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In-center hemodialysis six times per week versus three times per week

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In-Center Hemodialysis Six Times per Week versus Three Times per Week

The FHN Trial Group*

ABSTRACT

BACKGROUND

In this randomized clinical trial, we aimed to determine whether increasing the frequency of in-center hemodialysis would result in beneficial changes in left ventricular mass, self-reported physical health, and other intermediate outcomes among patients undergoing maintenance hemodialysis.

METHODS

Patients were randomly assigned to undergo hemodialysis six times per week (frequent hemodialysis, 125 patients) or three times per week (conventional hemodialysis, 120 patients) for 12 months. The two coprimary composite outcomes were death or change (from baseline to 12 months) in left ventricular mass, as assessed by cardiac magnetic resonance imaging, and death or change in the physical-health composite score of the RAND 36-item health survey. Secondary outcomes included cognitive performance; self-reported depression; laboratory markers of nutrition, mineral metabolism, and anemia; blood pressure; and rates of hospitalization and of interventions related to vascular access.

RESULTS

Patients in the frequent-hemodialysis group averaged 5.2 sessions per week; the weekly standard Kt/V_{urea} (the product of the urea clearance and the duration of the dialysis session normalized to the volume of distribution of urea) was significantly higher in the frequent-hemodialysis group than in the conventional-hemodialysis group (3.54±0.56 vs. 2.49±0.27). Frequent hemodialysis was associated with significant benefits with respect to both coprimary composite outcomes (hazard ratio for death or increase in left ventricular mass, 0.61; 95% confidence interval [CI], 0.46 to 0.82; hazard ratio for death or a decrease in the physical-health composite score, 0.70; 95% CI, 0.53 to 0.92). Patients randomly assigned to frequent hemodialysis were more likely to undergo interventions related to vascular access than were patients assigned to conventional hemodialysis (hazard ratio, 1.71; 95% CI, 1.08 to 2.73). Frequent hemodialysis was associated with improved control of hypertension and hyperphosphatemia. There were no significant effects of frequent hemodialysis on cognitive performance, self-reported depression, serum albumin concentration, or use of erythropoiesis-stimulating agents.

CONCLUSIONS

Frequent hemodialysis, as compared with conventional hemodialysis, was associated with favorable results with respect to the composite outcomes of death or change in left ventricular mass and death or change in a physical-health composite score but prompted more frequent interventions related to vascular access. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov number, NCT00264758.)

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When 90% or more of usual kidney function is lost, either kidney transplantation or dialysis is required to sustain life. Nearly 400,000 persons in the United States and 2 million worldwide are dependent on dialysis; of these, approximately 90% in the United States and 70% in Canada undergo hemodialysis, which is typically delivered three times a week.[1] The rationale for thrice-weekly hemodialysis was derived from a combination of physiological experiments, assessments of patient acceptance, feasibility, logistics, and costs.[2-4] Mortality remains high (approximately 18 to 20% per year) despite improvements in the technology for dialysis, the development of new pharmaceutical agents, and experience over the course of more than 40 years since maintenance dialysis became available. Moreover, although dialysis can sustain life, it rarely restores health; patients undergoing dialysis have considerable complications (including frequent and extended hospitalizations)[1] and relatively poor functional status and health-related quality of life.[5-7]

The optimal "dose" of hemodialysis remains uncertain. Anchored to a thrice-weekly regimen and typically expressed as a metric of small-solute (urea) clearance, dialysis dosing has been informed by numerous observational studies[8-10] and a few carefully conducted, randomized clinical trials.[11,12] Despite ample observational data suggesting that the dose of hemodialysis (expressed as the per-session Kt/V_{urea}, which is the product of the urea clearance and the duration of the dialysis session normalized to the volume of distribution of urea) correlates directly with survival, the Hemodialysis (HEMO) Study showed that there was no benefit from more intensive hemodialysis (higher per-session Kt/V_{urea}) when patients underwent hemodialysis three times a week.[12] However, solute removal can be dramatically augmented by increasing the frequency of hemodialysis sessions.[13] Several uncontrolled studies showed that there were significant improvements in patient-reported outcomes and results of laboratory tests when patients were treated with more frequent in-center or at-home hemodialysis.[14,15] Because of ongoing uncertainty regarding the optimal dose of hemodialysis, we tested the hypothesis that frequent (six times per week) in-center hemodialysis, as compared with conventional thrice-weekly hemodialysis, would improve an array of objective and patient-reported outcomes.

Methods

Study Protocol

The Frequent Hemodialysis Network (FHN) Daily Trial was a multicenter, prospective, randomized, parallel-group trial of frequent (six times per week), as compared with conventional (three times per week) in-center hemodialysis. The study was conducted between January 2006 and March 2010 at 11 university-based and 54 community-based hemodialysis facilities in North America (for a list of participating sites, see the Supplementary Appendix, available with the full text of this article at NEJM.org). The design of the FHN Daily Trial has been described previously.[16]

The FHN Daily Trial and a companion Nocturnal Trial (ClinicalTrials.gov number, NCT00271999) were sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Centers for Medicare and Medicaid Services, with additional support from DaVita, Dialysis Clinics, Fresenius Medical Care, Renal Advantage, Renal Research Institute, and Satellite Healthcare. The dialysis companies donated several weekly dialysis sessions; they had no role in the design of the study or in the analysis of the data. Recruitment and data collection were performed by site investigators and study coordinators. An independent data and safety monitoring board reviewed the safety data and interim results. The study was approved by the institutional review board at each participating study site. The protocol for the study, including the statistical analysis plan, is available at NEJM.org. The authors attest to the fidelity of this report to the trial protocol.

Study Population

Specific inclusion and exclusion criteria are listed in Table 1 in the Supplementary Appendix. Written informed consent was obtained from all patients 18 years of age or older; patient assent and written parental consent were obtained from participants younger than 18 years of age.

Study Design

Randomization

Randomization was stratified according to clinical center and diabetes status, with the use of randomly permuted blocks. Although treatment assignments could not be concealed, between-group comparisons of the outcomes were concealed from the investigators throughout the course of the trial.

Intervention

After randomization, prescriptions for dialysis were determined centrally and were transmitted to each clinical center. Patients who were assigned to thrice-weekly hemodialysis (120 patients) continued their usual dialysis prescriptions, which included a minimum target equilibrated Kt/V_{urea} of 1.1 and a session length of 2.5 to 4.0 hours. The equilibrated Kt/V_{urea} is the ratio of the equilibrated urea clearance during each dialysis session (Kt) to the patient's volume of urea distribution (V).[17] The target equilibrated Kt/Vn, where $Vn = 3.271 \times V^{2/3}$, in the group that underwent hemodialysis six times per week (125 patients) was 0.9 provided that the length of the session was between 1.5 and 2.75 hours. These prescriptions were factored by $V^{2/3}$ rather than V (similar to scaling surface area from body mass) to reduce the dependence of dialysis prescriptions on body mass and to avoid unfeasibly long dialysis treatments for patients with large body mass. Simulation studies indicated that these interventions would provide substantial differences in targeted weekly standard Kt/V_{urea} between the treatment groups.

Other Measurements

We obtained data on demographic characteristics at baseline, with clinical data and laboratory-test results obtained at baseline and serially over the course of the study. We calculated adherence as the ratio of outpatient dialysis sessions attended to outpatient dialysis sessions prescribed, by month. We obtained standardized assessments of coexisting conditions with the use of a modified version of the Charlson Comorbidity Index[18] supplemented with additional items from the Index of Coexistent Diseases.[19] Questionnaires were administered by telephone in either English or Spanish through a centralized call center; personnel administering the questionnaire were unaware of the participants' intervention assignment. Cardiac magnetic resonance imaging (MRI) was performed with the use of a standardized protocol; images were analyzed in a blinded fashion at a central core laboratory. A committee overseeing standards of care periodically reviewed and reported to the clinical centers the results of prespecified measures (serum phosphate and bicarbonate and blood hemoglobin concentrations; normalized protein nitrogen appearance; and blood pressure relative to the achieved target weight after dialysis) that were outside the ranges recommended in published guidelines.

Outcomes

It was not feasible to recruit a sample large enough to provide adequate statistical power to assess individual end points of death, cause-specific death, hospitalization, or other events. Therefore, we selected two composite coprimary outcomes: death or 12-month change in left ventricular mass, as assessed by cardiac MRI, and death or 12-month change in the physical-health composite score from the RAND 36-item health survey (RAND-36).[20] We determined that favorable effects on both coprimary outcomes would be required to provide evidence of overall benefit. We selected nine domains for secondary analysis; within eight of those domains, we selected a main secondary outcome: for the domain of cardiovascular structure and function, the outcome was left ventricular mass; for the domain of physical health, the outcome was the physical-health composite score of the RAND-36; for the domain of mental health, the outcome was the score on the Beck Depression Inventory; for the domain of cognitive function, the outcome was the score on the Trail Making Test, Part B; for the domain of nutrition, the outcome was the serum albumin concentration before dialysis; for the domain of mineral metabolism, the outcome was the serum phosphorus concentration before dialysis; for the domain of anemia, the outcome was the dose of an erythropoiesis-stimulating agent; and for the domain of death and hospitalization, the outcome was the rate of the composite of death or the first hospitalization unrelated to vascular access. For the ninth domain, hypertension, we specified two main secondary outcomes: systolic blood pressure before dialysis and the number of antihypertensive agents the patient was taking. We focused on several potential risks, including the need for interventions related to vascular access. Deaths, hospitalizations, and complications related to vascular access were adjudicated by an outcomes committee whose members were unaware of the patients' intervention assignment. Complications related to vascular access were defined as access failure, infection requiring a procedure, thrombectomy, angioplasty, and fibrin stripping of catheters or replacement of catheters.

STATISTICAL ANALYSIS

We used the Hochberg modification of the Bonferroni procedure to provide a studywide two-sided significance level approximating 0.05 when considering the two coprimary composite outcomes.[21]

Assuming a 20% reduction in mortality with frequent hemodialysis, we estimated that a sample size of 250 participants would give the study 90% power to detect clinically meaningful mean reductions in left ventricular mass of 12.1 to 13.3 g and increases in the physical-health composite score of the RAND-36 (in which scores range from 0 to 100 and higher scores indicate better physical status) of 4.6 to 5.0 points, with the detectable effect on each coprimary outcome varying slightly depending on the size of the treatment effect on the other coprimary end point.

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	P Value
Age (yr)	52.0±14.1	48.9±13.6	0.07
Female sex (%)	39.2	37.6	0.80
Race or ethnic group (%)†			0.32
Black	44.2	39.2	
White	38.3	34.4	
Native American, Aboriginal Canadian, Alaskan Native, or First Nation	3.3	3.2	
Asian	4.2	8.8	
Native Hawaiian or other Pacific Islander	2.5	0.8	
Other or mixed	7.5	13.6	
Body-mass index‡	27.5±7.1	27.3±6.5	0.82
Weight after dialysis (kg)	78.7±20.5	77.6±20.6	0.68
Anthropometric volume (liters)§	39.5±8.3	39.3±8.1	0.90
Cause of end-stage renal disease (%)			0.89
Diabetic nephropathy	32.5	36.0	
Glomerulonephritis	19.2	19.2	
Hypertensive nephrosclerosis	20.0	21.6	
Polycystic kidney disease	5.0	3.2	
Other	23.3	20.0	
Duration of end-stage renal disease (%)			0.38
<2 yr	16.7	16.0	
2–5 yr	42.5	35.2	
>5 yr	40.8	48.8	
Coexisting medical conditions (%)			
Hypertension	87.3	91.5	0.12
Myocardial infarction	13.3	8.8	0.26
Heart failure	20.0	20.0	1.00
Atrial fibrillation	7.5	4.0	0.24
Peripheral arterial disease	8.3	12.0	0.34
Abdominal aortic aneurysm repair or bypass grafting	1.7	2.4	0.68
Stroke	7.5	7.2	0.93
Dementia	0.8	0.0	0.31
Tumor without metastases	6.7	1.6	0.04
Diabetes and complications of diabetes	41.7	40.0	0.79
Hemiplegia	0.8	1.6	0.59
Chronic pulmonary disease	4.2	4.8	0.81
Moderate or severe liver disease	0.8	0.8	0.98

Table 1. (Continued.)

Characteristic	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	P Value
Residual kidney function (%)			0.17
Anuria	60.0	72.0	
>0 to 1 ml/min	15.8	14.4	
>1 to 3 ml/min	24.2	13.6	
Diastolic blood pressure before dialysis (mm Hg)	78.4±11.7	81.0±11.2	0.08
Serum creatinine (mg/dl)¶	10.3±2.5	10.8±3.0	0.21
Kt/V_{urea}‖			
Weekly standard	2.54±0.39	2.50±0.31	0.45
Equilibrated	1.43±0.28	1.43±0.25	0.94
Dialysis access (%)**			0.86
Fistula	62.5	65.6	
Synthetic graft	18.3	16.0	
Catheter	19.2	18.4	

* Plus–minus values are means ±SD.
† Race or ethnic group was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Anthropometric volume was calculated with the use of the Watson equation.
¶ To convert the values for creatinine to micromoles per liter, multiply by 88.4.
‖ The weekly standard Kt/V_{urea} is defined as the ratio of the generation rate of urea to the average urea concentration before dialysis and is commonly used to compare small-molecule clearance among different methods and schedules of dialysis.[22] The equilibrated Kt/V (the ratio of the equilibrated urea clearance during each dialysis session [Kt] to the patient's urea distribution volume [V]) is computed with the use of a modified Tattersall correction to single-pool Kt/V.[17]
** The proportions of upper arm and forearm fistulas were 47% and 52%, respectively; the proportions of upper arm and forearm grafts were 62% and 29%, respectively.

The analysis of the coprimary composite outcomes was performed with the use of a rank-based procedure, as follows: patients who died before 12 months were ranked from lowest (indicating the poorest outcome) to highest on the basis of survival time before death. Patients who survived 12 months were ranked on the basis of a favorable or unfavorable change in left ventricular mass (or physical-health composite score of the RAND-36) from baseline to 12 months. We right-censored (i.e., censoring when the event had not yet occurred at the time of measurement) patients at the time of transplantation or loss to follow-up, so that patients who survived but did not provide measurements of left ventricular mass (or physical-health composite score) were included as 1-year survivors. We compared ranks between treatment groups with the use of the log-rank test and calculated hazard ratios and 95% confidence intervals with the use of Cox proportional-hazards regression. We prespecified subgroup analyses according to sex, history or no history of heart disease, anthropometric volume (volume calculated with the use of the Watson equation, <35 liters vs. ≥35 liters), duration of end-stage renal disease (<4 years vs. ≥4 years), and presence or absence of residual kidney function (defined as >100 ml of daily urine volume). We analyzed the time to death or first hospitalization unrelated to vascular access using Cox regression, and we used the Andersen–Gill method for the analysis of recurrent events. All analyses were performed according to the intention-to-treat principle. Analytic methods used for the quantitative secondary outcomes are described in the Supplementary Appendix. We performed analyses of the main secondary outcomes without adjusting for multiple comparisons. Statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

STUDY POPULATION

Between January 1, 2006, and March 31, 2009, a total of 378 patients were enrolled, and 245 underwent randomization (Fig. 1 in the Supplementary Appendix). As shown in Table 1, the base-

Table 2. Features of Intervention.*

Variable	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	Ratio of Means (Frequent vs. Conventional)	P Value
Hemodialysis treatments per week (no.)	2.88±0.39	5.17±1.11	1.80	<0.001
Expected treatments attended (% of patients)†				
>80%	94.9	77.7	—	<0.001
65–80%	3.4	8.0	—	
<65%	1.7	14.4	—	
Time per dialysis session (min)	213±28	154±25	0.72	<0.001
Total dialysis time per week (hr)	10.4±1.6	12.7±2.2	1.23	<0.001
Blood flow rate (ml/min)	402±41	396±42	0.99	0.26
Dialysate flow rate (ml/min)	710±106	747±68	1.05	0.001
Dialyzer urea clearance (ml/min)	269±22	271±21	1.01	0.47
Ultrafiltration				
Per session (liters)	3.06±0.99	2.12±0.74	0.69	<0.001
Per session (% of weight after dialysis)	3.99±1.26	2.83±1.00	0.71	<0.001
Per week (liters)	8.99±3.03	10.58±3.83	1.18	<0.001
Kt/V_{urea}‡				
Total weekly standard	2.57±0.26	3.60±0.57	1.40	<0.001
Dialysis weekly standard	2.49±0.27	3.54±0.56	1.42	<0.001
Equilibrated per session	1.41±0.21	1.06±0.21	0.75	<0.001
Blood urea nitrogen (mg/dl)§				
Before dialysis	58.4±13.8	46.5±14.4	0.80	<0.001
After dialysis	15.9±4.9	16.5±5.6	1.04	0.38

* Plus–minus values are means ±SD. With the exception of number of treatments per week and treatments attended, all treatment features were first averaged over each patient's first modeled dialyses (sessions in which solutes are measured before and after the session) over each month of follow-up. Treatment attendance was monitored for all sessions during the time that the patient remained under the care of investigators at the participating centers.

† Adherence rates of 65% and 80% represent an average of 1.95 and 2.40 treatments per week, respectively, in the conventional-hemodialysis group and 3.9 and 4.8 treatments per week, respectively, in the frequent-hemodialysis group.

‡ The weekly standard Kt/V_{urea} is defined as the ratio of the generation rate of urea to the average urea concentration before dialysis and is commonly used to compare small-molecule clearance among different methods and schedules of dialysis.[22] The dialysis weekly standard is the component of the total weekly standard Kt/V_{urea} that remains after correction for residual renal function.[23] The equilibrated Kt/V (the ratio of the equilibrated urea clearance during each dialysis session [Kt] to the patient's urea distribution volume [V]) is computed with the use of a modified Tattersall correction to single-pool Kt/V.[17]

§ To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357.

line characteristics of the participants in the two study groups were similar; the study population was diverse with respect to age, sex, race or ethnic group, the primary cause of kidney disease, coexisting conditions, income, and education; the median duration of end-stage renal disease was 3.6 years (10th and 90th percentiles, 0.6 and 14.3).

CHARACTERISTICS OF THE STUDY INTERVENTION

Details of the characteristics of the intervention are provided in Table 2. A total of 78% of the patients who were assigned to undergo hemodialysis six times per week attended at least 80% of the prescribed hemodialysis sessions. As expected, the per-session dialysis dose, ultrafiltration volume, and weight gain between dialysis sessions were lower, and corresponding weekly values were higher, in the group that underwent hemodialysis six times per week than in the group that underwent the procedure three times per week. Figure 2 in the Supplementary Appendix shows the number of treatments per week, the

weekly treatment time, and the weekly standard[23] Kt/V_{urea} in both treatment groups.

COPRIMARY OUTCOMES

Five patients in the frequent-hemodialysis group died, as compared with 9 in the conventional-hemodialysis group; 11 patients in the frequent-hemodialysis group underwent transplantation, as compared with 13 in the conventional-hemodialysis group. Of the 5 patients in the frequent-hemodialysis group who died, 4 died suddenly, and the fifth died from hemorrhage (from the vascular access). In the conventional-hemodialysis group, 3 patients died suddenly, and 1 each died from myocardial infarction, stroke, sepsis, lung cancer, hemorrhage (from the gastrointestinal tract), and enterocolitis. Data on left ventricular mass at 12 months were missing for 22 patients, and data on baseline or 12-month RAND-36 physical-health composite scores were missing for 12 patients. Overall, the composite outcome of death or change in left ventricular mass was ascertained in 199 patients, and the composite outcome of death or change in the RAND-36 physical-health composite score was ascertained in 211.

Frequent hemodialysis was associated with favorable changes in both coprimary outcomes (hazard ratio for death or increase in left ventricular mass, 0.61; 95% confidence interval [CI], 0.46 to 0.82; hazard ratio for death or a decrease in the RAND-36 physical-health composite score, 0.70; 95% CI, 0.53 to 0.92) (Fig. 1A and 1B). The effects of frequent hemodialysis on the coprimary composite outcomes were not appreciably different in subgroups according to sex, history or no history of heart disease, anthropometric volume, duration of end-stage renal disease, or presence or absence of residual kidney function (data not shown).

SECONDARY OUTCOMES

There was no significant effect of frequent hemodialysis on the composite outcome of death or hospitalization unrelated to vascular access (hazard ratio, 0.93; 95% CI, 0.62 to 1.39). The adjusted mean (±SE) left ventricular mass decreased by 16.4±2.9 g in patients in the frequent-hemodialysis group, as compared with 2.6±3.2 g in patients in the conventional-hemodialysis group ($P<0.001$). Patients in the frequent-hemodialysis group had an increase in adjusted mean RAND-36 physical-health composite score of 3.4±0.8; the corresponding change in patients in the conventional-hemodialysis group was 0.2±0.8 ($P=0.004$) (Fig. 3 in the Supplementary Appendix). Frequent hemodialysis was associated with significantly improved control of hypertension and hyperphosphatemia. Table 3 shows the baseline and 12-month results for the main secondary outcomes; standardized changes in the secondary outcome domains are shown in Figure 1C.

COMPLICATIONS OF THERAPY

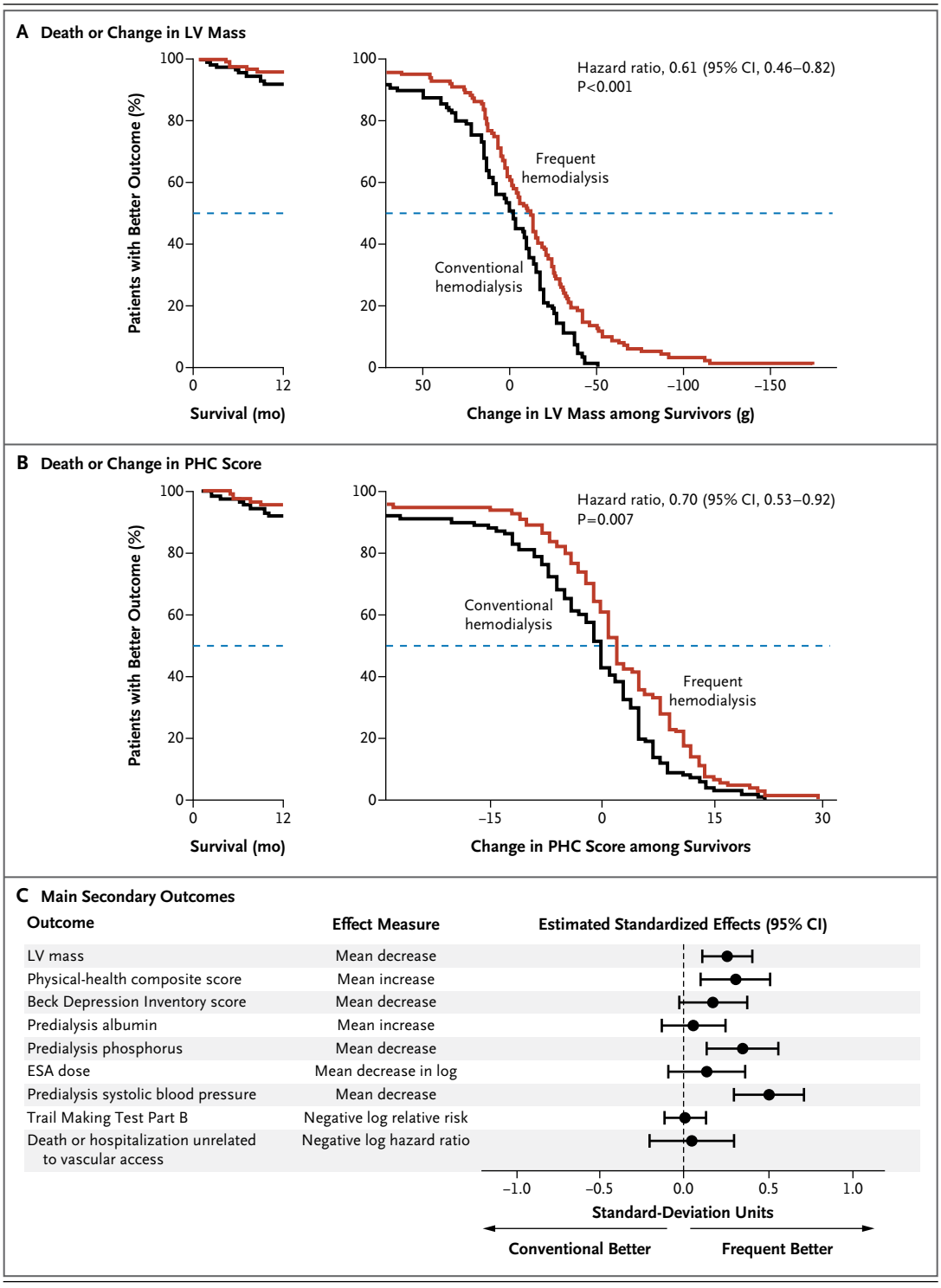
As compared with patients in the conventional-hemodialysis group, patients undergoing frequent hemodialysis were more likely to undergo interventions related to vascular access, both in the analysis of the time to the first intervention (hazard ratio, 1.71; 95% CI, 1.08 to 2.73) (Fig. 4 in the Supplementary Appendix) and in the analysis of multiple interventions (hazard ratio, 1.35; 95% CI, 0.84 to 2.18). There were 95 interventions related to vascular access (19 interventions to correct access failure and 76 other procedures) in the frequent-hemodialysis group and 65 interventions (23 to correct access failure and 42 other procedures) in the conventional-hemodialysis group; 47% of the patients in the frequent-hemodialysis group underwent at least one procedure, as compared with 29% in the conventional-hemodialysis group. The percentages of events affecting fistulas, grafts, and catheters were 51%, 32%, and 17%, respectively, in the frequent-hemodialysis group and 48%, 38%, and 14%, respectively, in the conventional-hemodialysis group.

The rates of adverse events are summarized in Table 4. Episodes of hypotension during dialysis in relation to the number of treatments were less common in the frequent-hemodialysis group than in the conventional-hemodialysis group (10.9% vs. 13.6% of monitored sessions with at least one recorded episode, $P=0.04$).

DISCUSSION

In this multicenter, randomized trial of frequent, as compared with conventional, in-center hemodialysis, we observed statistically significant and clinically meaningful benefits with respect to both coprimary composite end points — death or 12-month change in left ventricular mass and death or 12-month change in self-reported physical health.

Our results extend those that have been shown in several observational studies and clinical trials



comparing conventional and more frequent hemodialysis. DePalma et al.[25] reported the initial findings regarding an increased frequency of hemodialysis more than 40 years ago; in 1988, Buoncristiani et al.[26] found that control of hypertension and multiple metabolic factors were improved when patients underwent hemodialysis five to six times per week. Ting et al.[27] showed that among 42 patients who responded poorly to conventional hemodialysis, frequent in-center he-

Figure 1 (facing page). Coprimary Composite Outcomes and Main Secondary Outcomes.

Kaplan–Meier curves are shown for the composite outcomes of death or change in left ventricular (LV) mass (Panel A) and death or change in the physical-health composite (PHC) score from the RAND 36-item health survey (Panel B). For each value for the coprimary composite outcome on the horizontal axis, the Kaplan–Meier curve indicates the proportion of patients in the respective treatment groups with an equal or more favorable outcome. The horizontal distance between the Kaplan–Meier curves at the 50% value on the vertical axes indicates the median composite outcome results. Median outcomes for the composite outcome of death or change in LV mass correspond to a reduction in LV mass of 12.3 g in the frequent-hemodialysis group, as compared with a reduction of 2.2 g in the conventional-dialysis group (difference in medians, 10.1 g). The greater separation in the two curves on the right side of the graph of the change in LV mass is because nine patients had reductions in LV mass of at least 60 g; all of them were in the frequent-hemodialysis group. The median results for the composite outcome of death or change in physical-health composite score correspond to an increase in the physical-health composite score of 2 points in the frequent-hemodialysis group as compared with no change in the conventional-dialysis group (difference in medians, 2 points). Changes in LV mass ranged from a decrease of 51.2 g to an increase of 68.8 g in the conventional-dialysis group and from a decrease of 174.5 g to an increase of 61.9 g in the frequent-hemodialysis group. Changes in the physical-health composite score ranged from a decrease of 27 points to an increase of 22 points in conventional-dialysis group, and from a decrease of 28 points to an increase of 29 points in the frequent-hemodialysis group. The standardized effect sizes for the main secondary outcomes (Panel C) were calculated as follows: the mean differences in LV mass, physical-health composite score (in which higher scores indicate better physical health), Beck Depression Inventory score (in which higher scores indicate more severe depression), albumin concentration before dialysis, phosphorus concentration before dialysis, and systolic blood pressure before dialysis were divided by the baseline standard deviation; the mean difference in log dose of erythropoiesis-stimulating agent (ESA) was divided by the standard deviation of the log baseline ESA dose; the log risk ratio for failure to complete the Trail Making Test Part B was divided by square root ([1−p]/p), where p is the fraction of participants who did not complete the test within 5 minutes at baseline; the log hazard ratio for hospitalization unrelated to vascular access or death was divided by square root (1/p), where p is the fraction of patients with a hospitalization unrelated to vascular access or death. ESA doses of less than 5000 erythropoietin equivalent units were set to 5000 before log transformation.

modialysis was associated with fewer days in the hospital, improved health-related quality of life, and improved control of hypertension and anemia. Ayus et al.[28] compared 23 patients undergoing frequent in-center hemodialysis with 51 matched controls and found that patients undergoing frequent hemodialysis had a reduction in left ventricular hypertrophy and lower concentrations of phosphate and C-reactive protein. Other studies have examined the effects of frequent home-based hemodialysis, often performed overnight (so-called nocturnal hemodialysis).[29,30]

Although these studies were pioneering, they were limited by small sample sizes, inadequate or no controls, selection bias, dropout bias, and an emphasis on within-group, rather than between-group, inference tests. We elected not to allow participants to perform frequent hemodialysis at home, so that the benefits and risks of home-based therapies and the effects of session frequency could be disentangled.

In the conventional-hemodialysis group, the prescribed dialysis dose was at or above the levels recommended in clinical practice guidelines. In both groups, other aspects of hemodialysis and related care were standardized and monitored. Given the excellent adherence to both treatment regimens, the difference between the groups with respect to solute clearance was maintained. The vast majority of participants in the frequent-hemodialysis group completed at least five sessions per week; participants in the conventional-hemodialysis group rarely had extra hemodialysis sessions.

The trial met its prespecified criteria for showing overall benefit. The results of the FHN Daily Trial can be compared with those of the HEMO Study,[12] in which 1846 patients were randomly assigned to conventional or more intensive thrice-weekly in-center hemodialysis. In the HEMO Study, there was no overall effect on mortality, the rate of hospitalization, or health-related quality of life among patients randomly assigned to a target per-session equilibrated Kt/V_{urea} of 1.45 or 1.05, although subgroup analyses suggested a possible benefit among women and a trend toward harm among men with the more intensive treatment.[31] It is possible that the benefit we observed in the FHN trial among patients in the frequent-hemodialysis group was due to an even greater between-group difference with respect to urea clearance, a marker of low-molecular-weight solutes. Alternatively, the benefit of frequent hemodialysis may result from improved control of other metabolic by-products, such as phosphate or other retained uremic solutes, more physiologic removal of solutes (yielding lower

Table 3. Secondary Outcomes.*

Outcome	No. with Data†	Baseline	12 Months	Change from Baseline to 12 Months	Adjusted Mean (±SE) Change from Baseline‡	Difference in Change (Frequent–Conventional) (95% CI)	P Value
Left ventricular mass — g§							
Conventional hemodialysis	84	141±49	138±52	−2.4±25.9	−2.6±3.2	−13.8 (−21.8 to −5.8)	<0.001
Frequent hemodialysis	101	142±59	125±46	−16.3±35.3	−16.4±2.9		
Physical-health composite score¶							
Conventional hemodialysis	93	38.5±9.3	38.5±9.6	0.1±8.7	0.2±0.8	3.2 (1.0 to 5.4)	0.004
Frequent hemodialysis	104	38.4±11.0	41.7±10.7	3.3±8.9	3.4±0.8		
Beck Depression Inventory‖							
Conventional hemodialysis	88	12.4±9.0	12.2±9.9	−0.2±7.7	−0.4±0.7	−1.6 (−3.4 to 0.3)	0.10
Frequent hemodialysis	101	12.6±8.7	10.4±8.5	−2.2±6.5	−2.0±0.7		
Predialysis albumin — g/dl							
Conventional hemodialysis	94	3.98±0.44	3.96±0.40	−0.02±0.36	−0.02±0.03	0.02 (−0.06 to 0.10)	0.56
Frequent hemodialysis	103	3.99±0.37	4.00±0.36	−0.01±0.31	0.01±0.03		
Predialysis phosphorus — mg/dl**							
Conventional hemodialysis	94	5.68±1.55	5.65±1.75	−0.03±1.54	−0.08±0.14	−0.56 (−0.91 to −0.22)	0.002
Frequent hemodialysis	102	5.88±1.65	5.24±1.20	−0.63±1.60	−0.64±0.14		
Erythropoiesis-stimulating agents — EPO equivalent units††							
Conventional hemodialysis	90	57,070±65,456	53,093±63,552	−3,976±69,525	−5%±10%		0.24
Frequent hemodialysis	103	56,176±102,288	41,877±44,636	−14,299±76,191	−18%±8%		
Weekly average predialysis systolic blood pressure — mm Hg							
Conventional hemodialysis	93	146±18	147±18	0.9±16.2	0.9±1.6	−10.1 (−14.3 to −6.0)	<0.001
Frequent hemodialysis	104	147±19	137±19	−9.7±18.2	−9.2±1.5		
Antihypertensive agents consumed — no.							
Conventional hemodialysis	92	2.80±1.69	2.58±1.68	−0.23±1.35	—	—	<0.001‡‡
Frequent hemodialysis	103	2.69±1.80	1.82±1.73	−0.87±1.85	—		

Outcome	No. with Data†	Baseline	12 Months	Risk Ratio (95% CI)	P Value
Failure to complete Trail Making Test Part B in 5 min — no. of patients (%)					
Conventional hemodialysis	81	22 (27.2)	19 (23.5)	0.99 (0.81 to 1.21)	0.27‡‡
Frequent hemodialysis	95	25 (26.3)	23 (24.2)		
Death or hospitalization unrelated to vascular access — no. of patients (%)					
Conventional hemodialysis	120		46 (38.3)	0.93 (0.62 to 1.39)	0.71
Frequent hemodialysis	125		48 (38.4)		

* Plus–minus values are means ±SD, except where noted otherwise. All the outcomes listed were prespecified main secondary outcomes except for weekly average systolic blood pressure before dialysis and number of antihypertensive agents consumed.

† For all outcomes except for death or hospitalization unrelated to vascular access, the number with data refers to the number of patients for whom both baseline and 12-month data were available; for the outcome of death or hospitalization unrelated to vascular access, the number includes all patients who underwent randomization.

‡ For all but the final three outcomes listed in the table, mixed-effects analyses were adjusted for the baseline level of the factor analyzed, presence or absence of diabetes, age, and clinical center. The adjusted mean changes for erythropoiesis-stimulating agents indicate percent changes in geometric mean values from baseline to 1 year. Standard errors of the adjusted means for erythropoiesis-stimulating agents were computed with the use of the delta method. The time to death or first hospitalization unrelated to vascular access was analyzed with the use of Cox regression, adjusted for presence or absence of diabetes, age, and clinical center. Additional details are provided in the Supplementary Appendix.

§ When calculated per 1.73 m^2 of body-surface area, the mean (±SD) left ventricular mass index at baseline was 131±46 g per 1.73 m^2 in the conventional-hemodialysis group and 131±51 g per 1.73 m^2 in the frequent-hemodialysis group. The estimated between-group difference in the change from baseline to 12 months (frequent hemodialysis – conventional hemodialysis) was −12.5 g per 1.73 m^2 (95% CI, −20.1 to −4.9).

¶ The physical-health composite score was derived from the RAND 36-item health survey; scores range from 0 to 100, with higher scores indicating better health status.

‖ Scores on the Beck Depression Inventory range from 0 to 63, with higher scores indicating more severe depression.

** To convert the values for phosphorus to millimoles per liter, multiply by 0.3229.

†† When darbepoetin was used, the dose levels were converted to the approximate equivalent erythropoietin (EPO) dose with the use of the following equation: EPO dose (in units) = 250 × darbepoetin (in μg).[24] The EPO (or equivalent transformed darbepoetin) dose was set to a minimum 5000 units per 4-week period for patients taking less than 5000 units and was log transformed before statistical analysis. From baseline to 12 months, the mean (±SD) hemoglobin level before dialysis decreased from 12.0±1.3 g per deciliter to 11.7±1.0 g per deciliter in the conventional-hemodialysis group, and remained stable at 12.0±1.2 g per deciliter and 12.0±0.9 g per deciliter at baseline and 12 months, respectively, in the frequent-hemodialysis group. The estimated between-group difference in the change from baseline to 12 months (frequent hemodialysis – conventional hemodialysis) was 0.29 g per deciliter (95% CI, 0.02 to 0.55; P=0.03).

‡‡ P values for the number of antihypertensive agents and the failure to complete the Trail Making Test Part B in 5 minutes were calculated with the use of exact Wilcoxon rank-sum tests, stratified according to quartiles of the corresponding baseline values.

Table 4. Adverse Events during the 12-Month Follow-up Period of the Study.*

Outcome	Conventional Hemodialysis (N=120)		Frequent Hemodialysis (N=125)		Hazard Ratio (95% CI)	P Value
	no. of events	*no. of patients with event*	*no. of events*	*no. of patients with event*		
Death	9		5		—	—
All hospitalizations	114	47	109	58	0.88 (0.60–1.28)	0.50
Unrelated to vascular access	90	44	79	47	0.80 (0.53–1.21)	0.30
Related to vascular access	24	14	30	20	0.99 (0.54–1.82)	0.97
Cardiovascular-related	15	12	17	15	0.83 (0.44–1.59)	—
Infection related	27	20	27	23	0.83 (0.49–1.40)	—
All interventions related to vascular access	65	29	95	47	1.35 (0.84–2.18)	0.22
Correction of access failure	23	15	19	15	0.71 (0.35–1.44)	0.35
Other procedures	42	21	76	38	1.71 (0.98–2.97)	0.06
Episodes of hypotension†	470	87	724	99	—	—
Hypokalemia						
Potassium <3.0 mmol/liter	0	0	0	0	—	—
Potassium <3.5 mmol/liter	6	5	13	8	—	0.57‡
Hypophosphatemia§	9	7	15	9	—	0.80‡

* The hazard ratios and P values for rates of events (including multiple events per patient) between the frequent-hemodialysis group and the conventional-hemodialysis group were calculated with the use of the Andersen–Gill model, except where otherwise noted.

† The percentage of dialysis treatments with recorded hypotensive episodes, defined as the need for a lower ultrafiltration rate, reduced blood flow, or saline administration to ameliorate hypotension, was 10.9% in the frequent-hemodialysis group and 13.6% in the conventional-hemodialysis group (P=0.04 with the use of generalized estimating equations).

‡ The P values for the comparison of the number of patients with at least one event of hypokalemia or hypophosphatemia were calculated with the use of Fisher's exact test.

§ Hypophosphatemia was defined as a phosphorus concentration of less than 2.17 mg per deciliter (0.7 mmol per liter).

and less variable time-averaged solute concentrations), or improved control of extracellular volume excess (reducing the time-averaged fluid load). Consistently high weight gain between dialysis sessions may induce hypertension, left ventricular hypertrophy, and other adverse effects[32-34]; the lower weight gain between dialysis sessions in the frequent-hemodialysis group may be responsible for some of the benefit that we observed with respect to left ventricular mass. Although frequent hemodialysis is far from perfect, it may more closely approximate the capacity of a native or transplanted kidney to regulate extracellular volume and solute composition.

However, the benefits of hemodialysis performed six times per week were gained at the cost of more frequent interventions related to vascular access. Although we cannot exclude the possibility that these interventions were prompted by more frequent contact with the patient or by providers' fears, the fact that needle cannulation of a fistula or graft or manipulation of a catheter occurred approximately twice as frequently in the frequent-hemodialysis group as in the conventional-dialysis group could have contributed directly to the complications we observed.

The study has several strengths, including its relatively large sample size, the use of cardiac MRI for the assessment of left ventricular mass, the diversity of the study population, high adherence rates, and the wide array of outcomes linked to death and complications among patients with end-stage renal disease.[35,36] The study also has several important limitations. Owing to feasibility and other logistic concerns, the sample size was insufficient to determine the effects of frequent in-center hemodialysis on death, cause-specific death, hospitalization, or other events. Although we determined a priori that favorable effects on both coprimary composite outcomes would be required in order to consider the trial to have had positive results, the rate of death in both groups was low,

and the bulk of the treatment effect was seen in intermediate outcomes. Studies involving patients with[37] and patients without[38] end-stage renal disease have suggested that treatments targeted to reducing left ventricular mass are associated with lower rates of death and cardiovascular events. In observational analyses, differences in left ventricular mass[33] and self-reported physical health[39] of lesser magnitude than those shown in our study have been associated with significantly improved outcomes in this population. We excluded patients who had ample residual kidney function and patients who were not expected to survive for more than 6 months; we cannot generalize the study's results to these large and important segments of the population undergoing hemodialysis. To limit the risk of the "false discovery" of multiple effects, we designated a single outcome for each domain as a key secondary outcome (except in the case of hypertension, for which we specified two main secondary outcomes). These designations were somewhat arbitrary.

In summary, as compared with conventional hemodialysis, frequent hemodialysis was associated with favorable changes in the composite coprimary outcomes of death or 12-month change in left ventricular mass and death or 12-month change in the RAND-36 physical-health composite score. Frequent hemodialysis improved the control of hypertension and hyperphosphatemia but had no significant effects on cognitive performance, self-reported depression, serum albumin concentration, or use of erythropoiesis-stimulating agents. Patients who underwent frequent hemodialysis were significantly more likely to undergo interventions related to vascular access. Before major changes in practice can be recommended, the net effects of frequent hemodialysis will need to be balanced against the added burden for the patient and societal cost.

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APPENDIX

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