy, quality of life, and survival

by maintaining fluid and metabolic homeostasis, mitigating mineral abnormalities, optimizing uremic toxin clearance, and sustaining higher endogenous vitamin D and erythropoietin production.¹⁻⁴ Endogenous clearance conferred by RKF is associated with greater survival than dialysis clearance per se,^{1,5}

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and at a certain RKF level, higher dialysis dose may not influence clinical outcomes in both peritoneal dialysis and hemodialysis patients.⁶⁻⁸ Furthermore, randomized controlled trials have shown inconsistent results in terms of clinical benefit of higher dialysis dose or frequency,⁹⁻¹⁴ and they may accelerate RKF decline.¹⁵

Incremental hemodialysis regimens (eg, dialysis therapy initiation at a lower frequency) were first suggested based on urea kinetic models in the late 1990s.^{16,17} Less frequent hemodialysis has been commonly prescribed in countries such as China and India,¹⁸⁻²⁰ and its combination with low-protein diet has been suggested for select patients on transition to dialysis therapy.^{21,22} The NKF-KDOQI (National Kidney Foundation—Kidney Disease Outcomes Quality Initiative) guidelines also suggested a twice-weekly schedule for patients with “substantial residual renal urea clearance” (ie, ≥ 3.0 mL/min/1.73 m²) in 2006.¹ Nevertheless, most patients initiating maintenance hemodialysis therapy in the United States are prescribed thrice-weekly treatments irrespective of RKF. Given that estimated glomerular filtration rate is > 10 mL/min/1.73 m² upon initiation of maintenance dialysis therapy in up to 45% of patients in the United States,^{23,24} the incremental hemodialysis regimen may preserve RKF and offer both clinical and economic advantages.²⁵⁻²⁸

More frequent hemodialysis may lead to faster loss of RKF through several mechanisms, such as the release of nephrotoxic inflammatory mediators during hemodialysis and ischemic kidney damage caused by intradialytic hypotension and postdialytic hypovolemia.^{29,30} The marked reduction in blood urea levels by more frequent hemodialysis therapy can also decrease osmotic diuresis,³¹ and intense dialysis may deactivate the remaining nephrons (intact nephron hypothesis in reverse).³² Moreover, previous studies have suggested that hemodialysis patients on twice-weekly schedules may have similar or lower risk for death compared with those on thrice-weekly schedules.^{27,33,34} However, differences in RKF were not appropriately taken into account in these studies, an important consideration because higher RKF is consistently associated with better survival.⁴⁻⁶ Therefore, we investigated the association of the incremental regimen with longitudinal trends in RKF and survival in a cohort of incident hemodialysis patients from a large dialysis organization in the United States. We hypothesized that an incremental hemodialysis regimen is associated with greater preservation of RKF over time without compromising survival among patients with substantial RKF.

METHODS

Patients

We retrospectively extracted, refined, and examined electronic data from all incident in-center hemodialysis patients 18 years or

older treated in facilities operated by a large dialysis organization in the United States from January 1, 2007, through December 31, 2010.³⁵ Patient follow-up time was divided into patient-quarters (91-day periods from date of initial dialysis). For each patient-quarter, patients were assigned a modality if they received treatments at least 45 days within the patient quarter. Patient who received a consistent treatment schedule (eg, Monday/Thursday or Monday/Friday) of twice-weekly hemodialysis for more than 6 continuous weeks within the first patient-quarter were categorized as the incremental-regimen group. The rest of the patients were categorized as the conventional-regimen group.

To examine trends of RKF during 1 year after the baseline quarter (eg, the first 91 days of dialysis, or months 1-3),⁴ we selected 23,645 incident in-center hemodialysis patients who had both residual renal urea clearance and urine volume data at baseline and retained a mean treatment frequency of 1.5 to less than 3.5 times per week during the first 4 patient-quarters (Fig S1, available as online supplementary material). The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA and University of California Irvine Medical Center. Given the large sample size, anonymity of the patients studied, and noninvasive nature of the research, requirement for consent was exempted.

Demographic, Clinical, and Laboratory Measures

Information for self-reported race/ethnicity, primary insurance, access type, and the presence of comorbid conditions at baseline was obtained from the electronic database of the dialysis provider.

Among 61,492 urine collections during months 1 to 15, a total of 98% of samples were collected over 24 hours, whereas others were collected over 12 hours or 44 hours or longer and corrected to 24-hour-equivalent values. Blood samples were drawn using uniform techniques in all dialysis clinics and transported to the central laboratory in Deland, FL, typically within 24 hours. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, whereas serum ferritin and intact parathyroid hormone were measured at least quarterly and hemoglobin was measured weekly to biweekly in most patients. Dialysis dose, renal urea clearance, weekly percentage interdialytic weight gain (IDWG), and normalized protein catabolic rate (nPCR) were calculated using urea kinetic modeling equations (see Item S1 for details).^{1,36-41}

To minimize measurement variability, all repeated measures for each patient during any given patient-quarter (91 days) were averaged and the quarterly mean values in each quarter were used in all analyses.

Statistical Methods

To examine associations of incremental hemodialysis with changes in RKF indexes and survival, we matched patients by using coarsened exact matching with weighting based on baseline renal urea clearance (cutoff points: 1.5, 3.0, 6.0, and 9.0 mL/min/1.73 m²), urine volume (cutoff points: 300, 600, 1,200, and 1,800 mL/d), age (cutoff points: 50, 65, and 80 years), sex, race, central venous catheter as vascular access, and diabetes.⁴² Six of 351 patients with the incremental regimen were not matched originally with coarsened exact matching, but each was subsequently matched to the closest possible unmatched case with appropriate weighting.

Because of its right-skewed distribution, renal urea clearance and urine volume were natural log (ln)-transformed after adding 1 and 100, respectively. Changes in RKF indexes, dialysis frequency, dialysis treatment time, and selected laboratory variables between incremental versus conventional regimens were estimated by fitting linear mixed-effects models using the maximum-likelihood estimator, in which interaction terms between patient-quarters and hemodialysis regimen represent differences in the slopes for each

outcome from baseline. Changes in ln-transformed RKF indexes are expressed as relative ratios in the incremental versus conventional regimens with 2 levels of adjustment; (1) case-mix-adjusted models that included primary insurance (Medicare, Medicaid, and other) and history of hypertension and cardiovascular disease, and (2) fully adjusted models that included covariates in the case-mix model plus body mass index and 9 laboratory variables (normalized protein catabolic rate, hemoglobin, serum albumin, creatinine, albumin-corrected calcium, phosphorus, and natural log-transformed intact parathyroid hormone, ferritin, and bicarbonate). Because standard Kt/V delivered by dialysis (K_{dt}/V_{dial}) is inherently associated with the hemodialysis regimen, it was not included in multivariable models to avoid overadjustment.

Survival analyses with unadjusted Cox regressions after year 1 were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality in the matched cohort. Sensitivity analyses were conducted for the entire cohort of 23,645 patients, as well as those who met study criteria with different survival periods (3, 6, 9, and 12 months), where we adjusted for matching variables plus case-mix variables except for urine volume. Effect modification by baseline renal urea clearance, urine volume, and weekly percentage IDWG was examined by putting interaction terms with the incremental regimen into regression models without categorization, followed by subgroup analyses. Proportional hazards assumptions were tested using log-log against survival plots and Schoenfeld residuals.

Differences in patient characteristics between groups were compared by standardized differences, of which 80%, 50%, and 20% were considered large, medium, and small differences, respectively, and $\geq 10\%$ was defined as meaningful imbalance.^{43,44} In fully adjusted models, multiple imputation methods with 5 data sets were used for missing longitudinal covariate data ($<1\%$ for body mass index and most laboratory tests, 4% for creatinine, and 5% for nPCR) but not for renal urea clearance and urine volume, which were examined without imputation. We used multivariate normal regression, in which we accounted for clustering by incorporating all available data for up to 5 patient-quarters (from months 1-3 through 13-15). All analyses were carried out with STATA MP, version 13.1 (StataCorp LP).

RESULTS

Baseline Demographic, Clinical, and Laboratory Characteristics

Among 69,811 incident in-center hemodialysis patients who survived their first year of dialysis, prevalences of the twice-weekly schedule in the first 4 patient-quarters were 0.9% ($n = 647$), 1.4% ($n = 963$), 1.6% ($n = 1,114$), and 1.7% ($n = 1,173$), respectively. Of 63,368 patients who either received twice-weekly or thrice-weekly hemodialysis treatment (after removing lower and higher treatment frequencies; Fig S1), 23,645 (37%) patients had measured renal urea clearance at baseline (eg, the first patient-quarter or first 91 days of dialysis, or months 1-3) and were included in the study. Differences in characteristics between included and excluded patients are shown in Table S1. In the 23,645 patients who survived the first year and had baseline renal urea clearance, we identified 53,528 quarterly averaged data from simultaneous measurements for renal urea clearance and urine volume up to the fifth

patient-quarter (eg, months 1-15). There was a strong correlation between ln-transformed renal urea clearance and urine volume ($r = 0.85$; $P < 0.001$).

Median renal urea clearance and urine volume were 3.04 mL/min/1.73 m² (interquartile range [IQR], 1.70-4.82) and 800 mL/d (IQR, 500-1,300) at baseline, respectively, and the prevalence of patients with baseline renal urea clearance >3.0 mL/min/1.73 m² (ie, the minimum renal urea clearance recommended for twice-weekly hemodialysis per NKF-KDOQI guidelines)¹ was 51%. Baseline renal urea clearance and urine volume were higher in 351 patients who initiated hemodialysis treatment with a twice-weekly schedule in the first patient-quarter compared with the 23,294 other patients (Table 1). Older patients and non-Hispanic whites were more likely, whereas non-Hispanic blacks and those with a central venous catheter were less likely to receive twice-weekly hemodialysis. The incremental regimen was also associated with an average 17-minute shorter dialysis treatment time, less weekly cumulative percentage IDWG, and lower standard Kt/V. The prevalence of patients with 2.1 or higher total standard Kt/V (the recommended minimum level of urea removal per NKF-KDOQI guidelines)^{1,2} was $>95\%$ in patients with renal urea clearance >3.0 mL/min/1.73 m² irrespective of hemodialysis schedule, but was largely different between schedules in those with renal urea clearance ≤ 3.0 mL/min/1.73 m² (30% and 90% in twice-weekly vs conventional hemodialysis, respectively; standardized difference $>90\%$; Fig 1).

We then matched all 351 patients in the incremental-regimen group to 8,068 (35%) of 23,294 patients in the conventional-regimen group. Differences in baseline characteristics between the 2 groups were largely attenuated by this matching procedure except for variables potentially associated with treatment regimen, including weekly IDWG, dialysis treatment time, standard Kt/V delivered by dialysis, nPCR, hemoglobin, corrected calcium, ferritin, and bicarbonate values (Table 1). In this matched cohort, both renal urea clearance and urine volume showed significantly slower declines over time in the incremental versus conventional regimens ($P < 0.001$ for both; Fig 2). Case-mix-adjusted relative ratios from baseline at the second patient-quarter were 1.16 (95% CI, 1.05-1.28) and 1.15 (95% CI, 1.02-1.30) for renal urea clearance and urine volume, respectively, and remained significant across the following quarters irrespective of adjustment models. Trends in selected parameters showed that patients treated with the incremental regimen had less dialysis frequency, shorter dialysis time, lower hemoglobin and serum corrected calcium concentrations, and higher serum ferritin concentrations at baseline, but these differences were attenuated over time (Table S2). Nevertheless, the

Table 1. Baseline Characteristics of 23,645 Incident Hemodialysis Patients Who Survived for 12 Months and Had Urine Collection Data During First Year

	Incremental HD	Conventional HD			
		Matched	Std Diff ^a	Entire	Std Diff ^a
No. of patients	351	8,068		23,294	
Renal urea clearance	4.8 [3.2-6.7]	4.6 [3.2-6.5]	4%	3.0 [1.7-4.8]	35%
≤3.0 mL/min/1.73 m ²	73 (21%)	1,655 (21%)		11,568 (50%)	
>3.0-6.0 mL/min/1.73 m ²	169 (48%)	3,908 (48%)		8,335 (36%)	
>6.0 mL/min/1.73 m ²	109 (31%)	2,505 (31%)		3,391 (15%)	
Urine volume	1,150 [800-1,650]	1,150 [775-1,650]	2%	800 [500-1,300]	23%
≤600 mL/d	54 (15%)	1,241 (15%)		8,743 (38%)	
>600-1,200 mL/d	139 (40%)	3,195 (40%)		7,958 (34%)	
>1,200 mL/d	158 (45%)	3,632 (45%)		6,593 (28%)	
Weekly cumulative IDWG	4.6 ± 2.3	6.5 ± 3.2	70%	7.2 ± 3.3	>90%
<3%	87 (25%)	977 (12%)		1,880 (8%)	
3%-<6%	181 (51%)	2,814 (35%)		7,091 (30%)	
≥6%	83 (24%)	4,272 (53%)		14,313 (62%)	
Age, y	69 ± 14	68 ± 13	7%	61 ± 15	54%
Male sex	210 (60%)	4,827 (60%)	<1%	14,541 (62%)	5%
Race					
Non-Hispanic white	251 (72%)	5,769 (72%)	<1%	11,837 (51%)	42%
Non-Hispanic black	44 (13%)	1,011 (13%)	<1%	6,961 (30%)	42%
Hispanic	23 (7%)	722 (9%)	9%	2,724 (12%)	18%
Others	33 (9%)	565 (7%)	9%	1,772 (8%)	6%
Insurance					
Medicare	213 (61%)	4,463 (55%)	11%	11,691 (50%)	21%
Medicaid	11 (3%)	355 (4%)	7%	1,609 (7%)	17%
Other	127 (36%)	3,250 (40%)	8%	9,994 (43%)	14%
Comorbid conditions					
Diabetes	231 (66%)	5,310 (66%)	<1%	15,746 (68%)	4%
Hypertension	193 (55%)	4,124 (51%)	8%	12,178 (52%)	5%
Cardiovascular disease	172 (49%)	4,421 (55%)	12%	12,963 (56%)	13%
Weekly HD frequency	2.0 ± 0.2	2.7 ± 0.3	>90%	2.7 ± 0.3	>90%
Central venous catheter	196 (56%)	4,502 (56%)	<1%	16,774 (72%)	33%
Dialysis time, min/session	191 ± 24	203 ± 24	50%	208 ± 24	72%
Standard Kt/V per week					
Dialysis ^b	1.4 ± 0.2	2.1 ± 0.3	>90%	2.2 ± 0.3	>90%
Renal ^{b,c}	1.2 [0.8-1.7]	1.1 [0.8-1.6]	7%	0.7 [0.4-1.2]	41%
Total ^{b,c}	2.7 [2.3-3.1]	3.3 [2.9-3.7]	>90%	2.9 [2.6-3.4]	65%
Total >2.1 ^{b,c}	276 (81%)	7,626 (98%)	54%	21,281 (94%)	39%
BMI, kg/m ²	26.9 [23.3-31.6]	27.5 [23.8-32.1]	10%	27.6 [23.8-32.9]	18%
nPCR, g/kg/d ^{b,c}	1.0 ± 0.3	1.1 ± 0.3	17%	1.0 ± 0.3	12%
Laboratory data					
Hemoglobin, g/dL	11.4 ± 1.0	11.6 ± 1.0	17%	11.4 ± 1.1	<1%
Albumin, g/dL	3.7 ± 0.4	3.7 ± 0.4	6%	3.6 ± 0.4	20%
Creatinine, mg/dL	5.1 ± 2.0	5.2 ± 1.8	4%	6.1 ± 2.3	45%
Corrected calcium, mg/dL	9.0 ± 0.5	9.1 ± 0.6	17%	9.1 ± 0.5	15%
Phosphorus, mg/dL	4.8 ± 1.0	4.9 ± 1.0	5%	5.1 ± 1.1	26%
Intact PTH, pg/mL	276 [170-412]	275 [180-399]	3%	320 [211-480]	9%
Ferritin, ng/mL	215 [131-349]	243 [146-391]	13%	253 [146-422]	15%
Bicarbonate, mEq/L	22.6 ± 2.7	23.1 ± 2.6	21%	23.3 ± 2.6	27%

Note: Differences in patient characteristics between groups were compared by Std Diffs, of which 80%, 50%, and 20% were considered large, medium, and small differences, respectively, and ≥0.1 was defined as meaningful imbalance.^{42,43} Values for categorical variables are given as number (percentage); values for continuous variables, mean ± standard deviation or median [interquartile range]. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; creatinine in mg/dL to μmol/L, ×88.4; phosphorus in mg/dL to mmol/L, ×0.3229.

Abbreviations: BMI, body mass index; HD, hemodialysis; IDWG, interdialytic weight gain; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; Std Diff, standardized difference.

^aHD treatment regimen is based on treatment in first quarter (3 months).

^bCalculated using single-pool Kt/V delivered by dialysis.

^cCalculated using renal urea clearance.

Figure 1. Achievement rate of the minimum total standard Kt/V > 2.1 among patients with the incremental and conventional hemodialysis (HD), stratified by renal urea clearance (KRU).

2 regimen groups were clearly separated throughout the study period in terms of dialysis frequency.

In survival analyses after year 1, we did not detect a significant difference in all-cause mortality between the incremental and conventional hemodialysis regimens (HR, 1.11; 95% CI, 0.89-1.38; $P = 0.3$; Fig 3).

Subgroup analyses showed that the incremental regimen was associated with higher mortality risk in patients with inadequate RKF (HRs of 1.61 [95% CI, 1.07-2.44] and 1.61 [95% CI, 1.04-2.50] for renal urea clearance ≤ 3.0 mL/min/1.73 m² and urine volume ≤ 600 mL/d, respectively, but not in those with higher baseline RKF levels [HRs of 0.99 [95% CI, 0.76-1.28] and 1.02 [95% CI, 0.79-1.31] for renal urea clearance > 3.0 mL/min/1.73 m² and urine volume > 600 mL/d, respectively; Fig 4). Meanwhile, a significant trend toward better survival in patients with the incremental regimen was observed across higher increments of renal urea clearance and lower increments of weekly IDWG (P for trend = 0.05 and 0.03, respectively), but not in urine volume categories (P for trend = 0.2).

In order to examine potential survival bias that might have weakened the association between the incremental regimen and mortality, we conducted case-mix-adjusted Cox models without matching by using patients who had different survival periods (3, 6, 9, and 12 months) and met the other study criteria.

Figure 2. Trends over time of the mean and relative ratio of residual kidney function in the matched cohort of 8,419 patients across 5 patient-quarters (PQs; the conventional vs incremental hemodialysis [HD] regimen). Analyses of (A, C) renal urea clearance (KRU) and (B, D) urine volume (UV). Data are based on weighted match according to baseline KRU and UV, as well as age, sex, race, central venous catheter as vascular access, and history of diabetes. Points and error bars represent point estimates and 95% confidence intervals, respectively.

Figure 3. Kaplan-Meier survival curve and confidence intervals (CIs) for all-cause death after year 1 in the matched cohort of 8,419 patients. Abbreviations: HD, hemodialysis; HR, hazard ratio.

When the survival period exceeded 3 months, the mortality risk of the incremental regimen appeared to be enhanced in patients with inadequate RKF, whereas it remained similarly insignificant in those with higher RKF (Fig 5). A trend toward lower mortality risk for the incremental regimen was observed across higher increments of renal urea clearance in 6-, 9-, and 12-month survivors (P for trend = 0.02, 0.004, and 0.01, respectively), across higher increments of urine volume in 6- and 9-month survivors (P for trend = 0.02 and 0.01, respectively), and across lower increments of weekly IDWG in 3-, 9-, and 12-month survivors (P for trend = 0.05, 0.01, and 0.02, respectively).

DISCUSSION

In this longitudinal cohort of 23,645 patients who initiated in-center hemodialysis therapy in a large dialysis organization in the United States during 2007 to 2010, half of the patients had baseline renal urea clearance above the NKF-KDOQI-recommended level to qualify for twice-weekly hemodialysis,¹ but routine prescription of twice-weekly hemodialysis was infrequent (<2%) throughout the observation period. Most patients with baseline renal urea clearance >3.0 mL/min/1.73 m² had standard Kt/V >2.1 irrespective of regimens, but if they had less renal urea clearance, two-thirds of those with the incremental regimen did not meet that minimum dialysis adequacy dose. The incremental hemodialysis regimen was significantly associated with moderate preservation of renal urea clearance and urine volume independent of other clinically relevant factors. The incremental regimen was associated with higher all-cause mortality in patients with inadequate baseline RKF (renal urea clearance ≤ 3.0 mL/min/1.73 m² or

Figure 4. Overall and subgroup analyses of the association of the incremental regimen (vs conventional regimen) with all-cause mortality in the matched cohort of 8,419 patients. Points and error bars represent point estimates and 95% confidence intervals, respectively. Abbreviations: HD, hemodialysis; IDWG, interdialytic weight gain; KRU, residual renal urea clearance.

urine volume ≤ 600 mL/d), whereas survival was similar when RKF indexes were above these thresholds, and a trend toward greater survival with larger baseline renal urea clearance or less weekly IDWG was observed. Our results suggest that twice-weekly hemodialysis may be a safe and even preferred regimen to preserve RKF over time following the initiation of maintenance dialysis therapy, especially in patients with substantial RKF. However, caution against twice-weekly hemodialysis may be needed for patients with little or no RKF.

Less frequent hemodialysis may provide several benefits if appropriately implemented in qualified patients with substantial RKF. First, medical costs for hemodialysis at the individual and population-based levels would be substantially lower given that it typically costs \$200 to \$300 per session and as many as 10,000 patients ($\sim 50\%$) in our study had baseline renal urea clearance >3.0 mL/min/1.73 m² and hence could have been eligible for a twice-weekly schedule. Because approximately 110,000 patients initiate hemodialysis therapy annually in the United States and half of these incident hemodialysis patients have substantial RKF on dialysis therapy initiation,²³ our data suggest that if these patients are treated with the incremental hemodialysis regimen during the first several months of therapy, a quarter to half a billion dollars can be saved every year, with greater preservation of RKF. Other benefits of less frequent hemodialysis include greater preservation of vascular access and positive impact on various patient-centered outcomes, such as more time spent engaging in activities outside the hemodialysis unit, less fatigue following hemodialysis treatment, and potentially better quality of life.^{3,19,20} To that end, the incremental

Figure 5. Case-mix-adjusted mortality risk of the incremental hemodialysis regimen among patients in the entire cohort stratified by baseline renal urea clearance (KRU), urine volume, or weekly interdialytic weight gain (IDWG) across the survival periods of 3, 6, 9, and 12 months (M). Points and error bars represent point estimates and 95% confidence intervals, respectively.

regimen may gain acceptance among patients and medical providers by virtue of these advantages alone, whereas it may also confer superior survival benefits in patients who transition to dialysis therapy with higher RKF at baseline, which warrants controlled trials.

The NKF-KDOQI guidelines advise against twice-weekly hemodialysis among patients with renal urea clearance <2 mL/min/1.73 m², which is likely based on the estimation of a minimum standard Kt/V of 2.1 per week that was obtained from observational studies in which the association of Kt/V with survival was examined.^{1,2,9} However, with a regular dialysis dose of single-pool Kt/V of 1.2, renal urea clearance >3 mL/min/1.73 m² would be required to meet the minimum standard Kt/V with twice-weekly hemodialysis.²⁸ Our subgroup analyses provide additional evidence that patients who have substantial RKF (renal urea clearance >3 mL/min/1.73 m² or urine volume >600 mL/d) may safely initiate twice-weekly hemodialysis on their transition to renal replacement therapy. Our study also suggested the potential harm of twice-weekly hemodialysis for patients with little or no RKF. These results are consistent with some previous studies.¹⁰⁻¹⁵ The National Cooperative Dialysis Study, with rather limited participation of those with creatinine clearances <3 mL/min, showed the benefit of maintaining lower blood urea nitrogen concentrations.¹⁰ In the FHN (Frequent Hemodialysis Network) Daily Trial, which showed reduced left ventricular hypertrophy and better survival in patients with frequent in-center hemodialysis, most patients had dialysis vintages of 2 or more years and two-thirds of patients were anuric.^{11,12} In contrast, in the

FHN Nocturnal Trial, in which higher mortality was observed in the frequent nocturnal hemodialysis group, patients had comparatively shorter dialysis vintages (~ 1 year in median), and about half the patients had urine volumes >500 mL/d.¹³⁻¹⁵ Taken together, although the removal of uremic toxins by more frequent hemodialysis may have a favorable impact on survival for patients with little or no RKF, there may be more harm if more frequent hemodialysis leads to faster loss of RKF and inferior health-related quality of life for patients who had substantial RKF. The benefit versus harm of twice-weekly hemodialysis may depend on patients' RKF, while other factors, including comorbid conditions, life expectancy, medication adherence, medical resources, and dietary intake, may also play roles.²⁸

In addition to RKF, weekly cumulative percentage IDWG also significantly modified the relationship between hemodialysis frequency and mortality. This finding is in line with some previous studies that showed high mortality in hemodialysis patients with high IDWG or high ultrafiltration rate.⁴⁵⁻⁴⁹ It should also be noted that even after matching on renal urea clearance or urine volume, the incremental-regimen group had less weekly IDWG, resulting in almost equivalent ultrafiltration volumes at each hemodialysis session compared to the conventional-regimen group. Patients with the incremental hemodialysis regimen might have been instructed to limit their daily fluid intake, which potentially led to decreased food intake. IDWG is linked to nutritional status,⁵⁰ and our matched cohort showed a small but significant difference in nPCR favoring the conventional

regimen. Also, they might have received diuretics more frequently to manage their IDWG.^{1,51} It is unclear from our results whether patients should restrict their fluid intake when undergoing twice-weekly hemodialysis, and additional studies are needed to examine the effect of hemodialysis frequency on nutritional status and hemodynamics associated with fluid retention and ultrafiltration.

Our study should be qualified for several limitations. First, potential confounding by indication may exist, such that physicians may be less likely to prescribe twice-weekly hemodialysis to patients with lower RKF or higher comorbid condition burden. Second, patients who survived at least 1 year following hemodialysis therapy initiation were included, which might have introduced survivor bias. However, sensitivity analyses using different survival periods confirmed that the mortality risk of the incremental regimen remained similarly insignificant across survival periods in patients with higher RKF (Fig 5). Third, the relatively small sample size of patients with the incremental regimen resulted in wide CIs for the estimated associations, especially in subgroup survival analyses, and might have inflated the likelihood of type II error in our analyses. Additionally, available RKF measures may not be representative of the entire source population's RKF because dialysis patients with the lowest RKF are less likely to have undergone urine collections. Last, the estimated relative ratios of change in RKF were dominantly driven by patients who had subsequent RKF measurements over the upcoming 12 months (incremental regimen, 304 of 351 patients; conventional regimen, 17,585 of 23,294 patients). While this method might lead to selection bias, our matched and multivariable-adjusted analyses were an effort to account for these potential confounders.

In conclusion, in our select cohort of incident hemodialysis patients with measured RKF, the incremental hemodialysis regimen that starts with a twice-weekly schedule on transition to dialysis therapy is associated with greater preservation of RKF in the first 15 months and may be safely implemented among incident hemodialysis patients with substantial RKF. However, it was associated with high mortality in patients with less RKF after the first year. Periodical evaluation of RKF may be useful to individualize hemodialysis treatment. Further studies, especially randomized controlled trials, are needed to identify patients who would most benefit from the incremental regimen by evaluating its impact on RKF preservation, survival, and other relevant outcomes, including cost-effectiveness and patient-centered outcomes, before implementing incremental regimen protocols in practice.

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Contributions: Research idea and study design: YO, KK-Z; data acquisition: RM, KK-Z; data analysis/interpretation: YO, CMR, AC, JC, ANA, ATM, CPK, RM, KK-Z; statistical analysis: YO, ES, VR; supervision or mentorship: CPK, RM, KK-Z. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KK-Z takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Baseline demographic and clinical characteristics in 76,960 incident in-center HD patients who survived first year of treatment.

Table S2: Trends over time of HD frequency, treatment time, and laboratory variables at each quarter in matched cohort.

Figure S1: Study flow diagram.

Item S1: Dialysis dose, residual renal urea clearance, and nPCR.

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