Long-Term Effects of Frequent In–Center Hemodialysis

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ABSTRACT

The Frequent Hemodialysis Network Daily Trial randomized 245 patients to receive six (frequent) or three (conventional) in–center hemodialysis sessions per week for 12 months. As reported previously, frequent in–center hemodialysis yielded favorable effects on the coprimary composite outcomes of death or change in left ventricular mass and death or change in self–reported physical health. Here, we determined the long-term effects of the 12-month frequent in–center hemodialysis intervention. We determined the vital status of patients over a median of 3.6 years (10%–90% range, 1.5–5.3 years) after randomization. Using an intention to treat analysis, we compared the mortality hazard in randomized groups. In a subset of patients from both groups, we reassessed left ventricular mass and self–reported physical health a year or more after completion of the intervention; 20 of 125 patients (16%) randomized to frequent hemodialysis died during the combined trial and post–trial observation periods in contrast to 34 of 120 patients (28%) randomized to conventional hemodialysis. The relative mortality hazard for frequent versus conventional hemodialysis was 0.54 (95% confidence interval, 0.31 to 0.93); with censoring of time after kidney transplantation, the relative hazard was 0.56 (95% confidence interval, 0.32 to 0.99). Bayesian analysis suggested a relatively high probability of clinically significant benefit and a very low probability of harm with frequent hemodialysis. In conclusion, a 12-month frequent in–center hemodialysis intervention significantly reduced long-term mortality, suggesting that frequent hemodialysis may benefit selected patients with ESRD.

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Nearly 400,000 persons in the United States and >2 million worldwide are dialysis dependent; of these, >90% in the United States and 70% in Canada receive hemodialysis, typically delivered thrice weekly.[1] Mortality rates in the hemodialysis population remain high (approximately 15%–20% per year overall and >30% in patients over 65 years old),[1] and health–related quality of life (HRQoL) for most patients is quite poor.[2] A large randomized clinical trial (the Hemodialysis Study) compared high–dose versus conventional–dose thrice weekly hemodialysis (target equilibrated Kt/V_{urea} [eKt/V_{urea}] of 1.45 versus 1.05) and showed no benefit on mortality, cardiovascular events, or HRQoL.[3,4]

Small, uncontrolled studies showed that patients treated with frequent hemodialysis enjoyed favorable changes in multiple biochemical parameters, improved control of hypertension, and in many studies, improved HRQoL.[5–8] These preliminary results justified and informed the design and implementation of the Frequent Hemodialysis Network (FHN) randomized clinical trials.[9] Given the expense of frequent hemodialysis and other feasibility concerns, we chose to examine an array of intermediate outcomes measured at baseline and

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4 and 12 months to assess the safety and efficacy of the intervention rather than mortality or other hard outcomes. The FHN in–center (daily) trial randomized 245 patients (125 to frequent and 120 to conventional in–center hemodialysis). The frequent hemodialysis intervention showed significant improvements in both coprimary outcomes (death or change in left ventricular mass and death or change in self–reported physical health).[10] In this study, we examine the effects of randomization to the 12-month intervention of frequent versus conventional in–center hemodialysis on mortality during extended follow-up.

RESULTS

Between January 1, 2006 and March 31, 2009, 378 patients were enrolled, and 245 were randomized. Adherence to the intervention was excellent; the mean number of treatments per week was 5.2±1.1 and 2.9±0.4 in patients randomized to the frequent and conventional groups, respectively. A Consolidated Standards of Reporting Trials diagram shows the disposition of randomized patients through the 12-month intervention and beyond (Figure 1). Among patients randomized to six times per week hemodialysis who were alive and not transplanted at the completion of month 14 (n=106), 26 (25%), 66 (62%), and 14 (13%) received hemodialysis four or more times per week, fewer than four times per week, and at an unknown frequency, respectively, during months 13 and 14. Corresponding figures for patients randomized to three times per week hemodialysis (n=94) were 4 (4%), 77 (82%), and 13 (14%), respectively. Hemodialysis session frequency was not regularly tracked thereafter.

Table 1 shows baseline characteristics of randomized patients and the same clinical characteristics in patients alive and nontransplanted after the 12-month intervention. We followed patients over a median of 3.6 years (10%–90% range, 1.5–5.3 years) after randomization.

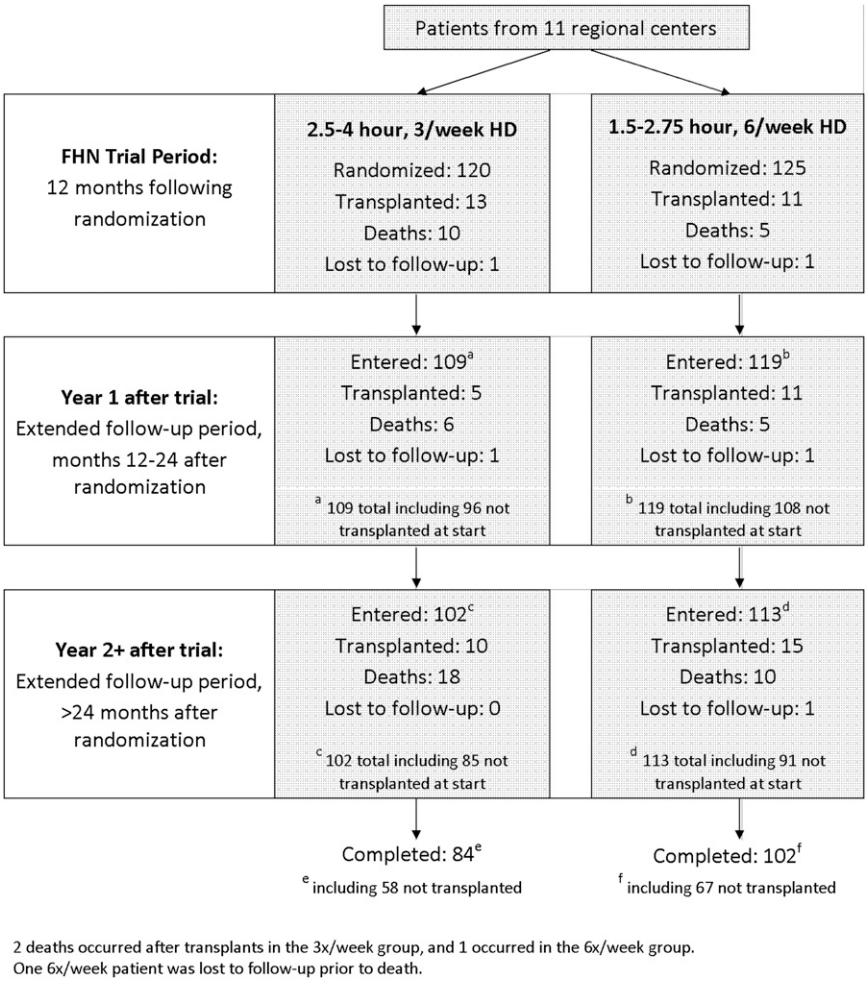

Figure 1. CONSORT diagram. Disposition of Study Subjects. Consolidated Standards of Reporting Trials diagram. HD, hemodialysis.

Mortality

In total, 20 of 125 (16%) patients randomized to frequent hemodialysis died within the combined trial and extension period in contrast to 34 of 120 (28%) patients randomized to conventional hemodialysis. The number of deaths was nominally lower in patients randomized to frequent hemodialysis during the 12-month intervention (5 versus 10), the first year after completion of the intervention (5 versus 6), and the second year after completion of the intervention and beyond (10 versus 18), with an integrated mortality rate substantially lower than that experienced by patients randomized to conventional hemodialysis (0.043 versus 0.082 deaths per patient-year); 37 (30%) and 28 (23%) patients were transplanted in the frequent and conventional groups, respectively.

Figure 2 shows Kaplan–Meier survival curves over the entire follow-up period. Including all months of follow-up time, the relative hazard (frequent versus conventional hemodialysis) was 0.54 (95% confidence interval [95% CI], 0.31 to 0.93) (Figure 2A). When we censored study months after kidney transplantation, the corresponding relative hazard was 0.56 (95% CI, 0.32 to 0.99) (Figure 2B). Causes of death are shown in Table 2. There was no obvious pattern of cause-specific death by randomized group.

Bayesian Analyses

Figure 3 displays posterior relative hazard distributions under the conservative and enthusiastic prior distributions. The posterior

Table 1. Baseline characteristics by randomized group

Patient Characteristics	Baseline					Month 12				
	Three Times		Six Times		*P* Value	Three Times		Six Times		*P* Value
	N	Mean or %	*N*	Mean or %		*N*	Mean or %	*N*	Mean or %	
Left ventricular mass (g)	120	142.0±53.1	125	139.8±55.3	0.75	84	138.1±51.5	100	126.0±46.0	0.09
Physical health composite	120	38.0±9.7	124	38.1±11.2	0.96	93	38.5±9.6	103	41.7±10.8	0.03
Age (yr)	120	52.0±14.1	125	48.9±13.6	0.07	97	52.0±14.0	108	49.2±13.3	0.15
Diabetes	120	50 (42%)	125	50 (40%)	0.79	97	41 (42%)	108	45 (42%)	0.93
Black race	120	53 (44%)	125	49 (39%)	0.43	97	44 (45%)	108	43 (40%)	0.42
ESRD vintage (yr)	120	3.4 (1.7, 6.4)	125	3.9 (1.7, 8.3)	0.28	97	2.8 (1.2, 6.8)	108	3.8 (1.6, 8.0)	0.21
Weekly predialysis diastolic BP (mmHg)	120	78.5±11.8	125	81.0±11.3	0.09	92	79.6±12.1	102	76.4±11.3	0.06
Weekly predialysis systolic BP (mmHg)	120	146.0±17.6	125	147.3±18.4	0.57	92	147.5±18.6	102	137.8±18.8	<0.001
Weekly postdialysis weight (kg)	120	78.7±20.5	125	77.7±20.7	0.69	92	79.3±19.9	102	78.3±21.0	0.73
Predialysis serum albumin (g/dl)	120	3.94±0.46	125	3.94±0.37	0.88	93	3.95±0.39	102	3.97±0.35	0.77
Predialysis serum phosphorus (mg/dl)	120	5.64±1.53	125	5.91±1.73	0.20	93	5.67±1.75	100	5.25±1.21	0.06
Predialysis hemoglobin (mg/dl)	119	12.02±1.24	125	11.87±1.28	0.34	94	11.70±1.03	102	12.00±0.90	0.03
Urine volume (ml/d)										
<50	120	72 (60%)	125	90 (72%)	0.03	82	66 (80%)	98	85 (87%)	0.52
50–500		34 (28%)		18 (14%)			14 (17%)		11 (11%)	
>500		14 (12%)		17 (14%)			2 (2%)		2 (2%)	
Access type	120		125			97		107		0.97
Fistula		71 (59.2%)		82 (65.6%)			62 (62.9%)		69 (64.5%)	
Graft		23 (19.2%)		22 (17.6%)			18 (18.6%)		19 (17.8%)	
Catheter		26 (21.7%)		21 (16.8%)			18 (18.6%)		19 (17.8%)	

Data is presented as mean±standard deviation. ESRD vintage units in brackets refer to the 25th and 75th percentile range.

probabilities for a clinically significant benefit (relative hazard, <0.80) were 0.61 under the conservative prior and 0.87 under the enthusiastic prior.

Long-Term Effects on Left Ventricular Mass and Self–Reported Physical Health

At 12 months, there were 205 patients alive and not transplanted (108 patients randomized to frequent hemodialysis and 97 patients randomized to conventional hemodialysis; 1 patient in each group was lost to follow-up); 61 (30%) underwent cardiac magnetic resonance imaging (MRI), and 88 (43%) completed the RAND-36 health survey at baseline, at 12 months, and again during the extended observation period. Table 3 shows long-term results of the intervention on changes in left ventricular mass and self–reported physical health. A reduction in left ventricular mass was maintained in the frequent hemodialysis group over time (adjusted mean change from baseline, 14.1±3.4 g), although the between-groups difference did not reach statistical significance (P=0.06). Within- and between-group changes in the Physical Health Composite of the RAND-36 health survey were small and not significant, suggesting nonpersistence of the shorter-term benefit of frequent hemodialysis on self–reported physical health.

DISCUSSION

The FHN trials are the largest prospective randomized trials conducted to date examining the feasibility, safety, and efficacy of frequent in–center (Daily Trial) and frequent home–based nocturnal (Nocturnal Trial) hemodialysis. The Daily Trial aimed to recruit 250 patients on the basis of feasibility and available resources; 245 (98% of goal) were recruited. With this modest sample size, the power to detect a difference in mortality or a composite of mortality and other major nonfatal events over a 12-month intervention period would have been extremely low. Therefore, the FHN investigators tested the hypothesis that frequent in–center hemodialysis would exert favorable effects on two coprimary composite outcomes: death or change in left ventricular mass and death or change in self–reported physical health. We also examined effects of frequent in–center hemodialysis on vascular access, physical health, mental health, cognitive function, residual kidney function, and control of hyperphosphatemia, hypertension, and anemia. We tracked death, kidney transplantation, and other health events over the 4+ years during which we conducted the trial.

The conclusion of the 12-month intervention provided an opportunity to conduct a natural experiment, in which the persistence of effects of frequent hemodialysis could be evaluated after patients resumed their pretrial thrice weekly hemodialysis schedules. Thus, after completion of the trial, we arranged for follow-up evaluation of the nondiscrete components of the two coprimary composite outcomes—left ventricular mass and self–reported physical health. In addition, we continued to track patients' vital status through data collection at all participating sites and linkage with the US Renal Data System (USRDS).

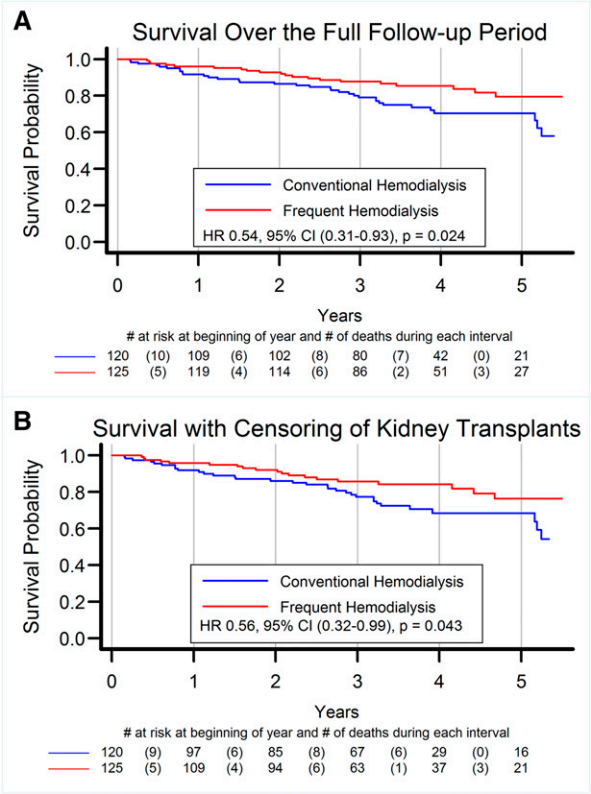

Figure 2. Kaplan-Meier curves depicting survival of patients randomized to the frequent and conventional hemodialysis groups. (A) Displays the survival curves including follow-up after transplantation; (B) displays the survival curves with follow-up censored at transplantation. The relative hazards were computed using Cox proportional hazards regression. HR, hazard ratio.

Patients randomized to frequent in–center hemodialysis experienced a >40% relative reduction in the mortality hazard, irrespective of whether follow-up time was censored after kidney transplantation. The companion Bayesian analyses serve to quantify our interpretation of the study results in the context of limited power. Too often, underpowered trials with statistically significant findings are disseminated without considering plausible prior probabilities or recognizing that significant *P* values might represent false-positive results. These analyses suggest that, although the actual benefit of frequent in–center hemodialysis may be smaller than the trial-derived estimate, frequent in–center hemodialysis is very unlikely to be harmful in contrast to results suggested by a large observational study on the basis of the International Quotidian Dialysis Registry.[11] We also concluded that a clinically significant benefit is reasonably likely; posterior probabilities of a ≥20% hazard reduction ranged from 0.61 to 0.87 depending on the prior distributions that we considered.

The reason for enhanced long–term survival in patients randomized to frequent in–center hemodialysis is unknown. During the 12-month intervention, frequent in–center hemodialysis reduced left ventricular mass, facilitated control of hypertension and hyperphosphatemia, and seemed to reduce extracellular fluid volume, whereas there was no benefit on objective physical performance, nutrition, or control of anemia. Analogous findings were described in the National Cooperative Dialysis Study, the first of the major randomized clinical trials comparing the intensity of hemodialysis therapy, wherein benefits on survival were observed years after completion of the randomized interventions (higher versus lower time–averaged concentration of urea and longer versus shorter session lengths).[12]

Strengths of these analyses include the trial design—a randomized controlled trial—which reduces the likelihood of confounding and bias, especially bias relating to receiving dialysis in the home versus in center.[13] The FHN Daily Trial participants were of a broad age range and diverse by sex, race-ethnicity, geographic origin, and primary cause of kidney disease. Vital status was ascertained on all but three patients who were lost to follow-up. Cardiac MRI studies were analyzed by a consistent team of readers throughout the trial and follow-up.

There are also several limitations. Although we captured the frequency of hemodialysis in the first few months after completion of the 12-month intervention period, we were unable to collect detailed information on dialytic or nondialytic care more remotely. With respect to determining the cause of death, for some patients, we had detailed medical records reviewed by the Outcomes Committee, but in others, we could only incorporate data from the Center for Medicare and Medical Services Death Notification Form. A large fraction of patients did not complete a third cardiac MRI and/or RAND-36 health survey scheduled during the extension phase. Thus, there is considerable uncertainty in the results examining longer-term effects on left ventricular mass and self–reported physical health and probable bias, recognizing that patients who agreed to (and/or survived until) long–term follow-up examination were likely to differ from those who did not. Relative to the entire North American hemodialysis population, participants in the FHN Daily Trial were younger, had longer dialysis vintage, and by design, had low levels of residual kidney function; therefore, these results may not be generalizable to all patients. Finally, these results should not be extrapolated to other methods of daily hemodialysis that do not provide the hours of dialysis time or solute clearance achieved in the FHN Daily Trial.

In summary, in addition to yielding largely favorable effects on several objective and self–reported intermediate outcomes, a 12-month frequent in–center hemodialysis intervention significantly reduced long-term mortality. Frequent hemodialysis may benefit selected patients with ESRD.

CONCISE METHODS

The FHN Daily Trial was a multicenter, prospective, randomized, parallel group trial of frequent (six times per week) compared with conventional (three times per week) in–center hemodialysis conducted between January of 2006 and March of 2010 at 11 university– and 54

Table 2. Short- and long-term effects of frequent in–center hemodialysis on left ventricular mass and the physical health composite score

Variable/Tx	Observed Data[a] Mean±SD |N|			Unadjusted Change[b] from Baseline to Extension (±SD) |N|	Adjusted Means and Treatment Effects[c] (±SEs or 95% CIs) [*P* Value]			
					Month 12		Extension	
	Baseline	Month 12	Extension		Change from Baseline	Treatment Comparison (Six Versus Three Times)	Change from Baseline	Treatment Comparison (Six Versus Three Times)
Left ventricular mass (g)								
Three times	142.0±53.1 |120|	138.1±51.5 |84|	137.6±50.7 |29|	−8.6±19.1 |28|	−2.4±3.1	−13.7 (−21.7 to −5.6) [<0.001]	−5.4±3.6	−8.7 (−17.9 to 0.5) [0.06]
Six times	139.8±55.3 |125|	125.5±46.0 |101|	124.0±43.8 |33|	−12.6±32.9 |33|	−16.0±2.9		−14.1±3.4	
Physical health composite score (SF36)								
Three times	38.1±9.7 |120|	38.5±9.3 |93|	37.7±10.3 |44|	−0.5±8.4 |43|	0.2±0.9	3.2 (0.9 to 5.4) [<0.01]	−0.6±1.1	0.2 (−2.6 to 3.1) [0.87]
Six times	38.1±11.2 |124|	38.4±11.0 |104|	39.3±12.1 |46|	−1.4±8.1 |45|	3.4±0.8		−0.3±1.0	

Tx, treatment.
[a]The observed baseline data reflect all records for randomized patients. The observed month 12 data represent patients who provided data at both baseline and month 12. The observed extension data represent patients who provided data at both baseline and during the extended follow-up period, regardless of whether they provided a month 12 measure.
[b]For the unadjusted change, numbers are the randomized patients providing baseline, 12-month, and Extension Study measurements. For adjusted results, all available data are used.
[c]Results of mixed effects analyses controlling for the baseline level of the factor analyzed, clinical center, and time between baseline and extended follow-up measures.

community–based hemodialysis facilities in North America. Trial design,[9] baseline characteristics,[14] primary results,[10] and the effects of the intervention on several secondary outcomes[15–22] have been published.

Intervention

After randomization, patients assigned to the thrice weekly arm remained on their usual dialysis prescriptions subject to a minimum target eKt/V_{urea} of 1.1 and a session length of 2.5–4.0 hours. The eKt/V_{urea} is defined as the ratio of the equilibrated urea clearance during each dialysis (Kt) to the patient's urea distribution volume (V), and it is commonly used as an indicator of the efficiency of hemodialysis. In the frequent hemodialysis group, the target dose was set as a function of V_n, where $V_n=3.271\times V^{2/3}$. The prescription was adjusted by $V^{2/3}$ rather than V, analogous to scaling dose by body surface area, as previously described.[23] The target session eKt/V_n for the frequent dialysis group was 0.9, provided that session length remained between 1.5 and 2.75 hours.

Other Measurements

During the 12-month intervention period, we calculated adherence as the ratio of attended to prescribed outpatient dialysis sessions by month. Questionnaires, including the RAND-36 health survey, were administered by telephone in either English or Spanish by a centralized call center blinded to the intervention assignment. Cardiac MRI was performed using a standardized protocol; images were analyzed in a blinded fashion at a central core laboratory.

Extended Follow-Up

After completion of the 12-month intervention, we obtained institutional review board approval to repeat cardiac MRI and the RAND-36 health survey among reconsenting patients to evaluate whether the effects of frequent hemodialysis on left ventricular mass and self–reported physical health were sustained. We also captured longer-term data on mortality and transplant status for all patients alive after the intervention period, supplementing this with information from the USRDS.

Outcomes

During the 12-month intervention period, deaths, hospitalizations, and vascular access complications were adjudicated by an Outcomes Committee and a Vascular Access Subcommittee blinded to the intervention assignment. We obtained extended follow-up information on mortality and transplantation through July 31, 2011 for 218 patients who survived past the trial intervention; 190 of these consented for linkage of their health data with the USRDS. Cause of death was classified by at least two members of the Outcomes Committee by review of medical records and/or USRDS data using a standard classification and methodology used previously in hemodialysis studies.[3]

Bayesian Analyses

Because of random error, results reaching statistical significance in relatively small trials with limited power tend to exaggerate the true effect of the treatment and incur an elevated risk of false-positive

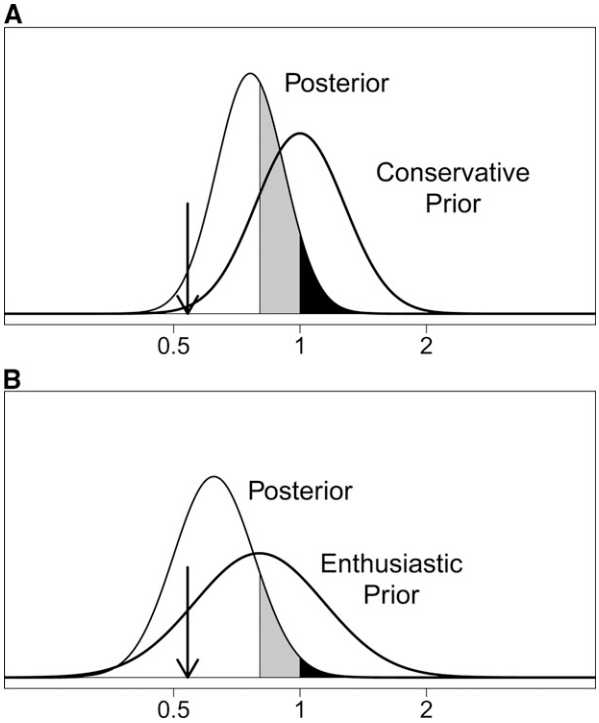

Figure 3. Posterior distributions of the relative hazard comparing mortality during extended follow-up among patients randomized to frequent and conventional hemodialysis under prior distributions representing neutral (A) and optimistic (B) perspectives on the probability of a treatment benefit. The posterior distributions characterize the implications of the observed relative hazard of 0.54 (downward pointing arrow) for individuals with the perspectives indicated by the conservative and enthusiastic priors before observing the results. The posterior probabilities of harm (black region), a small benefit with relative hazard between 0.8 and 1 (gray region), and a substantial benefit with relative hazard ≤0.8 are 0.07, 0.32, and 0.61, respectively, under the neutral prior and 0.02, 0.11, and 0.87, respectively, under the optimistic prior.

Table 3. Causes of death

Cause of Death Category	Treatment Group		
	Three times	Six Times	Total
Atherosclerosis/ischemic	3	2	5
CHF/cardiomyopathy	2	0	2
Arrhythmias	3	2	5
Other cardiac	1	1	2
Access infection	0	1	1
Nonaccess infection death	8	3	11
Other dialysis death	1	1	2
Other access death	0	1	1
GI bleed	2	3	5
Cancer	3	1	4
Respiratory, cerebrovascular, other	5	1	6
Unknown sudden death	1	1	2
Unknown	5	3	8
Total	34	20	54

CHF, congestive heart failure; GI, gastrointestinal.

conclusions.[24,25] As such, we performed Bayesian analyses to better quantify the uncertainty of the trial results under two prior distributions in which extreme relative hazards are unlikely. Posterior distributions of the relative hazards were simulated using Monte Carlo Markov chains to describe the implications of the trial results under each prior assumption. Posterior probabilities of a relative hazard <0.80 were computed to represent the probabilities of a clinically significant benefit. We considered a conservative prior to represent a perspective that assumes equal probabilities of benefit or harm of the intervention and attributes relatively small (0.05) probabilities to both substantial benefit (≥33.3% reduction in hazard for the treatment versus the control) and substantial harm (≥33.3% reduction in hazard for the control versus the treatment). The small probabilities assigned to substantial treatment effects can be viewed as reflecting a view that, even if the intervention might have produced a substantial effect during the 1-year trial period, this effect would likely have attenuated over the extended follow-up period after the intervention was discontinued. We also considered an enthusiastic prior with a median relative hazard of 0.80 and a 0.74 probability of a relative hazard <1. In contrast, standard survival analysis assumes that all relative hazards between zero and infinity are equally likely on the logarithmic scale.

Statistical Analyses

We analyzed all data according to the intention to treat principle. We calculated Kaplan–Meier product limit estimates and compared survival curves using the log-rank test. We calculated relative hazards and 95% CIs using proportional hazards (Cox) regression. In a companion analysis, we censored follow-up time after kidney transplantation. Our primary analysis examined mortality over the entire follow-up period—the 12-month trial plus the post-trial period, which varied in length depending on the time of recruitment and duration of follow-up. We used mixed effects analysis to compare mean changes in left ventricular mass and self–reported physical health from baseline with those from the 12-month and the extension study visits after controlling for baseline levels and clinical center. We also controlled for the time interval between randomization and the extension study visit. We used an unstructured covariance matrix to account for serial correlations in outcome measurements. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

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DISCLOSURES

None.

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