Title

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Journal

American Journal of Kidney Diseases, 80(2)

ISSN

0272-6386

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Publication Date

2022-08-01

DOI

10.1053/j.ajkd.2021.12.001

Twice-Weekly Hemodialysis With Adjuvant Pharmacotherapy and Transition to Thrice-Weekly Hemodialysis: A Pilot Study

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Rationale & Objective: Thrice-weekly hemodialysis (HD) is the most common treatment modality for kidney failure in the United States. We conducted a pilot study to assess the feasibility and safety of incremental-start HD in patients beginning maintenance HD.

Study Design: Pilot study.

Setting & Participants: Adults with estimated glomerular filtration rate (eGFR) ≥5 mL/min/1.73 m^2 and urine volume ≥500 mL/d beginning maintenance HD at 14 outpatient dialysis units.

Exposure: Randomized allocation (1:1 ratio) to twice-weekly HD and adjuvant pharmacologic therapy for 6 weeks followed by thrice-weekly HD (incremental HD group) or thrice-weekly HD (conventional HD group).

Outcome: The primary outcome was feasibility. Secondary outcomes included changes in urine volume and solute clearance.

Results: Of 77 patients invited to participate, 51 consented to do so, representing 66% of eligible patients. We randomized 23 patients to the incremental HD group and 25 patients to the conventional HD group. Protocol-based loop diuretics, sodium bicarbonate, and patiromer were prescribed to 100%, 39%, and 17% of patients on twice-weekly HD, respectively. At a mean follow-up of 281.9 days, participant adherence was 96% to the HD schedule (22 of 23 and 24 of 25 in the incremental and conventional groups, respectively) and 100% in both groups to serial timed urine collection. The incidence rate ratio for all-cause hospitalization was 0.31 (95% CI, 0.08-1.17); and 7 deaths were recorded (1 in the incremental and 6 in the conventional group). At week 24, the incremental HD group had lower declines in urine volume (a difference of 51.0 [95% CI, −0.7 to 102.8] percentage points) and in the averaged urea and creatinine clearances (a difference of 57.9 [95% CI, −22.6 to 138.4] percentage points).

Limitations: Small sample size, time-limited twice-weekly HD.

Conclusions: It is feasible to enroll patients beginning maintenance HD into a randomized study of incremental-start HD with adjuvant pharmacotherapy who adhere to the study protocol during follow-up. Larger multicenter clinical trials are indicated to determine the efficacy and safety of incremental HD with longer twice-weekly HD periods.

Funding: Funding was provided by Vifor Inc.

Trial Registration: Registered at ClinicalTrials.gov, identifier NCT03740048.

Visual Abstract online

Complete author and article information provided before references.

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Am J Kidney Dis. 80(2):227-240. Published online December 18, 2021.

doi: 10.1053/j.ajkd.2021.12.001

Almost all Americans with kidney failure initiated on treatment with maintenance hemodialysis (HD) are prescribed standard dialytic therapy of fixed frequency (thrice-weekly HD) and dose (dialysis single-pool Kt/V urea [spKt/V] ≥1.2, corresponding to standard Kt/V urea [stdKt/V] ≥2.1).[1] This standard HD therapy disregards individual levels of residual kidney function.[2,3] The HD dose, validated in clinical trials that involved solely patients on HD for >2 years and with no residual kidney function, was generalized as the "optimal" dialysis dose to all patients prescribed maintenance HD.[4,5] However, more than 90% of incident dialysis patients have an estimated glomerular filtration rate (eGFR) ≥5 mL/min/1.73 m^2 at dialysis initiation,[6] and those with substantial levels of residual kidney function could likely be treated safely and effectively with less frequent dialysis therapy until residual kidney function diminishes.[7,8]

In retrospective studies, incremental HD (ie, twice-weekly HD at initiation of dialysis therapy) later switched to thrice-weekly HD according to changes in residual kidney function and/or other clinical indications yielded adequate symptom control.[9,10] Compared to outright thrice-weekly HD, incremental HD conferred similar or better patient survival[11,12]; similar or better quality of life[13,14]; and longer preservation of residual kidney function.[15] Because residual kidney function might afford excretion of toxins not removed by dialysis,[16] reduce systemic inflammation,[16,17] and prolong patient survival,[17-20] there is biological plausibility for potential benefits of incremental HD. Notwithstanding these data, prospective studies with randomized HD frequency assignments are needed to test the emerging concept that incremental HD is effective and safe in defined clinical scenarios.[21] Herein, we report the results of the TWOPLUS Pilot

PLAIN-LANGUAGE SUMMARY

At dialysis initiation some patients have substantial levels of residual kidney function and may not require full-dose thrice-weekly hemodialysis. We performed a randomized pilot study to assess the feasibility of incremental-start hemodialysis in the incident hemodialysis population. The intervention group received twice-weekly hemodialysis with pharmacoadjuvant therapy for 6 weeks and then changed to thrice-weekly hemodialysis (n = 23). The conventional group received thrice-weekly hemodialysis (n = 25). We found that 41% of the patients met the preliminary eligibility criteria, 66% consented, 96% adhered to protocol-defined frequency of hemodialysis treatments, and all adhered to protocol-defined timed urine collections. Larger multicenter clinical trials are indicated to determine the efficacy and safety of incremental hemodialysis with individualized periods of twice-weekly hemodialysis.

Study (ClinicalTrials.gov identifier NCT03740048) designed to assess the feasibility of individual randomization to incremental-start versus conventional HD.[22]

Methods

Study Design

A detailed study protocol has been published elsewhere.[22] In brief, the TWOPLUS Pilot Study was a prospective, individually randomized, unblinded, parallel-group controlled trial with the primary objective of assessing the feasibility of time-limited twice-weekly HD with protocol-based pharmacotherapy in patients beginning HD who had residual kidney function. The research team considered that, on account of resource limitation (ie, budget, personnel, and stakeholder negotiation) the model of time-limited twice-weekly HD permits evaluation of the achievability of key processes of care that pertain to treatment of patients and implementation of incremental HD at outpatient dialysis units.

The study design was reviewed by dialysis administration leadership before implementation, and the protocol was approved by the institutional review board of Wake Forest School of Medicine in North Carolina. All participants provided written informed consent, and study conduct adhered to the Declaration of Helsinki. The preparatory processes before recruitment commencement consisted of (1) establishing schedules of outpatient twice-weekly HD at the participating dialysis units; (2) training of research coordinators; (3) providing instructional guidance to dialysis personnel about study-related procedures; (4) procuring, storing, and dispensing of patiromer potassium binder from the sponsoring agency; and (5) establishing procedures required to deliver study biosamples to a centralized laboratory. These processes are detailed in Item S1.

Study Setting

The study was conducted at 14 outpatient and 1 inpatient dialysis units affiliated with a large health care system in North Carolina.

Participant Recruitment and Randomization

The eligibility criteria are listed in Table S1. Recruitment began on June 14, 2019, was paused between March 13, 2020, and May 31, 2020, due to the coronavirus disease 2019 pandemic, resumed on June 1, 2020, and ended on December 10, 2020, with the last randomization (Fig S1 and Item S1).[22,23] Randomization was determined by a computer algorithm in random blocks of 2 or 4 size and 1:1 allocation, stratified by type of vascular access used at HD initiation (catheter or arteriovenous access).

Intervention and Control

The incremental HD group received the experimental intervention, which consisted of twice-weekly HD for 6 weeks coupled with adjuvant pharmacologic therapy (loop diuretic, sodium bicarbonate, potassium binder patiromer required according to the protocol) followed by transition to thrice-weekly HD at week 7. The conventional HD group served as the control group and continued to receive thrice-weekly HD (Table S2). The dialysis prescription (eg, duration, blood flow rate, dialysate flow rate) was adjusted by the treating team in both treatment groups to achieve dialysis spKt/V of ≥1.2 and urea reduction ratio of ≥65%.[1]

Study Visits and Data Collection

All study-specific assessments occurred during the patients' regularly scheduled hemodialysis session. Baseline timed 24-hour urine collections were obtained before randomization. Follow-up interdialytic urine collections were obtained during the longest interdialytic interval in week 6, week 12, and week 24, with a time frame window of 2 weeks for each assessment time point. Blood samples to calculate residual renal clearances were collected at the end of the HD treatment preceding timed urine collection and the beginning of the successive HD treatment ending the period of timed urine collection.[22] Renal stdKt/V, dialysis stdKt/V, and total stdKt/V were calculated at each assessment time point.[24] All tests were performed at one LabCorp laboratory in North Carolina.

Outcomes

The primary outcome was feasibility, assessed as (1) ≥70% of eligible patients are recruited, (2) ≥95% of participants randomized in the intervention group will adhere to the HD regimen, (3) ≥80% patients adhere to study-specific timed urine collection, and (4) ≤5% of participants

randomized in the control group will cross over to a regimen of less frequent HD. Feasibility metrics were selected based on a consensus opinion among investigators regarding medically acceptable rates of adherence to the tested intervention.[22] Adherence to protocol operationalization at outpatient dialysis facilities was monitored. Serious adverse events related to hospitalization and death and events of additional outpatient HD treatments for volume overload or metabolic imbalances were recorded (Item S1). Secondary outcomes included changes in residual kidney function parameters (24-hour urine volume, renal urea clearance, and renal creatinine clearance) from baseline to weeks 6, 12, and 24; dialysis and total (dialysis + renal) urea solute clearance; and volume management parameters.

Sample Size

This pilot study was designed to evaluate study feasibility (rate of enrollment and adherence) of a future multicenter controlled trial of incremental HD and to get an estimate of the standard deviation on outcomes related to clinical events and changes of residual kidney function parameters. A total sample of 50 would be able to estimate feasibility with a 95% confidence interval width at most ±14.5%. Within each group, feasibility could be estimated with a confidence interval width no greater than ±20.5%.[25]

Statistical Analyses

Continuous variables are summarized with mean (standard deviation [SD]), median (interquartile range), or mean (95% confidence interval [CI]), and categorical variables are given as proportion per participant or per visit, as appropriate. Standardized differences for baseline characteristics were calculated.[26] Descriptive statistics were used to report feasibility outcomes. The results are reported based on intention-to-treat analysis. Participants were censored at death, HD withdrawal, or conversion to peritoneal dialysis. Not included in data analysis were participants who withdrew consent, were withdrawn from the study because of nonadherence to HD treatments, or were lost to follow-up.

To analyze the relationship between cumulative all-cause hospitalization and treatment assignment, a Cox proportional hazards model utilizing the counting process for recurrent events was used; this model produces estimates of the hazard distribution for the 2 treatment groups.[27] All-cause hospitalization rates (number of days total, taking into account time on study) were analyzed using a negative binomial regression model with an offset of time at risk and incidence rate ratio were reported. Cox proportional hazards regression was used to assess the association between group assignment and overall survival. Fisher's exact test was used to estimate the 95% CI around the proportion estimates.[28]

Changes in least squares mean level of biochemical parameters, tested at successive time points, were analyzed across individuals with data available at both analysis time points using pairwise comparisons within a repeated measures mixed effect regression model. Estimate percent change from baseline to week 6, week 12, and week 24 in residual kidney function parameters and stdKt/V were analyzed using mixed effect linear models. Each set of data was viewed as a separate experiment; as such, for consistency, analyses were not adjusted for multiple comparisons or covariates. Statistical analyses were performed using SAS, version 9.4 (SAS Institute).

Results

Primary Outcome: Feasibility

Recruitment

Over a 15.5-month period, 185 adult patients diagnosed with kidney failure were started on thrice-weekly maintenance HD. After prescreening, 77 patients (41%) were approached for study participation. Of those, 51 (66%) consented to participate, resulting in 48 patients randomized to treatment with twice-weekly HD and adjuvant pharmacotherapy for 6 weeks followed by thrice-weekly HD (incremental HD group, n = 23) or continued usual care treatment with thrice-weekly HD (conventional HD group, n = 25) (Fig 1; Fig S1). Participant characteristics at the time of enrollment are summarized in Table 1. Patients randomized to conventional HD had a higher urine volume and eGFR and higher prevalence of diabetes, congestive heart failure, cerebrovascular disease, and malignancy.

Adherence to Study Protocol

At the participant level, at a mean follow-up period of 288.9 days in the incremental HD group and 275.3 days in the conventional HD group, adherence to the prescribed HD regimen was 96% in each group (22 of 23 in the incremental HD group and 24 of 25 in the conventional HD group). The dropout rate was 13% (3 of 23) in the incremental HD group and 12% (3 of 25) in the conventional HD group, corresponding to a dropout rate of 0.76 (95% CI, 0.25-1.78) per 1,000 participant-days in each group. All participants who completed 6 and 12 months of follow-up completed interdialytic timed urine collections. Two patients crossed over from the twice-weekly to thrice-weekly HD regimen in the first 6 weeks (as discussed later). There was no crossover from the thrice-weekly to twice-weekly HD regimen.

At the facility level, we noted incidents of missed laboratory data; these were due to missed collection of blood samples before or after HD surrounding the time frame of urine collection or mishandling of urine specimens by the laboratory personnel. Overall, these events occurred at higher rate in the first 2 months of the study (up to 36%) and declined (<10%) at later time points during the study.

Pharmacologic Therapy

According to the protocol, all patients randomized to incremental HD group received diuretics at a furosemide-

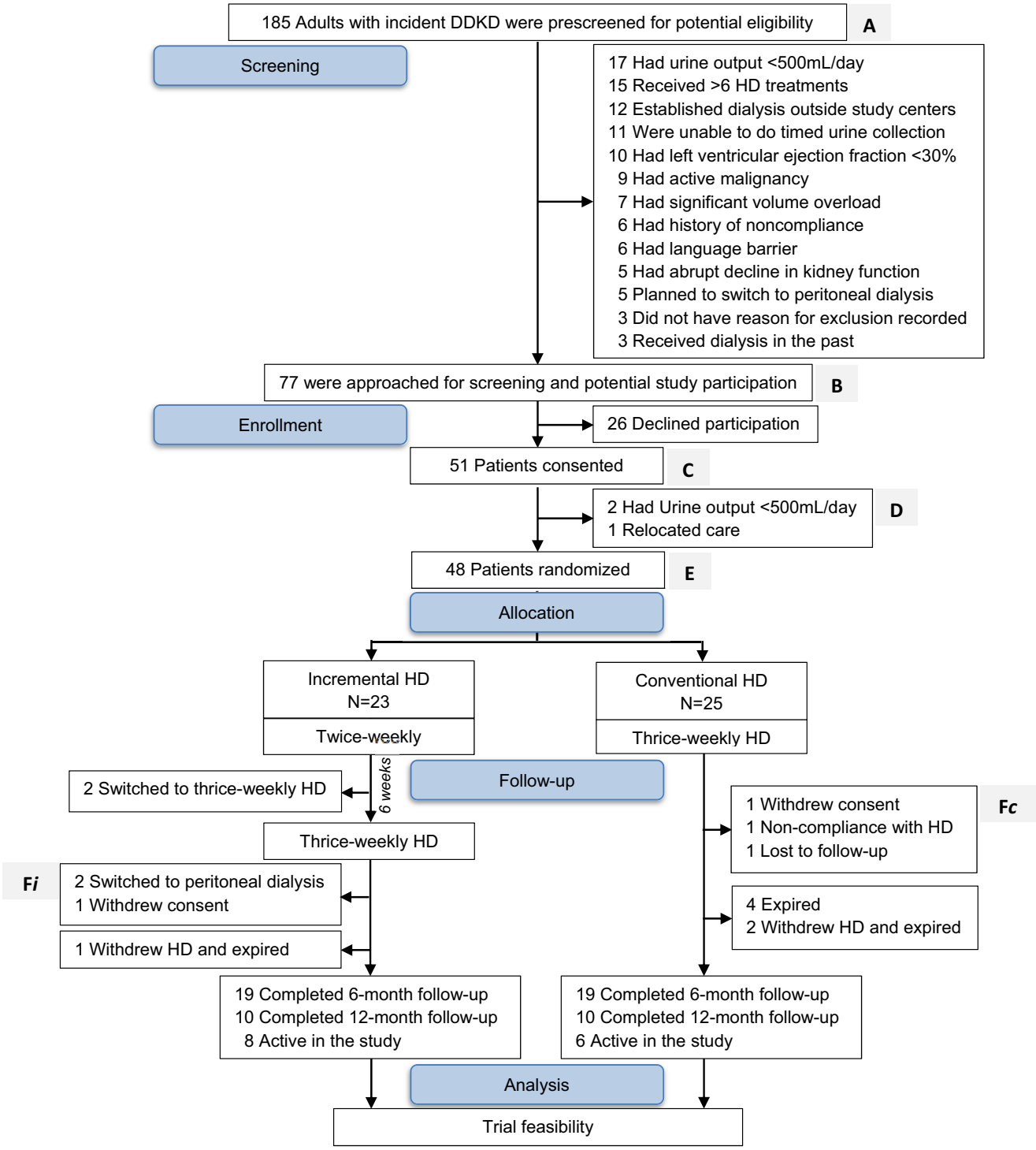

Figure 1. Study flow diagram. Eligibility, best case scenario if patients who refused to participate (n = 26) were to be eligible: (B-D)/A; worst case scenario if patients who declined study participation were to not be eligible: (B-D-26)/A. Consent rate, C:B; Number randomized, E:A; Dropout, (F*i*+F*c*)/E. Abbrevations: DDKD, dialysis-dependent kidney disease; HD, hemodialysis.

equivalent mean level of 120 ± 40 (SD) mg/d. Thirty-nine percent of the participants (9 of 23) in the incremental HD group received sodium bicarbonate, with a mean dose of 1,300 ± 650 mg/d. Seventeen percent of the participants (4 of 23) in the incremental HD group received patiromer at a dose of 8.4 g/d on non-HD days. Sodium bicarbonate and patiromer were discontinued after the transition from twice-weekly to thrice-weekly HD. Other medications prescribed during the study by the treating team, according to standard care, are listed in Table S3.

Table 1. Participant Sociodemographic and Clinical Characteristics, Overall and According to Treatment Allocation

Variable	Overall (N = 48)	Incremental HD (n = 23)	Conventional HD (n = 25)	Standardized Difference[a]
Sociodemographic Characteristics at Enrollment				
Age at enrollment, y	61.3 ± 14.0	59.1 ± 15.0	63.3 ± 12.8	0.31
Female sex	21 (44%)	10 (44%)	11 (44%)	0.02
Race				
White	19 (40%)	11 (48%)	8 (32%)	0.08
Black	27 (56%)	11 (48%)	16 (64%)	0.09
Hispanic	2 (4%)	1 (4%)	1 (4%)	0.00
Body mass index, kg/m^2	32.1 ± 8.8	32.5 ± 9.4	31.8 ± 8.4	0.08
Body surface area, m^2	2.06 ± 0.3	2.1 ± 0.2	2.0 ± 0.3	0.34
Clinical Characteristics at Enrollment				
Received HD before randomization[b]	35 (73%)	17 (74%)	18 (72%)	0.01
No. of HD sessions before randomization	3.0 ± 1.7	3.0 ± 1.7	3.0 ± 1.9	0.00
Kidney failure etiology				
Diabetes mellitus	21 (44%)	8 (35%)	13 (52%)	0.12
Glomerulonephritis/vasculitis	1 (2%)	1 (4%)	0 (0)	0.52
Other	26 (54%)	14 (61%)	12 (48%)	0.04
Urine volume, mL/d	1,215 ± 820	914 ± 522	1,424 ± 955	0.66
Vascular access[c]				
Arteriovenous fistula	10 (21%)	5 (22%)	5 (20%)	0.00
Central venous catheter	38 (79%)	18 (78%)	20 (80%)	0.03
Comorbidities				
Diabetes mellitus	31 (65%)	12 (52%)	19 (76%)	0.11
Coronary artery disease	8 (17%)	4 (17%)	4 (16%)	0.00
Congestive heart failure	12 (25%)	4 (17%)	8 (32%)	0.16
Peripheral arterial disease	5 (10%)	2 (9%)	3 (12%)	0.10
Cerebrovascular disease	8 (17%)	3 (13%)	5 (20%)	0.12
COPD/asthma	8 (17%)	4 (17%)	4 (16%)	0.00
Malignancy	9 (19%)	3 (13%)	6 (24%)	0.16
HIV	2 (4%)	2 (9%)	0 (0%)	0.52
Dementia	0 (0%)	0 (0%)	0 (0%)	0.00
Medications				
Renin-angiotensin-aldosterone inhibitor	12 (29%)	6 (26%)	6 (24%)	0.00
Statin	31 (65%)	14 (61%)	17 (68%)	0.05
β-blocker	33 (69%)	18 (78%)	15 (60%)	0.04
Antiplatelet agent	4 (8%)	0 (0%)	4 (16%)	0.52
Anticoagulant	8 (17%)	3 (13%)	5 (20%)	0.12
Laboratory Data Before First HD Treatment				
Serum urea nitrogen, mg/dL	54.2 ± 24.4	51.6 ± 23.2	58.3 ± 25.7	0.27
Serum creatinine, mg/dL	5.9 ± 3.2	5.5 ± 2.8	6.4 ± 3.6	0.28
eGFR, mL/min/1.73 m^2	9.9 ± 5.1	9.4 ± 3.3	10.3 ± 6.4	0.17
Serum sodium, mEq/L	137.9 ± 2.8	138.3 ± 2.9	137.5 ± 2.7	0.28
Serum potassium, mEq/L	4.2 ± 0.6	4.1 ± 0.6	4.2 ± 0.6	0.17
Serum bicarbonate, mEq/L	22.9 ± 3.4	22.5 ± 3.7	23.3 ± 3.1	0.24
Hemoglobin, g/dL	9.5 ± 1.6	9.4 ± 1.4	9.5 ± 1.8	0.06
Ferritin, μg/L	248.9 ± 243.5	279.7 ± 188.2	220.6 ± 294.3	0.24
Transferrin saturation, %	37.8 ± 45.7	43.4 ± 48.4	30.9 ± 43.2	0.27
Serum calcium, mg/dL	8.4 ± 0.8	8.3 ± 1.0	8.4 ± 0.7	0.12
Serum phosphorus, mg/dL	5.3 ± 1.9	5.0 ± 1.7	5.6 ± 2.0	0.32
Parathyroid hormone, intact, μg/L	400.9 ± 274.9	388.6 ± 225.0	412.3 ± 320.8	0.08
Albumin, g/dL	3.4 ± 0.5	3.4 ± 0.4	3.3 ± 0.6	0.19
HD Prescription Before Randomization[d]				
Treatment time, min	201.9 ± 35.5	204.1 ± 39.6	199.8 ± 32.0	0.12
Blood flow, mL/min	304.2 ± 60.9	295.7 ± 63.8	312.0 ± 58.2	0.27
Dialysate flow, mL/min	539.6 ± 84.4	530.4 ± 75.5	548.0 ± 91.8	0.22

(Continued)

Table 1 (Cont'd). Participant Sociodemographic and Clinical Characteristics, Overall and According to Treatment Allocation

Variable	Overall (N = 48)	Incremental HD (n = 23)	Conventional HD (n = 25)	Standardized Difference[a]
Potassium bath, mEq/L	2.5 ± 0.5	2.5 ± 0.5	2.4 ± 0.5	0.20
Calcium bath, mEq/L	2.6 ± 0.2	2.6 ± 0.2	2.6 ± 0.3	0.00

Percentages may not total 100 because of rounding. Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4. Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (as assessed by Chronic Kidney Disease Epidemiology equation)[22,23]; HD, hemodialysis; HIV, human immunodeficiency virus.
[a]The standardized mean difference is reported in absolute values.
[b]Patients were excluded if they received > 6 HD sessions by the date all eligibility criteria were met and randomization was enacted.
[c]Vascular access used at dialysis initiation.
[d]HD prescription parameters, prescribed thrice-weekly by treating provider before study enrollment and randomization.

Serious Adverse Events

During the first 6 weeks of the study, 2 of 23 patients (9%) in the incremental HD group were electively switched by the treating provider from twice- to thrice-weekly HD (at day 21 and day 30 for anemia and volume management, respectively). No events of unscheduled outpatient HD treatments or hospitalizations due to volume overload, metabolic imbalances, or uremia occurred in the incremental HD group.

Table 2 summarizes the serious adverse events in each treatment group. A total of 52 hospitalizations occurred, 19 in the incremental HD group and 33 in the conventional HD group (Item S1). The cumulative hazard function for hospitalization in each treatment group is shown in Figure 2. The annual cumulative hospitalization rate was 1.06 (95% CI, 0.64-1.66) in the incremental HD group and 1.84 (95% CI, 1.31-2.59) in the conventional HD group, with an incidence rate ratio for all-cause hospitalization of 0.31 (95% CI, 0.08-1.17).

Seven deaths were recorded: 1 in the incremental HD group and 6 in conventional HD group. Comparing the incremental HD group with the conventional HD group, the hazard ratio for death was 0.18 (95% CI, 0.02-1.47), with an estimated first-year survival of 95.0% ± 4.9% (standard error) in the incremental HD group and 63.2% ± 13.1% (standard error) in the conventional HD group (Table S4).

Table 2. Serious Adverse Events According to Trial Group

Event	Incremental HD	Conventional HD
No. of patients in analysis	22	22
Days in study, per patient	288.9 ± 80.3	275.3 ± 98.0
No. of patients hospitalized	11	12
Total no. of hospitalizations	19	33
Total days hospitalized	71	172
Hospitalization rate, per 1,000 person-days[a]	11.0 (8.6-13.8)	26.3 (22.5-30.5)
Cumulative hospitalization rate, per person-year[b]	1.06 (0.64-1.66)	1.84 (1.31-2.59)
Time to first hospitalization, days	30.0 [17.0-94.5]	58.0 [17.0-110.0]
Proportion of hospitalizations in the first 90 days	42% (8/19)	33% (11/33)
Length of hospital stay, days (per hospitalization, per person)	2.0 [2.0-5.0]	5.0 [2.5-6.5]
Patients with ≥1 hospitalization	3/22 (14%)	7/22 (32%)
Hospitalization cause[c]		
Cardiovascular	1 (5%)	4 (12%)
Cerebrovascular	4 (21%)	1 (3%)
Fluid management	—	6 (18%)
Hyperkalemia	1 (5%)[d]	—
Encephalopathy	—	5 (15%)
Vascular access infection	2 (11%)	—
Vascular access complication, noninfectious	—	1 (33%)
Infection, not related to vascular access	4 (21%)	9 (27%)
Other	6 (32%)	7 (21%)
All-cause death rate, per 1,000 person-days	0.15 (0.004-0.85)	0.92 (0.34-1.99)

Unless otherwise indicated, values given as mean ± SD and median [interquartile range]; values in parentheses are 95% CI. Participants who withdrew consent, were lost to follow-up evaluation, or were withdrawn from the study were excluded from serious adverse events analysis. Events were calculated from date of randomization. Abbreviation: HD, hemodialysis.
[a]Hospitalization rate per 1,000 person-days takes into account the number of hospital days per 1,000 days.
[b]The cumulative hospitalization rate takes into account the total number of hospitalizations per each individual, independent of hospital length of stay.
[c]Percentage is based on all hospitalizations.
[d]Event occurred with thrice-weekly HD prescription, 299 days after transition from twice-weekly HD.

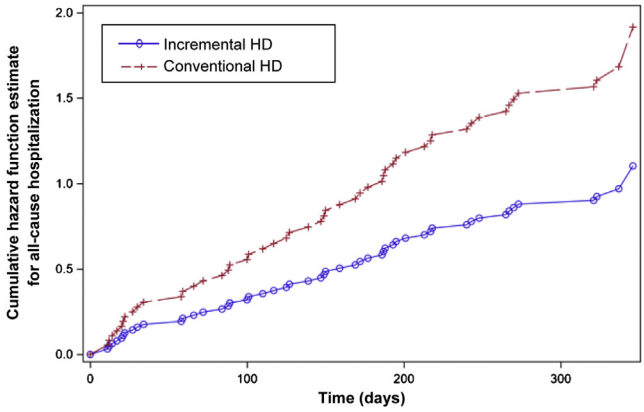

Figure 2. Cumulative hazard of hospitalization. Abbreviation: HD, hemodialysis.

Secondary Outcomes

Residual Kidney Function and Urea Solute Clearance

The estimated mean and percentage changes in the residual kidney function parameters from baseline to the scheduled time points are shown in Tables 3 and 4, respectively.

At the end of week 6, the urine volume decreased by 35.3% (95% CI, 19.5%-51.0%) in the incremental HD group and by 57.0% (95% CI, 40.8%-73.2%) in the conventional HD group, for an estimated difference of 21.7 (95% CI, −0.9 to 44.3) percentage points lower decline in urine volume in the incremental HD group compared with the conventional HD group (Table 4). Both groups experienced a rise in urine output between weeks 6 and 24. By the end of week 24, the urine volume increased by 22.8% (95% CI, −13.7% to 59.2%) in the incremental HD group and decreased by 28.2% (95% CI, 8.5% to 65.0%) in the conventional HD group, corresponding to an estimated difference of 51.0 (95% CI, −0.7 to 102.8) percentage points lower decline in urine volume in the incremental HD group compared with the conventional HD group.

At baseline, the proportion of patients with renal urea clearance ≥ 2 mL/min was 86% in the incremental HD group and 88% in the conventional HD group. From baseline to week 24, the averaged renal urea and creatinine clearances increased by 12.4% (95% CI, −45.3% to 70.0%) in the incremental HD group and decreased by 45.5% (95% CI, −10.7% to 101.7%) in the conventional HD group, largely due to a more pronounced difference in percent change in renal creatinine clearance as compared with renal urea clearance between the 2 groups (Table 4). The proportion of patients in the incremental HD group with different cutoffs of residual kidney function at the time of transition from twice-weekly to thrice-weekly HD is shown in Figure S2.

In terms of dialysis adequacy, in accordance with the study design, a significant increase in dialysis stdKt/V was present in the incremental HD group at week 12 (Table 3). The predialysis biochemical parameters were largely similar between the groups (Table S5).

Volume Management

Parameters related to volume management with HD are shown in Table 5.

Discussion

This pilot study randomly allocated incremental-start HD versus conventional HD in eligible patients who were beginning maintenance HD. The study met 3 of 4 a priori defined feasibility criteria (Table 6). Several important lessons were learned.

First, the study demonstrates that multistakeholder collaboration between patients, investigators, dialysis administration, dialysis personnel, and treating providers is required to proceed with a larger multicenter clinical trial. We note a lower than expected consent rate, which can negatively impact enrollment efficiency and generalizability of results. Thus, for a larger clinical trial partnership between investigators and large dialysis organizations is necessary to (1) broaden the pool of eligible candidates and (2) test implementation acceptability and sustainability across varied dialysis establishments and patient populations. Indeed, multistakeholder engagement has been recognized as a requisite to facilitate the conduct of clinical trials in nephrology.[29]

Second, this study uncovered the need for refining eligibility for future studies. Based on the residual kidney function eligibility criteria chosen for this pilot, 13% of participants had renal urea clearance <2.0 mL/min/1.73 m^2, compromising the achievement of total (dialysis + renal) stdKt/V ≥2.10 with twice-weekly HD at spKt/V ≥1.20 in those with low residual renal urea clearance.[1,24] For implementation purposes and intervention scalability, a chief practical consideration is that patients in the incremental HD group receive HD treatments targeted for the same metrics (ie, urea reduction ratio ≥65% and spKt/V ≥1.20) as the patients in the conventional HD group, the only difference being the frequency of HD. Urea kinetic models have identified thresholds of renal urea clearance that confer validity to this practical approach.[24] Thus, renal urea clearance of ≥2.0 mL/min/1.73 m^2 should be among the residual kidney function eligibility criteria in future clinical trials, particularly with protocols consisting of longer, individualized periods of twice-weekly HD.

Our preliminary results suggest incremental-start HD may confer better preservation of residual kidney function than conventional HD, a finding previously reported in observational studies.[12,15,30-33] Both groups had a significant decline in urine volume at week 6 and week 12, followed by a rebound in urine output by week 24, possibly related to dialysis-induced kidney injury followed by recovery.[34] The estimated treatment effect on urine volume at week 24 seemed to favor incremental HD,

Table 3. Parameters of Residual Kidney Function and stdKt/V Urea Solute Clearance

	Baseline[a]				Week 6[a]				Week 12[a]				Week 24[a]			
	Incremental HD		Conventional HD		Incremental HD		Conventional HD		Incremental HD		Conventional HD		Incremental HD		Conventional HD	
Parameter	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Residual Kidney Function by Treatment Group																
Urine volume, mL/d	23	914 (654-1,174)	25	1,424 (976-1,872)	19	504 (335-673)	17	553 (384-723)	19	479 (288-670)	19	484 (292-676)	17	862 (624-1,099)	15	876 (638-1,114)
Renal Cl_{urea}, mL/min/1.73 m^2	18	3.3 (2.0-4.5)	17	4.1 (2.9-5.3)	19	2.3 (1.6-2.9)	17	2.3 (1.6-3.0)	19	2.1 (1.4-2.8)	19	2.0 (1.4-2.7)	17	1.6 (0.9-2.2)	15	2.2 (1.6-2.8)
Renal CL_{cr}, mL/min/1.73 m^2	18	8.4 (5.6-11.3)	18	10.8 (8.1-13.5)	15	5.5 (2.9-8.1)	19	6.8 (4.7-9.0)	15	5.3 (3.2-7.4)	17	5.8 (4.1-7.5)	16	5.6 (3.9-7.3)	15	5.4 (3.7-7.2)
Averaged renal CL_{urea} and CL_{cr}, mL/min/1.73 m^2	18	6.1 (4.1-8.1)	17	7.2 (5.3-9.1)	11	4.0 (2.8-5.3)	13	3.9 (2.7-5.0)	15	4.4 (2.9-5.8)	17	4.3 (3.0-5.6)	16	3.6 (2.6-4.6)	15	3.8 (2.7-4.8)
StdKt/V Urea Solute Clearance by Treatment Group																
Dialysis spKt/V_{urea}	22	1.43 (1.32-1.53)	21	1.30 (1.20-1.40)	22	1.42 (1.32-1.51)	18	1.40 (1.30-1.10)	21	1.42 (1.34-1.50)	18	1.36 (1.29-1.45)	18	1.45 (1.29-1.61)	17	1.53 (1.37-1.69)
eKt/V_{urea}	22	1.23 (1.14-1.32)	21	1.10 (1.01-1.19)	22	1.22 (1.40-1.31)	18	1.19 (1.10-1.28)	21	1.22 (1.15-1.29)	18	1.16 (1.09-1.23)	18	1.24 (1.11-1.38)	17	1.30 (1.16-1.43)
Dialysis stdKt/V_{urea}	22	1.47 (1.40-1.54)	21	2.10 (2.03-2.17)	22	1.48 (1.42-1.55)	18	2.19 (2.12-2.26)	21	2.25 (2.18-2.33)	18	2.17 (2.09-2.25)	18	2.28 (2.19-2.37)	17	2.28 (2.19-2.37)
Renal stdKt/V_{urea}	18	0.99 (0.63-1.36)	17	1.24 (0.88-1.61)	19	0.67 (0.42-0.92)	17	0.66 (0.37-0.95)	19	0.49 (0.32-0.66)	17	0.59 (0.41-0.77)	17	0.41 (0.27-0.55)	15	0.54 (0.39-0.68)
Total stdKt/V_{urea} (dialysis + renal stdKt/V)	18	2.46 (2.09-2.84)	17	3.37 (3.00-3.74)	19	2.15 (1.90-2.39)	17	2.90 (2.61-3.18)	19	2.76 (2.59-2.94)	17	2.77 (2.59-2.96)	17	2.71 (2.55-2.87)	15	2.82 (2.66-2.99)
Dialysis spKt/V_{urea}	22	1.43 (1.32-1.53)	21	1.30 (1.20-1.40)	22	1.42 (1.32-1.51)	18	1.40 (1.30-1.50)	21	1.42 (1.34-1.50)	18	1.36 (1.29-1.45)	18	1.45 (1.29-1.61)	17	1.53 (1.37-1.69)

Data are presented as least squares mean (95% CI). Residual renal clearance was calculated based on 24-hour urine collection performed at baseline at enrollment; and interdialytic urine collection performed during weeks 6, 12, and 24. Interdialytic urine collection started at the end of first HD session and ended at the beginning for the second HD session for both treatment groups. Duration of interdialytic urine collection (minute) was calculated as 72 × 60 − HD treatment time, if on twice-weekly HD; and as 48 × 60 − HD treatment time, if on thrice-weekly HD. To calculate renal clearances, blood samples were collected at the end of the HD treatment preceding timed urine collection and the beginning of the successive HD treatment ending the period of timed urine collection.[22,23] Dialysis spKt/V_{urea} was obtained at the outpatient dialysis facility according to standard of care, during the first week of the month, before the second HD treatment of the week. Dialysis stdKt/V was calculated using an equation that includes effects of fluid removal. Urea distribution volume (V) was normalized using the formula $3.271 \times V^{(2/3)}$, where V was determined based on Watson formula.[24] Renal stdKt/V_{urea} was calculated based on renal urea clearance (mL/min) obtained at baseline and at weeks 6, 12, and 24. Abbreviations: CL, clearance; CL_{cr}, creatinine clearance; eKt/V, equilibrated Kt/V; HD, hemodialysis; n, number of participants with data at the respective time point; stdKt/V, standard Kt/V; spKt/V, single-pool Kt/V; total stdKt/V_{urea}, sum of dialysis stdKt/V and renal stdKt/V at each respective time point.
[a]Approximate study time point ± 2 weeks.

Table 4. Percent Change in Parameters of Residual Kidney Function and stdKt/V Urea Solute Clearance Over Time

Outcome	Baseline to Week 6			Week 6 to Week 12			Baseline to Week 12			Baseline to Week 24		
	Incremental HD	Conventional HD	Difference (95% CI)	Incremental HD	Conventional HD	Difference (95% CI)	Incremental HD	Conventional HD	Difference (95% CI)	Incremental HD	Conventional HD	Difference (95% CI)
Residual Kidney Function by Treatment Group												
Urine volume, mL/d	−35.3 (−51.0 to −19.5); n = 18	−57.0 (−73.2 to −40.8); n = 17	21.7 (−0.9 to 44.3)	6.0 (−25.5 to 37.6); n = 18	3.8 (−27.8 to 35.4); n = 17	2.2 (−42.4 to 46.8)	−36.3 (−53.4 to 19.2); n = 17	−60.8 (−78.1 to −43.4); n = 17	24.5 (0.1 to 48.8)	22.8 (−13.7 to 59.2); n = 14	−28.2 (−65.0 to −8.5); n = 14	51.0 (−0.7 to 102.8)
Renal CL_{urea}, mL/min/1.73 m^2	−1.2 (−41.7 to 39.2); n = 15	−3.7 (−43.9 to 36.6); n = 15	2.4 (−54.6 to 59.5)	0.8 (−32.6 to 34.2); n = 18	7.8 (−27.2 to 42.8); n = 16	−7.0 (−55.3 to 41.4)	−4.2 (−43.0 to 34.6); n = 16	−24.3 (−62.9 to 14.3); n = 16	20.1 (−34.7 to 74.8)	2.8 (−50.0 to 55.7); n = 14	−4.8 (−58.4 to 48.8); n = 13	7.6 (−67.6 to 82.9)
Renal CL_{cr}, mL/min/1.73 m^2	−31.3 (−70.2 to 7.6); n = 11	−17.7 (−49.2 to 13.9); n = 17	−13.6 (−63.7 to 36.5)	11.5 (−27.8 to 50.9); n = 14	−2.4 (−33.4 to 28.5); n = 18	14.0 (−36.1 to 64.1)	−30.1 (−63.8 to 3.6); n = 12	−22.5 (−49.8 to 4.8); n = 18	−7.6 (−59.9 to 35.8)	17.9 (−53.7 to 89.5); n = 13	−20.8 (−91.8 to 50.3); n = 13	38.6 (−62.3 to 139.5)
Averaged renal CL_{urea} and CL_{cr}, mL/min/1.73 m^2	−27.9 (−55.8 to −0.1); n = 9	−31.2 (−56.0 to −6.4); n = 11	3.2 (−34.1 to 40.5)	22.5 (−11.2 to 56.2); n = 9	23.0 (−7.7 to 53.8); n = 11	−0.5 (−46.1 to 45.1)	−17.7 (−51.8 to 16.5); n = 9	−14.9 (−45.3 to 15.5); n = 11	−2.7 (−48.4 to 43.0)	12.4 (−45.3 to 70.0); n = 13	−45.5 (−101.7 to 10.7); n = 13	57.9 (−22.6 to 138.4)
StdKt/V Urea Solute Clearance by Treatment Group												
Dialysis stdKt/V_{urea}	1.2 (−3.2 to 5.7); n = 20	4.9 (0.1 to 9.8); n = 16	−3.7 (−10.3 to 3.0)	52.1 (47.7 to 56.4); n = 19	−0.7 (−5.5 to 4.2); n = 15	52.7 (46.2 to 59.3)	53.5 (47.2 to 59.7); n = 19	3.9 (−2.7 to 10.4); n = 16	49.6 (40.5 to 58.6)	55.3 (47.5 to 63.0); n = 17	8.6 (1.1 to 16.1); n = 19	46.6 (35.8 to 57.4)
Renal stdKt/V_{urea}	−22.7 (−46.7 to 1.3); n = 17	−11.7 (−40.6 to 17.2); n = 11	−11.0 (−48.5 to 26.6)	−0.9 (−39.4 to 37.6); n = 16	15.6 (−29.3 to 60.4); n = 11	−16.4 (−75.5 to 42.7)	−24.5 (−62.2 to 13.2); n = 17	−22.4 (−63.7 to 18.9); n = 14	−2.1 (−58.1 to 53.8)	−17.8 (−55.9 to 20.2); n = 17	−32.2 (−72.8 to 8.5); n = 15	14.3 (−41.4 to 70.0)
Total stdKt/V_{urea} (dialysis + renal stdKt/V)	−10.6 (−21.3 to 0.2); n = 17	−6.7 (−19.4 to 5.9); n = 11	−3.8 (−20.4 to 12.8)	34.8 (21.7 to 47.3); n = 16	−1.1 (−16.2 to 14.0); n = 11	35.6 (15.8 to 55.3)	18.6 (4.6 to 32.6); n = 17	−9.7 (−24.8 to 5.3); n = 14	28.3 (7.7 to 48.9)	18.9 (4.5 to 33.3); n = 17	−9.8 (−25.2 to 5.5); n = 15	28.7 (7.7 to 49.8)

Percent change was calculated based on least squares mean values at different assessment time points as [(Value time point *b* − Value time point *a*)/Value time point *a*] × 100; where time points *a* and *b* represent the earlier and the later time points, respectively, in the interval calculated. For each percent change, the number of patients in the group is indicated. Difference in estimated percent change in residual kidney function parameters between groups was calculated as Mean % change in incremental HD group − Mean % change in conventional HD group. Values in parentheses are 95% confidence interval. Clearance was normalized to body surface area. Abbreviations: CL, clearance; CL_{cr}, creatinine clearance; stdKt/V, standard Kt/V

Table 5. Parameters Related to Volume Management

	Baseline		Week 6[a]		Week 12[a]		Week 24[a]	
	Incremental HD	Conventional HD	Incremental HD	Conventional HD	Incremental HD	Conventional HD	Incremental HD	Conventional HD
Parameter	n Value	n Value	n Value	n Value	n Value	n Value	n Value	n Value
Dry weight, kg	23 92.0 ± 20.1	25 87.5 ± 21.7	21 91.8 ± 20.7	21 88.4 ± 21.2	20 90.9 ± 21.1	20 87.6 ± 20.6	19 92.1 ± 22.7	19 87.5 ± 21.0
HD treatment time, min	23 232.6 ± 24.8	25 209.2 ± 21.9	21 234.8 ± 27.3	21 214.8 ± 34.3	20 230.6 ± 23.5	20 211.4 ± 29.8	19 224.7 ± 28.0	19 218.1 ± 32.2
Interdialytic weight gain, % of dry weight[b]	23 1.3 [0.4 to 2.5]	25 1.2 [0.3 to 2.4]	21 1.5 [0.0 to 2.2]	21 0.9 [−0.4 to 2.1]	20 1.9 [0.4 to 2.9]	20 2.2 [1.0 to 3.6]	19 2.5 [1.0 to 3.8]	19 1.8 [0.6 to 2.5]
Residual weight, % of dry weight[b]	23 −0.4 [−0.9 to 0.2]	25 −0.2 [−0.5 to 04]	21 −0.6 [−1.1 to −0.2]	21 −0.4 [−0.8 to 0.2]	20 −0.6 [−1.0 to 0.0]	20 0.0 [−0.3 to 0.6]	19 0.1 [−0.5 to 1.3]	19 −0.1 [−0.6 to 0.5]
Ultrafiltration rate, mL/kg/h[b]	23 4.7 ± 3.3	25 5.0 ± 3.6	21 4.7 ± 3.7	21 4.4 ± 3.3	20 5.9 ± 3.3	20 6.4 ± 4.0	19 6.4 ± 3.7	19 4.8 ± 3.7
Drop in SBP, % of predialysis SBP[b]	23 14.0 [7.2 to 20.6]	25 11.8 [5.1 to 15.3]	21 16.6 [10.0 to 23.8]	21 12.6 [9.4 to 25.3]	20 13.8 [5.8 to 31.1]	20 18.7 [8.5 to 28.9]	19 16.4 [5.1 to 23.4]	19 14.2 [4.4 to 23.3]

Values shown as mean ± SD or median [interquartile range]. Abbreviations: HD, hemodialysis; n, number of participants with data at the respective time point; SBP, systolic blood pressure.

[a]Approximate study time point ± 2 weeks.

[b]Calculated based on nadir value (SBP) or 1-week average values (all others), per each participant, observed during the week laboratory data were obtained at outpatient dialysis unit. These include baseline at enrollment and weeks 6, 12, and 24. Predialysis and postdialysis weights were recorded in kilograms. Dry weights were established by the treating providers. Interdialytic weight gain, as percentage of dry weight, was calculated as [(Predialysis weight − Dry weight)/Dry weight] × 100. Residual weight, as percentage of dry weight, was calculated as [(Postdialysis weight − Dry weight)/Dry weight] × 100. Ultrafiltration rate was calculated as {[(Predialysis weight − Postdialysis weight) × 1,000]/Dry weight]}/dialysis treatment time (in hours). Drop in SBP, as percentage of predialysis SBP, was calculated as [(Predialysis SBP − Nadir SBP)/Predialysis SBP] × 100.

Table 6. Lessons Learned From TWOPLUS Pilot Feasibility Trial

	Feasibility		
Parameter	**Expected**	**Observed**	**Lessons Learned**
Recruitment	≥70% of eligible patients are recruited	41% (77 of 185) of incident HD patients met preliminary criteria for study participation 66% (51 of 77) of study candidates consented 26% (48 of 185) of incident HD patients met all eligibility criteria and were enrolled in the study	Partnership between investigators and dialysis organizations is necessary to efficiently implement the study across a broader dialysis population and varied dialysis practice climates.
Adherence	≥95% of participants randomized adhere to the HD regimen	96% (22 of 23 and 24 of 25) adhered to the assigned HD protocol Changes in HD prescription from twice-weekly to thrice-weekly HD required in 9% (2 of 23) before end of week 6, based on patient's clinical status	Provider engagement is critical to ensure safety of study participants.
	≥80% patients adhere to study-specific assessments	100% adhered to timed urine collection Frequent communications between research team and dialysis personnel and laboratory personnel were necessary	Optimize stakeholder engagement, communication with dialysis personnel regarding urine and blood sample collection. Use Fidelity Checklist and Protocol Implementation Log with real-time observation and feedback to dialysis units in a larger multicenter clinical trial.
Crossovers	≤5% of participants randomized in the conventional HD group cross over to less frequent HD group	0 drop-in rate	Engaging on-the-ground clinicians is a requisite for the trial to become routinely incorporated into the delivery of clinical care.

Abbreviations: HD, hemodialysis; TWOPLUS, Twice-weekly Versus Thrice-weekly Hemodialysis in Patients With Incident End-stage Kidney Disease.

suggesting dialysis-induced kidney injury may had been less pronounced with twice-weekly HD.

Although we did not monitor the participants' adherence to pharmacotherapy, we speculate that the diuretic prescription, which was enforced at randomization in the incremental group, may have contributed to the observed between-group differences in urine output. Additionally, we identified solute-specific differences in residual kidney function between the groups, with a larger decline in renal creatinine clearance in the conventional HD group and a similar decline in renal urea clearance. This may suggest tubular secretory function could be better preserved with incremental HD, which in turn may be protective against adverse clinical outcomes.[35,36] A growing body of literature has indicated that several manifestations of kidney failure treated by maintenance HD (eg, heart failure, arrhythmias, and sudden death) are directly associated with accumulation of protein-bound uremic solutes that are not readily dialyzable but rather are actively secreted by transporters in the proximal renal tubule.[37]

Our results should be interpreted in the context of several limitations. Given (1) the imbalances in baseline characteristics between the 2 groups, (2) the small sample size, and (3) the time-delineated twice-weekly HD, the effect estimates are solely exploratory. Our testing of a time-delineated prescription of twice-weekly HD for 6 weeks may leave lingering concerns as to whether incremental HD with longer periods of twice-weekly HD can be effectively and safely implemented. We theorize that the patients' conformity to increasing HD frequency in the absence of clinical complications and when more than half had continued levels of substantial residual kidney function (Fig S2) lends assurance that responsible levels of adherence can be anticipated in a clinical trial of individualized incremental HD, which will employ ascending HD frequency with erosion of residual kidney function or clinical requirements.

This study showed core components of incremental HD can be achieved: intervention eligibility and enrollment among patients beginning maintenance HD with residual kidney function are favorable; intervention implementation at outpatient HD units is attainable; and patients' adherence to the recommended changes in HD prescription and to serial timed urine collection is good. We believe these results, coupled with the pilot study conducted in Europe,[38] provide the necessary data to advance the research in individualized HD to a larger multicenter clinical trial.

We propose individualized HD in the incremental study group will have individualized periods of twice-weekly HD with spKt/V urea ≥1.20 and adjuvant pharmacotherapy, with progress from twice-weekly to thrice-weekly HD being driven by changes in residual kidney function and/or clinical status. We emphasize that implementation of a practice-embedded incremental HD clinical trial at a

larger scale will require diligent planning consisting of systematic education of dialysis staff and nephrology providers about practical periodic patient assessments.[39]

With this framework, a multicenter controlled trial with the primary objective to establish noninferiority for the safety of incremental HD is justified. The proposed primary outcome is incidence rate of all-cause mortality, all-cause emergency department visits not leading to a hospitalization, and all-cause hospitalizations at 24 months. This rate would be calculated as the total number of safety events divided by the total number of person-years observed in the study. A participant could have recurring emergency department visits, hospitalizations, and/or die during the study, and all events would be included in the primary outcome analysis. A sample size of 350 total (175 per treatment group) would allow rejection of a noninferiority hazard ratio limit of 1.20 with ≥85% power at 1-sided level of significance equal to 0.025 under assumptions detailed in Item S1.

In conclusion, this pilot trial showed time-delineated treatment with twice-weekly HD and adjuvant pharmacologic therapy followed by conversion to thrice-weekly HD, along with serial timed urine collection is feasible. These findings support the indication to progress to a larger multicenter clinical trial with modified eligibility criteria and individualized periods of twice-weekly HD to conclusively investigate clinical effectiveness and safety of individualized HD.

Supplementary Material

Supplementary File (PDF)

Figure S1: Screening and enrollment.

Figure S2: Proportion of incremental-start participants over time potentially suitable for twice-weekly HD by cutoffs of residual kidney function.

Item S1: Supplementary methods.

Table S1: Eligibility criteria.

Table S2: Elements of HD prescription and pharmacologic therapy according to treatment allocation.

Table S3: Medications prescribed at the outpatient dialysis unit.

Table S4: Summary of dropout events and deaths during follow-up.

Table S5: Biochemical parameters over time by treatment group.

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Support: Dr Murea, the principal investigator, received funding for this trial from Relypsa Inc, Vifor Pharma, as an investigator-initiated study proposal (IE19-00819/GTS47902). Funding was used solely for study coordinators' financial compensation and procurement of patiromer potassium binding agent. The funders had no role in study design, did not have access to data collected during the study, and had no input on statistical analysis, results interpretation, and manuscript writing.

Financial Disclosure: Dr Kalantar-Zadeh has received commercial honoraria and/or support from Abbott, Abbvie, Alexion, Amag Pharma, Amgen, Ardelyx, AstraZeneca, Aveo, Baxter, Chugai, DaVita, Dr Schaer, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, Novartis, PCORI, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, UpToDate, Vifor, and ZS-Pharma. The remaining authors declare that they have no relevant financial interests.

Acknowledgements: The investigators wish to thank the study participants and the individuals who made the trial possible, including Dr John Burkart (former Chief Medical Officer for Health Systems Management, Inc, operationalizing outpatient dialysis services at Wake Forest University and Emory University, North Carolina); Dr Barry I. Freedman (Chief Medical Officer for Health Systems Management, North Carolina); Marshia Coe, Chief Operating Officer at Health Systems Management, Inc; Susan Trynosky and Sarah Morton for participant enrollment and questionnaire administration; Benjamin Bagwell for administrative help; all dialysis personnel from outpatient dialysis units affiliated with Wake Forest Baptist Medical Center for incorporating study-specific blood tests and timed urine collection testing into usual workflow; and all nephrology faculty providers for incorporating usual care administration to all study participants.

Data Sharing: Beginning 9 months and ending 36 months following article publication, deidentified participant data that underlie the results reported in this article will be available to investigators who provide a methodologically sound proposal and whose proposed use of the data has been approved by an independent review committee.

Peer Review: Received September 6, 2021. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form December 4, 2021.

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Twice-Weekly Hemodialysis With Adjuvant Pharmacotherapy and Transition to Thrice-Weekly Hemodialysis: A Pilot Study

Setting & Participants

Randomized Controlled Trial

14 dialysis facilities in North Carolina, USA

New start on chronic HD

- eGFR ≥5 mL/min/1.73 m^2
- Urine output ≥500 mL/24 h

Intervention & Control

Incremental HD
(N= 23)
2 HD/week
+
Adjuvant pharmacotherapy
for 6 weeks, then
3 HD/week

Conventional HD
(N= 25)
3 HD/week

Mean follow-up 281.9 days

Adjuvant pharmacotherapy:
Loop diuretics, patiromer, and/or sodium bicarbonate

Results

Primary Outcome: Feasibility

- 66% consent rate
- 96% adhered to assigned HD protocol
- 100% adhered to serial timed urine collection
- 0% cross over from 3 HD/week to 2 HD/week
- 9% cross over from 2 HD/week to 3 HD/week

Secondary outcomes, mean (95% CI)
Incremental HD vs Conventional HD

Urine output†*	51.0 percentage points lower decline (-0.7, 102.8)
Averaged urea and creatinine clearance‡*	57.9 percentage points lower decline (-22.6, 138.4)

*Percent change, baseline to week 24; †mL/24 h; ‡mL/min/1.73 m^2

CONCLUSION: Implementation of core components of incremental HD is feasible. Larger clinical trials are indicated to determine the efficacy and safety of incremental HD.

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@AJKDonline | DOI: 10.1053/j.ajkd.2021.12.001