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Treatment frequency and mortality among incident hemodialysis patients in the United States comparing incremental with standard and more frequent dialysis

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Most patients with end-stage renal disease in the United States are initiated on thrice-weekly hemodialysis (HD) regimens. However, an incremental approach to HD may provide several patient benefits. We tested whether initiation of incremental HD does or does not compromise survival compared with a conventional HD regimen. The survival of 434 incremental, 50,162 conventional, and 160 frequent HD patients were compared using Cox regression analysis after matching for demographic and comorbid factors in a longitudinal national cohort of adult incident HD patients enrolled between January 2007 and December 2011. Sensitivity analysis included adjustment for residual kidney function. After adjustment for residual kidney function, all-cause mortality was not significantly different in the incremental compared with conventional HD group (hazard ratio 0.88, 95% confidence interval 0.72–1.08), but was higher in the frequent compared with the conventional HD group (hazard ratio, 1.56, 95% confidence interval 1.21–2.03). The comorbidity burden modified the association of treatment frequency and mortality, with higher comorbidity associated with higher mortality in the incremental HD group (hazard ratio, 1.77, 95% confidence interval 1.20–2.62) for a Charlson Comorbidity Index of ≥5. Thus, among incident HD patients with low or moderate comorbid disease, survival was similar for patients initiated on an incremental or conventional HD regimen. Clinical trials are needed to examine the safety and effectiveness of incremental HD and the selected patient populations who may benefit from an incremental approach to HDs initiation.

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In the United States, there are >450,000 prevalent patients with end-stage renal disease treated with maintenance dialysis, with ~114,800 patients who newly initiated hemodialysis (HD) as of 2012.[1] Most HD patients are conventionally prescribed a standard thrice-weekly schedule with little individualization of the initial HD regimen.[2–4] Dialysis patients have a 6 to 8 times higher mortality risk than age-matched Medicare patients in the general population,[1] with the highest risk observed during the first 6 months after HD initiation.[5] Many potential risk factors may explain this early high mortality, such as a lack of predialysis nephrology care, a lack of permanent vascular accesses, and preexisting cardiovascular disease or other coexisting medical illnesses.[6] However, the impact of an abrupt transition to a "full-dose" thrice-weekly HD regimen versus a gradual transition by incrementally increasing the HD prescription over several months on mortality risk has not been examined in controlled trials. Randomized, controlled trials of a higher dialysis dose or frequency have shown inconsistent results[7–12] and may accelerate residual kidney function (RKF) decline.[13]

An incremental approach to HD initiation may offer many potential benefits to patients, including better preservation of an arteriovenous fistula, reduced cost, and preservation of RKF. Less frequent (i.e., twice weekly) HD has been associated with greater preservation of RKF after initiation of HD,[14–16] and higher RKF is associated with better patient survival in both PD and HD patients.[17,18] Preservation of RKF may play a key role in the potential association of less frequent HD and survival. This may be of particular importance among incident HD patients because many patients have substantial RKF when transitioning to end-stage renal disease.[16]

We examined a 5-year nationally representative cohort of incident HD patients to determine the outcome of mortality with a conventional HD treatment regimen compared with incremental or frequent HD regimen. We hypothesized that initiation of HD with an incremental approach does not compromise survival compared with a conventional HD regimen.

RESULTS

Baseline patient characteristics of entire and matched cohorts

The final entire study cohort comprised of 87,718 patients from 1737 facilities including 682 incremental (twice weekly or less) HD patients from 444 facilities and 201 frequent (≥4 times weekly) HD patients from 158 facilities (Supplementary Table S1). Compared with the conventional HD patients, the incremental HD patients tended to be older and non-Hispanic white and to have less comorbid burden, whereas the frequent HD patients tended to be younger, male, and non-Hispanic white and to have higher likelihood of having a central venous catheter and a higher comorbid burden (standardized difference >0.1). The final matched cohort included 434 incremental HD patients, 50,162 conventional HD patients, and 160 frequent HD patients (Table 1). Even after matching based on age, sex, race, ethnicity, Charlson

Table 1 | Baseline characteristics by treatment regimen in the matched cohort of 50,756 incident HD patients

Variable	Conventional HD, % n = 50,162	Frequent HD, % n = 160	Std. Diff.	Incremental HD, % n = 434	Std. Diff.
Charlson Comorbidity Index	3 (IQR, 2–4)	3 (IQR, 3–4)	0.03	3 (IQR, 3–4)	0.01
2 (renal disease only)	24	24	0	24	0
3–4	62	62	0	62	0
5	7	7	0	7	0
6	6	6	0	6	0
≥7	1	1	0	1	0
Age (yr)	63 ± 13	62 ± 14	0.06	64 ± 13	0.04
Male (%)	65	65	0	65	0
Race (%)					
Non-Hispanic white	58	58	0	58	0
Non-Hispanic black	29	29	0	29	0
Others	12	12	0	11	0.02
Medicare as primary insurance (%)	54	53	0.03	49	0.10
Central venous catheter use (%)	84	84	0	84	0
Primary disease (%)					
Diabetic nephropathy	49	46	0.06	43	0.11
Hypertensive nephrosclerosis	28	21	0.17	29	0.01
Glomerulonephritis	8	14	0.17	11	0.09
Polycystic kidney disease	1	1	0.05	3	0.11
Others	13	19	0.15	14	0.03
Comorbidities (%)					
Cardiovascular disease	28	36	0.18	31	0.06
Fluid overload	6	64	>0.9	7	0.03
Body mass index (kg/m^2)	26.8 (IQR, 23.1–31.9)	30.6 (IQR, 24.6–37.6)	0.38	26.3 (IQR, 22.8– 30.5)	0.17
Postdialysis body weight (kg)	77 (IQR, 65–92)	91 (IQR, 70–116)	0.36	77 (IQR, 64–91)	0.15
Weekly %IDWG	7.7 ± 3.5	9.5 ± 3.8	0.50	5.8 ± 3.2	0.54
Single-pool Kt/V	1.38 ± 0.30	1.27 ± 0.34	0.37	1.36 ± 0.33	0.09
Renal CL_{urea} (ml/min per 1.73 m^2)	3.1 (IQR, 1.8–4.8)	1.9 (IQR, 1.3–3.2)	0.48	5.4 (IQR, 3.1–.3)	0.88
Laboratory variables					
Hemoglobin (g/dl)	11.3 ± 1.2	10.6 ± 1.1	0.58	11.0 ± 1.2	0.24
Albumin (mg/dl)	3.54 ± 0.45	3.47 ± 0.44	0.18	3.56 ± 0.52	0.04
Creatinine (mg/dl)	5.9 ± 2.3	5.7 ± 2.6	0.07	4.4 ± 2.0	0.68
Calcium (mg/dl)	9.1 ± 0.6	9.0 ± 0.4	0.14	9.1 ± 0.5	0.01
Phosphorus (mg/dl)	5.0 ± 1.2	4.8 ± 1.3	0.12	4.3 ± 1.0	0.62
Intact PTH (pg/ml)	321 (IQR, 205–492)	275 (IQR, 187–443)	0.20	253 (IQR, 321–427)	0.24
Iron saturation (%)	23 ± 9	19 ± 7	0.49	23 ± 10	0.05
Ferritin (pg/nl)	270 (IQR, 158– 460)	256 (IQR, 138–418)	0.10	287 (IQR, 270– 511)	0.11
Bicarbonate (mmol/l)	23.7 ± 2.8	24.1 ± 2.7	0.13	24.3 ± 3.2	0.19

CL_{urea}, urea clearance; HD, hemodialysis; %IDWG, percentage of interdialytic weight gain; IQR, interquartile range; PTH, parathyroid hormone; Std. Diff., standardized difference.

Values are expressed as mean ± SD, median (IQR), or percentage, as appropriate. Data are based on weighted match according to age, sex, race, central venous catheter as vascular access, and the Charlson Comorbidity Index.

Data on laboratory tests were extracted during the first 91 days of dialysis, and those except for ferritin and iPTH were further restricted to the initial thrice-weekly HD period before starting infrequent or frequent HD.

Standardized differences were calculated against the conventional HD group; 0.8, 0.5, and 0.2 were considered large, medium, and small differences, and ≥0.1 was defined as meaningful imbalance.

The frequency of missing data was <2% for most laboratory tests, except for iron saturation (3%), creatinine (6%), and renal CL_{urea} (62%).

Conversion factors for units: albumin and hemoglobin in g/dl to g/l, 10; creatinine in mg/dl to mmol/l, 88.4; calcium in mg/dl to mmol/l, 0.2495; phosphorus in mg/dl to mmol/l, 0.3229. No conversion was necessary for ferritin in ng/ml and mg/l.

Comorbidity Index (CCI) category and the use of central venous catheter access, the frequent HD group compared with the conventional HD group had a higher prevalence of fluid overload (64% vs. 6%), greater weekly percentage of interdialytic weight gain (%IDWG) (9.5% vs. 7.7%), and larger body mass index (30.6 kg/m^2 vs. 26.8 kg/m^2). Although the prevalence of missing data on renal urea clearance (CL_{urea}) was high (65%), available data showed that the frequent HD group had less renal CL_{urea} (1.9 ml/min per 1.73 m^2 vs. 3.1 ml/min per 1.73 m^2). Conversely, the conventional HD group compared with the incremental HD group had less %IDWG (5.8% vs. 7.7%) and greater renal CL_{urea} (5.4 ml/min per 1.73 m^2 vs. 3.1 ml/min per 1.73 m^2). In support of greater renal CL_{urea} in the incremental HD group, creatinine (4.4 mg/dl vs. 5.9 mg/dl) and serum phosphorus (4.3 mg/dl vs. 5.0 mg/dl) were both lower in the incremental HD group compared with the conventional HD group. Figure 1 displays the quarterly-averaged treatment frequency per week and treatment time per session in the incremental HD, conventional HD, and frequent HD groups, with separation between groups maintained throughout the follow-up period.

Characteristics of treatment frequency and transition between regimens

Among 434 patients in the incremental HD group, 155 patients (36%) transitioned to conventional treatment frequency (i.e., 2.5–3.5 per week) after a median of 3 quarters (interquartile range [IQR], 1–5) on less treatment schedule (i.e., <2.5 per week) (Table 2). During the 91 days before transition to thrice-weekly HD, the mean weekly interdialytic weight gain was 6.6 ± 3.2% and mean serum concentrations of creatinine and phosphorus were 6.4 ± 3.2 mg/dl and 5.2 ± 1.1 mg/dl, respectively. Of 160 patients in the frequent HD group, 81 patients (49%) transitioned to conventional treatment frequency of HD (i.e., 2.5–3.5 per week) after median 1 quarter (IQR, 1–3) on a frequent treatment schedule (i.e., >3.5 per week). During the 91 days before transition to thrice-weekly HD, mean weekly interdialytic weight gain was 12.2 ± 4.4% and mean serum concentrations of creatinine and phosphorus were 6.7 ± 2.5 mg/dl and 5.1 ± 1.4 mg/dl, respectively.

Facility-level prevalence of treatment frequencies

The prevalence of the incremental regimen among incident HD patients was 0%, >0% to 3%, and >3% at 1293 (74%),

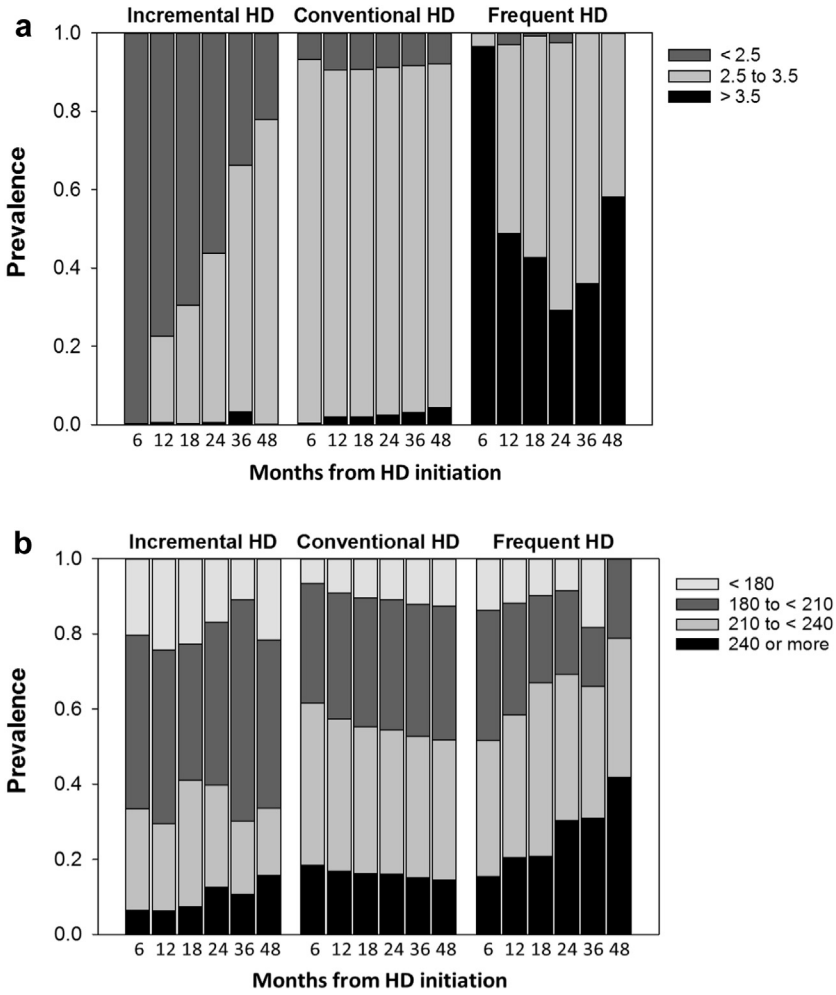

Figure 1 | The distribution of quarterly-averaged (a) treatment frequency per week and treatment time in minutes per session across the hemodialysis (HD) regimen groups in the matched cohort of 50,756 incident hemodialysis patients (b).

Table 2 | Characteristics during the 91 days before transition to thrice-weekly HD schedule among patients in the incremental HD group

Characteristics	Incremental HD 155 (36%)	Frequent HD 81 (49%)
Time to transition to thrice-weekly HD (quarter)	3 (1–5)	1 (1–3)
Weekly IDWG (%body weight)	6.6 ± 3.2	12.2 ± 4.4
Hemoglobin (g/dl)	10.9 ± 1.2	11.3 ± 0.9
Albumin (g/dl)	3.7 ± 0.4	3.6 ± 0.5
Creatinine (mg/dl)	6.4 ± 3.2	6.7 ± 2.5
Corrected calcium (mg/dl)	8.9 ± 0.7	9.1 ± 0.4
Phosphorus (mg/dl)	5.2 ± 1.1	5.1 ± 1.4
Intact PTH (pg/ml)	299 (182–375)	261 (155–363)
Iron saturation (%)	26 ± 9	26 ± 10
Ferritin (ng/ml)	500 (326–792)	417 (248–708)
Bicarbonate (mmol/l)	22.4 ± 2.9	23.2 ± 2.9

HD, hemodialysis; IDWG, interdialytic weight gain; PTH, parathyroid hormone.
Values are expressed as mean ± SD, median (IQR), or percentage, as appropriate.
Data are based on weighted match according to age, sex, race, central venous catheter as vascular access, and the Charlson Comorbidity Index.
The frequency of missing data was <2% for most laboratory tests, except for ferritin (3%).
Conversion factors for units: albumin and hemoglobin in g/dl to g/l, 10; creatinine in mg/dl to mmol/l, 88.4; calcium in mg/dl to mmol/l, 0.2495; phosphorus in mg/dl to mmol/l, 0.3229. No conversion was necessary for ferritin in ng/ml and mg/l.

288 (17%), and 156 (9%) facilities, respectively (Table 3). The median prevalence of urine collection during the first 91 days of dialysis was 33% (IQR, 11%–57%), 42% (IQR, 20%–63%), and 56% (IQR, 37%–64%) among those facilities with the prevalence of the incremental HD regimen 0%, >0% to 3%, and >3%, respectively. There was a significant trend toward a higher prevalence of urine collection as facility prevalence of patients with the incremental HD regimen increased ($P_{trend} < 0.001$). Compared with facilities that never prescribed incremental HD, those facilities with >0% to 3% and >3% prevalence of the incremental HD had 1.5% (95% CI 0.1%–2.9%) and 7.3% (95% CI 5.3%–9.5%) higher median renal CL_{urea} levels during the first 91 days of dialysis ($P_{trend} < 0.001$) and also had higher a likelihood of prescribing frequent HD (odds ratio 1.75 [95% CI 1.30–2.37] and odds ratio 1.96 [95% CI 1.25–3.07]), respectively. Conversely, the prevalence of a frequent HD regimen among incident dialysis patients was not associated with the prevalence of urine collection or median renal CL_{urea} levels during the first 91 days of dialysis ($P_{trend} = 0.12$ and 0.30, respectively) (Supplementary Table S2). Compared with facilities that never prescribed frequent HD, the likelihood of prescribing incremental HD was higher in those facilities with >0% to 2% (odds ratio 1.65 [95% CI 1.36–2.01]) but not in those with >2% patients with frequent HD (odds ratio 1.31 [95% CI 0.88–1.94]).

Mortality risk

In the matched cohort, 13,175 conventional HD patients, 91 incremental HD patients, and 62 frequent HD patients died during follow-up. For conventional HD, incremental HD, and frequent HD groups, the mortality rates were 17.8 per 100 patient-years, 17.6 per 100 patient-years and 35.2 per 100 patient-years, respectively. Kaplan-Meier survival estimates were lower in the frequent HD group compared with the incremental HD and conventional HD groups in both the entire (Supplementary Figure S1) and matched (Figure 2) cohorts. In the matched cohort, all-cause mortality was not significantly different in the incremental HD group compared with the conventional HD group. However, all-cause mortality was significantly higher in the frequent HD group compared with the conventional HD group. These findings remained robust across all adjustment models (Figure 3). Even with additional adjustment for RKF, the incremental HD group had no difference in survival compared with conventional HD group (HR 0.88, 95% CI 0.72–1.08) and the frequent HD group had significantly higher mortality compared with conventional HD (HR 1.56, 95% CI 1.21–2.03).

In prespecified subgroup analyses of the matched cohort comparing incremental HD with conventional HD, there was no statistical difference in all-cause mortality in subgroups of age, sex, race, central venous catheter use, or diabetic status. However, the incremental HD group showed a higher mortality risk among patients with a CCI ≥5 (HR 1.77, 95% CI 1.20–2.62). In the subgroup analyses comparing frequent HD with conventional HD, the mortality risk of frequent HD was consistently higher across all subgroups of age, sex, race, central venous catheter use, diabetic status, and higher comorbidity burden. However, in the lowest comorbidity risk category (CCI = 2), there was no statistical significant difference in mortality between frequent HD and conventional HD (HR 0.98, 95% CI 0.53–1.84) (Figure 4). Consistent results were found in the entire cohort (Supplementary Figures S2 and S3).

DISCUSSION

This study compared survival among 50,162 conventional HD patients, 434 incremental HD patients, and 160 frequent HD

Table 3 | Facility-level baseline characteristics according to the prevalence of the incremental regimen among 87,718 patients with end-stage renal disease who started hemodialysis from January 1, 2007 to December 31, 2011 at 1737 facilities

	Prevalence of incident HD patients with the incremental regimen		
	0% (*n* = 1293; 74%)	>0% to 3% (*n* = 288; 17%)	>3% (*n* = 156; 9%)
Total no. of incident HD patients	40 (IQR, 19–64)	72 (IQR, 52–93)[a]	32 (IQR, 20–58)
Patients with baseline RKF data	33% (IQR, 11%–57%)	42% (IQR, 20%–63%)[a]	56% (IQR, 37%–74%)[a]
Median renal CL_{urea} (ml/min per 1.73 m^2)	3.5 (IQR, 2.9–4.3)	3.6 (IQR, 3.2–4.1)	3.9 (IQR, 3.4–4.4)[a]
Ever prescribed frequent HD (%)	6%	20%[a]	16%[a]

HD, hemodialysis; CL_{urea}, renal urea clearance; IQR, interquartile range; RKF, residual kidney function.
[a]$P < 0.05$ compared with the 0% group.

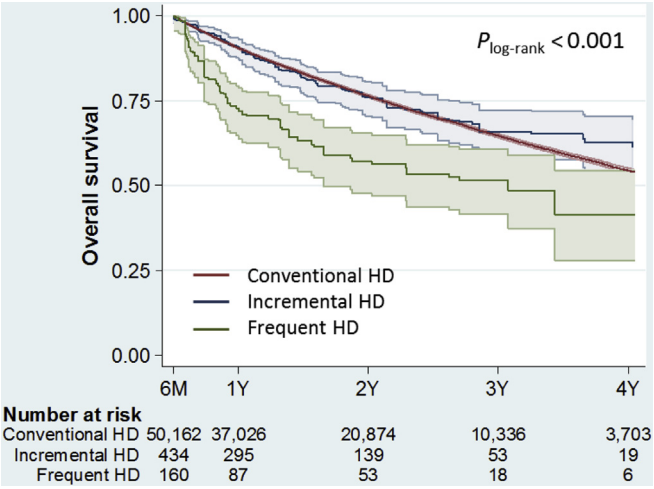

Figure 2 | Kaplan-Meier survival estimates and 95% confidence intervals by initial hemodialysis (HD) regimen in the matched cohort ($N = 50,756$). Weighted coarsened exact matching were used based on age, sex, race, central venous catheter as vascular access, and the Charlson Comorbidity Index.

patients who initiated HD treatment in a large US dialysis organization. After matching for key demographic and comorbid characteristics and comparison with the conventional HD group, overall mortality was not different in the incremental HD group but significantly higher in the frequent HD group. These results were robust across the adjustment models including a sensitivity analysis with adjustment for RKF. However, comorbidity burden modified the association

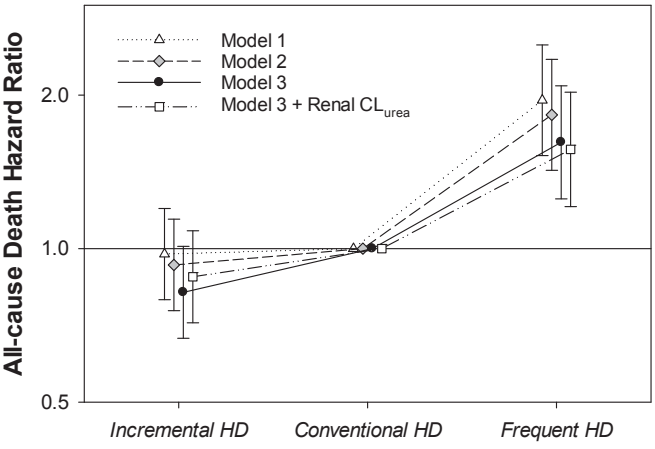

Figure 3 | Adjusted all-cause mortality risk of incremental and frequent hemodialysis (HD) in the matched cohort ($N = 50,756$). Weighted coarsened exact matching were used based on age, sex, race, central venous catheter as vascular access, diabetes, and the Charlson Comorbidity Index. Model 1 is the unadjusted model. Model 2 includes Medicare as primary insurance, single pool Kt/V, body mass index, hemoglobin, albumin, corrected calcium, iron saturation, bicarbonate, log-transformed ferritin, and intact parathyroid hormone (iPTH). Model 3 includes variables in Model 2, a history of fluid overload, interdialytic weight gain, creatinine, phosphorus. Data on laboratories were extracted during the first 91 days of dialysis, and those except for ferritin and iPTH were further restricted to the initial thrice-weekly HD period before starting infrequent or frequent HD. CL_{urea}, urea clearance.

between HD frequency and all-cause mortality; patients in the incremental HD group with greater comorbid burden (CCI ≥5) had a significantly higher risk of mortality.

To date, there are no randomized, controlled trials examining the effect of incremental compared with conventional HD on mortality risk, and only a few observational studies have been conducted. Lin *et al.*[19] reported a prospective observational study of 2572 Chinese patients undergoing maintenance HD. Multivariable adjusted patient survival was similar between the 2 groups. Given that the study cohort comprised prevalent HD patients and RKF was not measured, these findings have limited generalizability to incident HD patients who face a higher early mortality risk. Hanson *et al.*[20] reported outcomes of patients on twice-weekly HD compared with a conventional regimen. A total of 15,067 HD patients were studied, among whom 570 were treated with twice-weekly HD. RKF data were not collected during the study follow-up period. Twice-weekly HD was associated with a 24% lower mortality than conventional HD. However, in the subgroup of incident patients, there was no difference in mortality between the 2 and 3 times per week HD groups after adjustment for estimated glomerular filtration rate at the time of dialysis initiation. It is plausible that the observed survival advantage in twice-weekly HD may have been moderated by higher baseline RKF and longer preservation of RKF.[21] A recent US-based study of 23,645 incident HD patients compared conventional with incremental HD regimens by matching based on baseline renal clearance of urea, urine volume, gender diabetes, and use of central venous catheters. In that study, patients on an incremental HD regimen had significantly more preservation of renal clearance of urea, and those with adequate baseline RKF (i.e., ≥3 ml/min per 1.73 m^2) had no significant difference in mortality.[16] In addition, a prospective study of 168 incident HD patients found that the percentage of patients with RKF loss was significantly lower in patients initiated on twice-weekly HD compared with those initiated on conventional thrice-weekly HD.[15] Similar to this available literature, our study examines associations between incident dialysis regimens and outcomes, and our findings suggest that twice-weekly HD, a less costly and more patient-amenable regimen, may have no significant difference in mortality compared with conventional HD in certain selected patient populations with low or moderate comorbid disease burden (CCI <5). It should be also noted that a majority of our patients on incremental regimen had a certain level of RKF (i.e., median renal CL_{urea} of 5.3 [IQR, 3.1–7.3 ml/min per 1.73 m^2]), although available data on RKF were limited.

The mechanisms underlying the exceptionally high mortality in the first 6 months of dialysis are complex and multifactorial. Lack of predialysis nephrology care, using central venous catheters as the primary vascular access, and preexisting cardiovascular disease[6] likely contribute to this risk. In addition to these known risk factors, loss of RKF and frequency of dialysis may play a role. A large proportion of HD patients initiate dialysis with substantial RKF. Nearly half

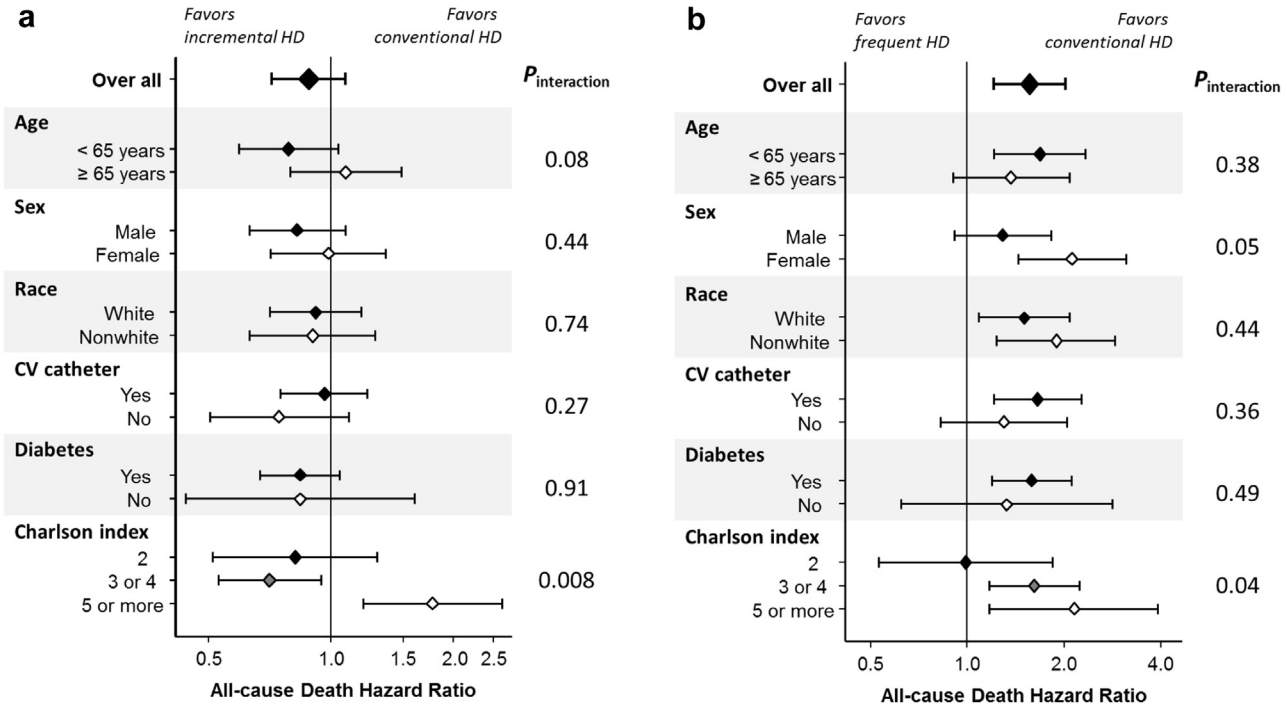

Figure 4 | Overall and subgroup analyses of the association between hemodialysis (HD) regimen and all-cause mortality risk: (a) incremental HD versus conventional HD and (b) frequent HD versus conventional HD. Data are based on weighted match according to age, sex, race, central venous (CV) catheter as vascular access, and the Charlson Comorbidity Index. Hazard ratios were from the fully adjusted model including renal urea clearance.

of all patients initiating dialysis in the United States have an estimated glomerular filtration rate of >10 ml/min per 1.73 m^2, and 90% are HD patients.[1,22] In observational studies, the presence of RKF in dialysis patients has been associated with improved quality of life, lower concentration of middle molecules, such as β_2-microglobulin,[23] decreased inflammation, and lower risk of death.[17,18,24] These benefits are thought to be mediated by continuous and efficient clearance of middle molecules and protein-bound solutes, better fluid management, more endogenous vitamin D and erythropoietin production, and less inflammation.[25–28]

Decline and loss of RKF are associated with higher mortality,[18] and the frequency of HD may contribute to loss of RKF. In our study, we found that patients initiated on a frequent HD regimen (≥4 times per week for at least 45 continuous days) had a higher mortality than patients initiated on an incremental or conventional regimen. Our results were consistent with a recent report from the Frequent Hemodialysis Network nocturnal study, which enrolled relatively new dialysis patients (median vintage ~1 year) with RKF (~50% with urine volume >500 ml/day) and showed a more rapid decline of RKF and higher mortality in the group randomized to frequent nocturnal HD compared with conventional HD (overall mortality HR 3.88[12,13]). Other studies have observed twice-weekly HD to be associated with better preservation of RKF than thrice-weekly HD.[14–16] Additionally, in a recent longitudinal cohort of 5686 patients initiating maintenance HD, higher RKF at 1 year after initiating dialysis was associated with better patient survival, with a linear association between mortality and both renal urea clearance and urine volume.[16] However, it is important to note the large differences in characteristics between the frequent HD and other groups in our study. Patients initiated on frequent HD had greater weekly interdialytic weight gains, higher prevalence of fluid overload, and larger body mass index compared with patients in the conventional HD group. Thus, the observed higher mortality in the frequent HD group must be weighed by the significant potential limitation of confounding by indication.

The effect of twice-weekly dialysis on mortality requires further careful study through randomized, controlled trials before routine use in clinical practice. However, compared with conventional thrice-weekly HD, twice-weekly HD has been associated with several other improved patient outcomes including fewer hospitalizations and fewer intradialytic hypotensive episodes[19] and would result in lower costs. The Frequent Hemodialysis Network randomized, controlled trials showed compromise of arteriovenous fistulae with more frequent dialysis.[29] It is reasonable to hypothesize that a lower frequency of dialysis would lengthen the patency of an arteriovenous fistula, although there is currently a lack of rigorous studies in this area.

Our study should be qualified by several potential limitations in this study. First, due to data limitations, we adjusted for only baseline characteristics, but adverse events such as cardiovascular events, changes in dialysis access, and infections during the course of follow-up could also affect

dialysis frequency. Second, although we used coarsened exact matching to reduce imbalance in selected variables, we still observed large differences in some characteristics, such as a history of fluid overload, weekly %IDWG, and renal CL_{urea} between the frequent HD group and the other groups. Hence, there may be residual confounding by indication in the mortality risk of incremental and frequent HD. Third, although the prevalence of missing renal CL_{urea} was high (62%), we rigorously adjusted for laboratory variables that dependent on residual kidney function (i.e., a history of fluid overload, interdialytic weight gain, creatinine, phosphorus) in Model 3. Sensitivity analyses using the multiple imputation method against missing data including renal CL_{urea} yielded consistent results with Model 3. Finally, the small number of patients in the incremental and frequent HD groups proportionate to the conventional HD groups may limit data interpretation. We suggest that the results of this study should not be extrapolated to those patients with RKF outside the common range across the study groups ($\sim$2.0–4.0 ml/min per 1.73 m^2 of renal CL_{urea}), consistent with the Kidney Disease Outcomes Quality Initiative recommendation that patients should not reduce dialysis frequency if they have $\leq$2.0 ml/min per 1.73 m^2 in renal CL_{urea}.

In conclusion, our study examines associations between HD treatment frequency and patient survival. In agreement with recent literature,[30,31] our findings suggest that in an incident HD population, certain selected patients with adequate RKF, adequate control of interdialytic weight gain, and low or moderate comorbid disease burden (CCI <5), an incremental HD approach may be considered a suitable alternative to conventional thrice-weekly HD. However, further studies, including prospective and randomized, controlled trials, are warranted to clarify the impact of incremental HD on safety and quality of life in incident HD patients and to identify patients who would benefit from incremental HD before an incremental approach to HD initiation can be recommended for routine clinical practice.

METHODS

Patients

We extracted, refined, and examined electronic data from all incident HD patients 18 years of age and older in facilities operated by a large dialysis organization in the United States from January 1, 2007 to December 31, 2011.[32] To compare survival among initial HD regimens of different treatment frequency, we selected 158,756 patients who started renal replacement therapy with in-center HD. Patient follow-up time was divided into quarters (91-day periods from the date of the first dialysis). Within each patient-quarter, patients who received a consistent treatment schedule (i.e., Monday/Thursday or Monday/Tuesday/Friday/Saturday) of HD at frequencies of $\leq$2 times and $\geq$4 times per week for at least 45 continuous days were considered to have received less-frequent and frequent HD, respectively. The remainder of patients were categorized as receiving a conventional thrice-weekly HD regimen. We excluded 10,827 patients who ever received peritoneal dialysis, home HD, or nocturnal HD during follow-up. Given that the fluctuating treatment pattern in the early period of dialysis initiation,[32] patients were categorized as the incremental and frequent HD regimens if assigned to less frequent and frequent HD during the second quarter (i.e., months 4–6) of HD treatment, respectively. We then excluded 51,818 patients who were censored during the first 2 quarters (i.e., months 1–6) in order to avoid immortal bias due to the definition of these treatment regimens. We further restricted the study population to patients who had available International Classification of Diseases 9 codes and laboratory data during the first quarter of dialysis (months 1–3) before starting less frequent or frequent HD (Supplementary Figure S4).

The study was approved by the Institutional Review Committees of the University of Washington, the Los Angeles Biomedical Research Institute at Harbor-UCLA, and the University of California Irvine Medical Center. Given the large sample size, anonymity of the patients studied, and nonintrusive nature of the research, requirement for consent was exempted.

Demographic, clinical, and laboratory measures

The information on self-reported race/ethnicity, primary insurance, access type, and the presence of comorbidities at baseline were obtained from the electronic database of the dialysis provider. To minimize measurement variability, all repeated measures for each patient during any given quarter (91 days) were averaged, and the quarterly means were used in all analyses. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the central laboratory in Deland, Florida, typically within 24 hours. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, including serum urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, and total iron binding capacity. Serum ferritin and intact parathyroid hormone were measured at least quarterly. Hemoglobin was measured at least monthly in essentially all patients and weekly to biweekly in most patients. Most blood samples were collected predialysis with the exception of the postdialysis urea, which was obtained to calculate urea kinetics.

We calculated dialysis dose and residual renal CL_{urea} assuming the average serum urea concentrations during the collection to be 90% of the predialysis concentrations according to the Daugirdas approach as follows[33–35]

$$\text{Renal } CL_{urea}\ (\text{ml/min}) = \frac{\text{urinary urea (mg/dl)} \times \text{urinary volume (ml)}}{\text{collected time (min)} \times [0.9 \times \text{serum urea (mg/dl)}]}$$

$$spKt/V = -\ln\left(R - \frac{0.0174}{PIDI} \times \frac{t}{60}\right) + \frac{(4 - 3.5 \times R) \times 0.55 \times UF}{V}$$

where R is the ratio of the pre- and post-HD concentrations of serum urea, t is the duration of HD treatment time (minutes), UF is the amount of ultrafiltration (in liters) during the given HD session, V is the estimated urea distribution volume, $spKt/V$ is the single-pool Kt/V, and $PIDI$ is the preceding interdialysis interval (days). Renal CL_{urea} was then adjusted for body surface area and expressed as ml/min per 1.73 m^2 and used as an index of RKF.[35,36] %IDWG was calculated at each single-pool Kt/V measurement by dividing weekly cumulative ultrafiltration volume (in liters) in the preceding week by postdialysis weight.

Statistical methods

Due to the large sample size, differences in patient characteristics between the 3 treatment groups were compared by standardized

differences, of which 0.8, 0.5, and 0.2 were considered large, medium, and small differences, respectively, and ≥10% was defined as meaningful imbalance.[37,38] The CCI was calculated using Quan's Enhanced ICD-9-CM[39] and then categorized into 5 groups; 2 (renal disease only), 3 to 4, 5, 6, and 7 or more.[40] Patients who had diabetic nephropathy as the primary kidney disease were considered to have diabetes with chronic complications.

We matched patients based on several demographic characteristics (age, sex, race, and central venous catheter as vascular access) and the CCI by using coarsened exact matching.[41] First, we coarsened age into 6 categories by using cut points of 35, 50, 65, 80, and 90 years. We then sorted all patients by each stratum of the age category as well as sex, race, central venous catheter as the vascular access, and the above CCI category. Within each stratum that included at least 1 patient on each regimen, patients on the conventional regimen were given a weight of 1, and those on the less frequent or frequent regimen were given a weight that equalized the ratio of sum of weights in each group of the stratum to the ratio of total matched patients in each group in the entire cohort. Coarsened exact matching has several advantages over other matching approaches including propensity-score matching: it requires fewer ad hoc postestimation assumptions about how to define a match, automatically balances different populations, has superior computational properties for large data sets, and is particularly suitable for applications in which most independent variables can be categorized appropriately.

We estimated Kaplan-Meier survival in both the matched and unmatched cohorts and compared survival among groups using the log-rank test. Mortality risk of the incremental or frequent HD versus conventional HD regimen was examined by conventional Cox regression analyses with hierarchical adjustments; (1) Model 1, which was unadjusted models in the matched cohort or minimally adjusted models that included the matching variables (i.e., age, sex, race, and ethnicity [non-Hispanic white, non-Hispanic black, and other race/ethnicity]), central venous catheter use as vascular access type, and the CCI category in the entire cohort; (2) Model 2, which included the variables in Model 1 plus Medicare as primary insurance, body mass index, single-pool Kt/V, hemoglobin, serum albumin, albumin-corrected calcium, iron saturation, bicarbonate, and natural log-transformed intact parathyroid hormone and ferritin; and (3) Model 3, which included variables in Model 2 plus RKF-related variables (i.e., a history of fluid overload, weekly %IDWG, serum creatinine, and phosphorus).

Covariate data were extracted during the first 91 days of HD, and laboratory tests except for ferritin and intact parathyroid hormone were further restricted to the initial period of thrice-weekly HD before starting infrequent or frequent HD. The adjusted mortality risk of incremental and frequent HD was also examined across prespecified subgroups including age (<65 vs. ≥65), sex, race (white vs. nonwhite), central venous catheter use, diabetes, and the CCI category (2, 3 to 4, and 5 or more). We also conducted sensitivity analyses with adjustment for natural log-transformed (renal $CL_{urea} + 1$) in addition to all covariates in Model 3. The multiple imputation method with 5 data sets was used for missing longitudinal covariate data (<2% for body mass index and most laboratory tests, 3% for iron saturation, 6% for creatinine, and 65% for renal CL_{urea}). We used multivariate normal regression for the multiple imputation method to account for clustering by incorporating all available data for up to 3 patient quarters (from months 1–3 through months 7–9). Proportional hazards assumptions were tested using log-log against survival plots and Schoenfeld residuals. All analyses were carried out with STATA MP V13.1 (StataCorp, College Station, TX).

DISCLOSURE

KK-Z has received honoraria from Abbott, AbbVie, Alexion, Amgen, Astra-Zeneca, Aveo, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS Pharma. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Baseline characteristics by treatment regimen in the entire cohort of 87,718 incident HD patients.

Table S2. Facility-level baseline characteristics according to the prevalence of the incremental regimen among 87,718 patients with end-stage renal disease who started hemodialysis from 1/1/2007 to 12/31/2011 in 1,737 facilities.

Figure S1. Kaplan-Meier survival curves by initial hemodialysis (HD) regimen in the entire cohort of 87,718 incident hemodialysis patients.

Figure S2. Adjusted all-cause mortality risk of incremental and frequent hemodialysis (HD) in the entire cohort of 87,718 incident hemodialysis patients.

Figure S3. Overall and subgroup analyses of the association between hemodialysis (HD) regimen and all-cause mortality risk; (**A**) incremental HD versus conventional HD and (**B**) frequent HD versus conventional HD.

Figure S4. Study flow diagram.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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