Effects of Frequent Hemodialysis on Measures of CKD Mineral and Bone Disorder

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ABSTRACT

More frequent hemodialysis sessions and longer session lengths may offer improved phosphorus control. We analyzed data from the Frequent Hemodialysis Network Daily and Nocturnal Trials to examine the effects of treatment assignment on predialysis serum phosphorus and on prescribed dose of phosphorus binder, expressed relative to calcium carbonate on a weight basis. In the Daily Trial, with prescribed session lengths of 1.5–2.75 hours six times per week, assignment to frequent hemodialysis associated with both a 0.46 mg/dl decrease (95% confidence interval [95% CI], 0.13–0.78 mg/dl) in mean serum phosphorus and a 1.35 g/d reduction (95% CI, 0.20–2.50 g/d) in equivalent phosphorus binder dose at month 12 compared with assignment to conventional hemodialysis. In the Nocturnal Trial, with prescribed session lengths of 6–8 hours six times per week, assignment to frequent hemodialysis associated with a 1.24 mg/dl decrease (95% CI, 0.68–1.79 mg/dl) in mean serum phosphorus compared with assignment to conventional hemodialysis. Among patients assigned to the group receiving six sessions per week, 73% did not require phosphorus binders at month 12 compared with only 8% of patients assigned to sessions three times per week ($P<0.001$). At month 12, 42% of patients on nocturnal hemodialysis required the addition of phosphorus into the dialysate to prevent hypophosphatemia. Frequent hemodialysis did not have major effects on calcium or parathyroid hormone concentrations in either trial. In conclusion, frequent hemodialysis facilitates control of hyperphosphatemia and extended session lengths could allow more liberal diets and freedom from phosphorus binders.

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Hyperphosphatemia is common in advanced CKD and ESRD and has been associated with bone disease and increased cardiovascular morbidity and mortality.[1,2] Phosphorus removal by conventional thrice-weekly hemodialysis and peritoneal dialysis is generally inadequate. Phosphorus control through the use of a low-phosphorus diet can potentially lead to low dietary protein intake and malnutrition.[3] The large number of phosphorus binder tablets needed to control hyperphosphatemia in ESRD can lead to poor adherence and low quality of life.[4] Even with a large pill burden, control of hyperphosphatemia in ESRD is poor, with fewer than half of patients achieving values recommended by several clinical practice guidelines.[4–6]

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Calcium-based phosphorus binders have been linked with vascular calcification.[7,8] The widespread use of non-calcium–based binders has been advocated by some, but these agents have failed to materially improve control of hyperphosphatemia and have not been shown to reduce rates of mortality, cardiovascular events, or fractures, despite high cost and claims of benefit.[9]

Several studies have suggested that more frequent hemodialysis sessions and longer session lengths offer improved phosphorus control.[10–12] We hypothesized that frequent daily in-center and nocturnal home hemodialysis would help to correct and facilitate control of hyperphosphatemia, resulting in lower predialysis serum phosphorus concentrations and the use of fewer phosphorus binders.

RESULTS

Baseline Characteristics

Baseline characteristics of participants in the Frequent Hemodialysis Network (FHN) Daily and Nocturnal Trials are presented in Table 1. Predialysis serum phosphorus concentrations were similar across both trials. Participants in the Nocturnal Trial tended to have a lower equivalent phosphorus binder dose (EPBD) and fewer were taking an activated vitamin D derivative.

Table 2 summarizes the results of cross-sectional multiple linear regression analyses relating baseline predialysis serum phosphorus to potential predictor variables. In the Daily Trial, higher baseline phosphorus concentrations were positively

Table 1. Baseline data for the Daily and Nocturnal Trials

Variable	Daily Trial			Nocturnal Trial		
	n	3 Sessions per Week (*n*=120)	6 Sessions per Week (*n*=125)	*n*	3 Sessions per Week (*n*=42)	6 Sessions per Week (*n*=45)
Age (yr)	245	52.0±14.1	48.9±13.6	87	54.0±12.9	51.7±14.4
Male sex	245	73 (60.8)	78 (62.4)	87	28 (66.7)	29 (64.4)
Race	245			87		
black		53 (44)	49 (39)		11 (26)	12 (27)
white		46 (38)	43 (34)		21 (50)	27 (60)
other/mixed		21 (18)	33 (26)		10 (24)	6 (13)
Diabetes	245	50 (41.7)	50 (40.0)	87	18 (42.9)	19 (42.2)
Postdialysis weight (kg)	245	78.7±20.5	77.7±20.7	87	83.3±23.8	87.6±27.0
ESRD vintage (yr)	245			87		
<1		20 (17)	20 (16)		25 (59)	20 (44)
1–2		15 (12)	17 (14)		5 (12)	8 (18)
2–5		42 (35)	34 (27)		5 (12)	8 (18)
>5		43 (36)	54 (43)		7 (17)	9 (20)
Residual renal clearance, (Kru + KCr)/2, ml/min	245			87		
0		72 (60)	90 (72)		11 (26)	13 (29)
>0–2		31 (26)	21 (17)		16 (38)	9 (20)
>2–4		14 (12)	6 (4.8)		6 (14)	11 (24)
>4		3 (2.5)	7 (5.6)		9 (21)	12 (27)
Taking no phosphorus binders	245	9 (7.5)	7 (5.6)	87	4 (9.5)	2 (4.4)
Types of phosphorus binders[a]	245			87		
taking 1 phosphorus binder		74 (61.7)	81 (64.8)		31 (73.8)	38 (84.4)
taking 2 phosphorus binders		36 (30.0)	33 (26.4)		7 (16.7)	5 (11.1)
taking 3 phosphorus binders		0 (0)	4 (3.2)		0 (0)	0 (0)
taking 4 phosphorus binders		1 (0.8)	0 (0)		0 (0)	0 (0)
EPBD (g/d)	245	5.92±4.32	7.17±5.48	87	4.54±3.17	3.63±2.39
Predialysis serum phosphorus (mg/dl)	245	5.64 (1.53)	5.91 (1.73)	87	5.77 (1.65)	5.82 (1.59)
Predialysis serum calcium (mg/dl)	245	9.04 (1.00)	8.99 (0.89)	87	8.96 (0.79)	8.71 (0.80)
Dialysate Ca (mEq/L)	245	2.49±0.24	2.53±0.30	87	2.59±0.27	2.59±0.27
Taking activated vitamin D derivative	245	94 (78.3)	96 (76.8)	87	18 (42.9)	24 (53.3)
Taking chole/ergocalciferol only	245	2 (1.7)	1 (0.8)	87	0 (0)	0 (0)
Taking both activated vitamin D derivative and chole/ergocalciferol	245	17 (14.2)	10 (8.0)	87	1 (2.4)	2 (4.4)

Results are shown as mean ± SD, median and 10th and 90th percentiles range, or frequency (%), as appropriate. For serum phosphorus values see Table 3, and for serum PTH values see Table 8.

[a]Types of phosphorus binders were those containing one of the following as a major ingredient: calcium carbonate, calcium acetate, sevelamer, lanthanum, aluminum carbonate or hydroxide, or magnesium-calcium combination.

associated with the equilibrated normalized protein catabolic rate (enPCR), a proxy for dietary protein intake, and were inversely associated with age. In the Nocturnal Trial, higher serum phosphorus was associated with higher enPCR and lower measured residual kidney function.

Follow-Up Treatment Measures

Table 3 shows the basic treatment measures at baseline, month 4, and the end of the study (12-month follow-up) for the two trials. The fact that the average number of sessions per week was not uniformly six times per week in each trial reflected a degree of nonadherence, which was more pronounced in the Nocturnal Trial. The mean stdKt/V_{urea} values ranged from 2.35 to 2.66 for participants assigned to receive treatments three times per week, averaged 3.49 at the end of the study for those assigned to receive treatment six times per week in the Daily Trial, and averaged 4.47 at the end of the study for those assigned to receive treatment six times per week in the Nocturnal Trial. The equilibrated protein catabolic rate (ePCR) as calculated from urea modeling was unchanged in the Daily Trial and was not affected by treatment assignment. In the Nocturnal Trial, ePCR was higher at month 12 compared with baseline in both groups; however, there was no between-group difference (see Table 3 and Kaysen *et al.*[13]). Table 3 also shows the duration (in hours) of the interdialytic interval preceding sampling (IDIPS) of blood for predialysis serum phosphorus and urea kinetic modeling parameters, as well as the average interdialytic interval across all dialysis treatments during the week of kinetic modeling. In the Daily Trial, the mean IDIPS corresponded roughly to the average interdialytic interval in both treatment groups. In the Nocturnal Trial, the IDIPS substantially exceeded the average interdialytic interval at month 12 in the group receiving treatment six times per week, as a relatively high percentage (42%) of study blood draws for serum phosphorus were performed on Sunday nights, after an off-night on Saturday.

Changes in Serum Phosphorus

Table 4 shows the effect of the randomized treatment assignments on predialysis serum phosphorus. In the Daily Trial, assignment to frequent hemodialysis was associated with a 0.46 mg/dl (95% confidence interval [95% CI], 0.13–0.78 mg/dl) decrease in mean serum phosphorus at month 12 relative to the conventional hemodialysis arm. In the Nocturnal Trial, assignment to frequent hemodialysis was associated with a 1.24 mg/dl (95% CI, 0.68–1.79 mg/dl) relative decrease in mean serum phosphorus.

We hypothesized that two baseline factors might modify the effect of the frequent

Table 2. Regression models relating serum phosphorus to potential correlates at baseline in the Daily and Nocturnal Trials

Predictor Variable	Daily Trial		Nocturnal Trial	
	Estimate ± SEM	*P* Value	Estimate ± SEM	*P* Value
Residual GFR (per ml/min)	−0.093±0.077	0.23	−0.202±0.065	0.003
Age (per 10 yr)	−0.36±0.07	<0.001	−0.18±0.12	0.16
Diabetes	0.09±0.21	0.68	0.52±0.36	0.15
enPCR (per 1 mg/g per day)	1.87±0.40	<0.001	1.63±0.64	0.01
EPBD (per 1 g/d)	0.02±0.02	0.26	0.05±0.07	0.46

Results adjusted for clinical center and IDIPS.

Table 3. Treatment parameters and phosphorus values during baseline and follow-up in the Daily and Nocturnal Trials

Variable	Dialysis Sessions per Week (*n*)	Daily Trial (*n*=92–104)			Nocturnal Trial (*n*=34–39)		
		Baseline	3–5 Mo	10–12 Mo	Baseline	3–5 Mo	10–12 Mo
Session time per treatment (min)	3	212±27	213±29	213±27	218±32	255±75	255±63
	6	216±26	150±26	152±27	227±25	376±68	361±83
Session time per week (h)	3	10.4±1.6	10.4±1.6	10.3±1.8	10.5±2.1	12.4±5.5	12.5±2.0
	6	10.7±1.5	12.9±2.4	12.4±2.6	11.1±1.5	30.5±9.0	28.2±11.4
Sessions per week, *n*	3	3.0±0.24	2.9±0.21	2.9±0.31	2.9±0.45	2.0±0.53	3.0±0.6
	6	3.0±0.21	5.2±0.97	5.0±1.08	3.0±0.23	4.8±1.02	4.6±1.18
Dialysis stdKt/V	3	2.49±0.38	2.47±0.26	2.47±0.27	2.35±0.35	2.66±1.10	2.61±0.44
	6	2.49±0.27	3.66±0.63	3.49±0.63	2.33±0.30	4.9±1.24	4.47±1.60
ePCR (g/d)	3	65±18	65±19	64±20	62±22	63±21	70±24
	6	65±21	68±22	65±23	63±21	71±22	75±39
IDIPS (h)[a]	3	51.8±12.6	51±11.2	53.3±13.6	54±11.7	59.3±16	56.3±15.2
	6	52.2±11.2	31.4±12.3	34.5±14.5	52.8±15.7	49.3±11.4	48.3±15.5
Mean interdialytic interval preceding dialysis (h)[b]	3	54.5±7.8	54.6±5.6	57.6±15.4	55.0±10.7	63.0±18.4	56.3±11.6
	6	54.1±7.2	31.9±9.8	34.9±16.0	53.3±5.0	41.2±9.6	44.2±14.2

Results presented for patients with measurements at all three time points (baseline, follow-up months 3–5, and follow-up months 10–12). Number of treatments per week and average interdialytic periods are based on the retrospective kinetic modeling data form.
[a]Sessions with reported interdialytic periods >3 days excluded.
[b]Sessions with <3 treatments in week preceding pre/post dialysis blood sampling excluded.

Table 4. Treatment effects on predialysis phosphorus (mg/dl) in the Daily and Nocturnal Trials

Trial	Dialysis Sessions per Week (*n*)	Observed Data (Mean ± SD) Patients with Complete Data[a]			Adjusted Means and Treatment Effects (±SEM or with 95% CIs)			
		Baseline	Months 3–5	Months 10–12	Months 3–5 Adjusted Mean Change ± SEM	Months 3–5 Treatment Effect (95% CI)	Months 10–12 Adjusted Mean Change ± SEM	Months 10–12 Treatment Effect (95% CI)
Daily	3	5.63±1.51	5.68±1.56	5.65±1.75	−0.06±0.12	−0.52[b]	−0.08±0.13	−0.46
	6	5.88±1.69	5.23±1.30	5.24±1.19	−0.58±0.12	(−0.82, −0.22)	−0.54±0.13	(−0.78, −0.13)[c]
Nocturnal	3	5.66±1.65	5.39±1.59	5.90±1.99	−0.33±0.22	−1.08[b]	0.12±0.23	−1.24
	6	5.74±1.53	4.38±1.42	4.72±1.32	−1.42±0.21	(−1.61, −0.56)	−1.11±0.23	(−1.79, −0.68)[b]

[a]Results provided for patients with nonmissing serum phosphorus at baseline, months 3–5, and months 10–12.
[b]$P<0.001$.
[c]$P<0.010$.

dialysis interventions on the change in serum phosphorus from baseline to month 12: baseline serum phosphorus and residual kidney function. In the Daily Trial, participants with higher serum phosphorus at baseline had a more pronounced effect of the frequent hemodialysis intervention; on the basis of a linear interaction model, the relative reduction in serum phosphorus at month 12 for treatment six times per week versus three times per week increased by 0.32±0.12 mg/dl for every 1 mg/dl higher baseline serum phosphorus (P=0.009 for baseline serum phosphorus × treatment assignment interaction). A similar trend was seen in the Nocturnal Trial (0.31±0.22 mg/dl increase in the treatment effect per 1 mg/dl increase); formal hypothesis testing was not performed due to the limited sample size of this trial. We found no clear evidence to suggest that baseline residual kidney function (expressed as the average of residual urea and creatinine clearance) modified the effect of frequent hemodialysis on serum phosphorus (P=0.24) in the Daily Trial.

The monthly mean changes in serum phosphorus in both trials are shown in Figure 1. For both trials, the separation in mean predialysis serum phosphorus remained roughly constant after the initial 3 months.

Histograms of serum phosphorus for both trials at baseline and month 12 are shown in Figure 2. At the study end (month 12), only 1.0% (1/102) of participants in the Daily Trial assigned to treatment six times per week had a serum phosphorus >8.0 mg/dl versus 9.6% (9 of 94) assigned to three times per week. Corresponding percentages in the Nocturnal Trial at month 12 were 0% (0 of 37, frequent arm) versus 18.0% (7 of 39, conventional arm). Comparing the proportion of patients with relatively normal predialysis serum phosphorus levels (<4.5 mg/dl) at month 12, there were 28.4% of such participants in the six times per week arm and 24.5% in the three times per week arm in the Daily Trial (Figure 2B). In the Nocturnal Trial (Figure 2B), the corresponding proportion was 51.4% (frequent arm) versus 28.2% (conventional arm).

Sensitivity Analyses of Effects of IDIPS on Serum Phosphorus

Because IDIPS lengths would be longer than the average interdialytic period when blood was drawn after the weekend break and because such differentials would depend on dialysis frequency, we investigated whether such scheduling discrepancies might bias the serum phosphorus treatment effects. Using a quadratic model, an increase of IDIPS from 1 to 3 days was associated with 0.49 mg/dl (95% CI, 0.14–0.83 mg/dl) higher serum phosphorus in the Daily Trial, and 0.63 mg/dl (95% CI, 0.31–0.95 mg/dl) higher serum phosphorus in the Nocturnal Trial. We obtained an approximate estimate of the bias due to the scheduling of the phosphorus blood draws by applying these interval-correction coefficients to the group mean values of IDIPS and the average interdialytic interval shown in the bottom two rows of Table 3 and computing the appropriate differences. The resulting bias estimate was negligible in the Daily Trial (0.03 mg/dl) but was 0.20 mg/dl

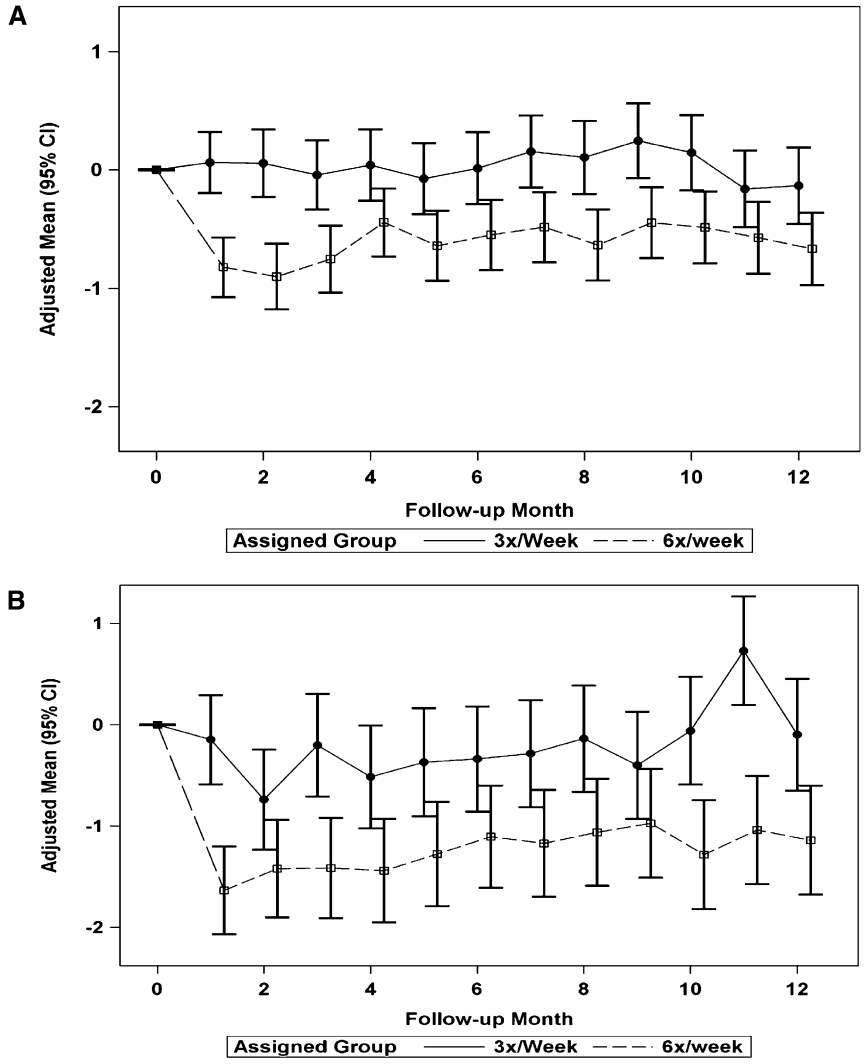

Figure 1. Adjusted mean levels of serum phosphorus. Monthly predialysis serum phosphorus in participants in the (A) Daily Trial and (B) Nocturnal Trial.

in the Nocturnal Trial. This suggests that the actual reduction in the mean predialysis serum phosphorus over all dialysis treatments could have been approximately 0.20 mg/dl greater than reported in Table 4 for the Nocturnal Trial.

Phosphorus Binder Use

The effect of randomized group on EPBD is shown in Tables 5 and 6. In both trials, there was a reduction in the total dose of phosphorus binders being prescribed. In the Daily Trial (Table 5), the mean difference between the two arms at month 12 was 1.35 g/d (95% CI, 0.20–2.50 g/d; P=0.02). In the Nocturnal Trial (Table 6), 73% of participants assigned to treatment six times per week had their EPBD reduced to 0 at month 12, compared with 8% of participants assigned to treatment three times per week (three versus six times per week Nocturnal Trial comparison, $P<0.001$). Furthermore, at month 12, 42% of patients on nocturnal hemodialysis added phosphorus into the dialysate to prevent hypophosphatemia (versus 0% in the control three times per week participants). Further examination of these data among participants who dialyzed >35 hours per week at month 12 showed that 20% (3 of 15) required phosphorus binders, 60% (9 of 15) required addition of phosphorus to the dialysate, and the remaining 20% (3 of 15) required no phosphorus supplementation.

In addition, participants in the frequent hemodialysis arms of both trials were prescribed fewer classes of phosphorus binders than participants in the conventional dialysis arms (Figures 3, A and B).

Serum Calcium, Dialysate Calcium, Activated Vitamin D Derivatives, and Parathyroid Hormone

Tables 7 and 8 compare the changes in dialzysate calcium, activated vitamin D derivative dosage, and serum parathyroid hormone (PTH) from baseline to month 12 between the treatment groups in the Daily and Nocturnal Trials, respectively.

There were no significant treatment effects on the change in serum calcium from baseline to month 12 in either trial (data not shown). In the Daily Trial, dialysate calcium was similar before and after randomization in both arms (Table 7). In the Nocturnal Trial, participants randomized to nocturnal hemodialysis six times per week used higher dialysate calcium (Table 7).

In the Daily Trial, the prescribed dose of activated vitamin D derivatives tended to be higher at baseline (10 μg/wk) than in the Nocturnal Trial (3 μg/wk). In the Daily Trial, there was a significant effect of treatment assignment on activated vitamin D derivative dose, with the dose increasing more in those assigned to dialysis six times per week (P=0.035). In the Nocturnal Trial, the activated vitamin D derivative dose, already low at baseline, tended to decrease further such that the mean dose being given at month 12 was <1 μg/wk in both arms. There was no effect of treatment assignment on the change in activated vitamin D derivate dose in the Nocturnal Trial.

Treatment effects on PTH are displayed in Table 8 and Figure 4. In the Daily Trial, there was a nonstatistically significant trend toward higher PTH in the frequent dialysis arm (26.0% difference in geometric means; 95% CI, −3.4% to 64.2%; P=0.09). In the Nocturnal Trial, there was a trend toward lower PTH in the frequent treatment arm (−0.38.2% difference in geometric means; 95% CI, −63.4% to 4.2%; P=0.07).

DISCUSSION

Our results confirm findings of previous investigators that frequent hemodialysis, given either daily as a 1.5- to 2.75-hour session or at night as an 6- to 8-hour session,[10–12] results in better control of serum phosphorus. In addition, we observed fewer prescribed phosphorus binders in the frequent hemodialysis groups. Because participants were taking different classes of binders (containing calcium salts, sevelamer, or lanthanum, with a handful taking aluminum- or magnesium-based binders), we elected to compare the phosphorus-binding potency of each patient's prescription using a recently described equivalent phosphorus binding dose (EPBD) metric.[14] Briefly, the EPBD operationally defines that the phosphorus binding ability of calcium acetate and calcium carbonate to be equal on a per-gram salt basis, the binding ability of sevelamer to be 75% that of the calcium salts, and that of lanthanum carbonate to be 200% that of the calcium salts comparing weight of elemental lanthanum versus weight of calcium salt.[14] Using this EPBD metric, in the Daily Trial, assignment to more frequent hemodialysis was associated with a reduced need for phosphorus binders. The reduction in EPBD associated with more frequent therapy compared with controls was in the range of 1.6 g/d. Although substantial, the baseline EPBD in the Daily Trial was about 6.5 g/d; with in-center hemodialysis six times per week, the EPBD was reduced but only by about 25%. In contrast, in the Nocturnal Trial, the EPBD reduction associated with assignment to treatment six times per week was much greater: 73% of participants assigned to receive treatment six times per week had their EPBD reduced to 0 at month 12; in fact, two-thirds of those participants not requiring binders were adding phosphorus to the dialysate, indicating the induction of negative phosphorus balance.

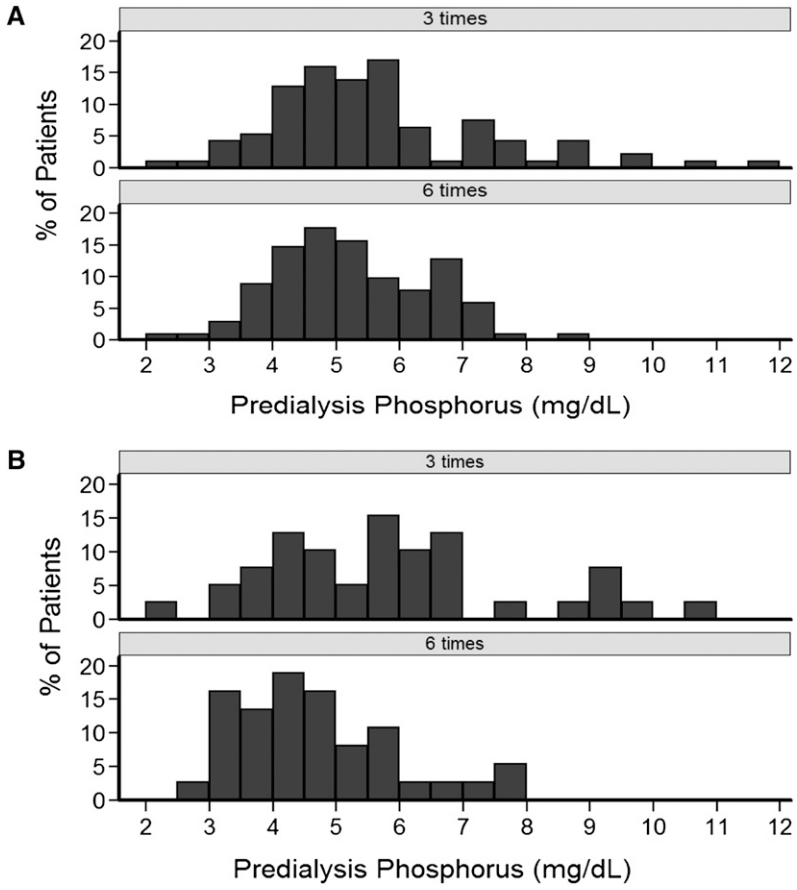

Figure 2. Predialysis phosphorus at the end of the study. Distribution of predialysis serum phosphorus among participants in the (A) Daily Trial and (B) Nocturnal Trial.

A marked increase in dietary protein intake could impede the ability to achieve control of serum phosphorus with more frequent hemodialysis, because phosphorus intake tends to be coupled with protein intake. In both the Daily and Nocturnal Trials, there was evidence for a very slight increase in dietary protein intake (as ePCR) between the conventional and frequent groups, although these changes were small in magnitude (about +5%), and probably had immaterial effects on the results.

Analysis of the control of serum phosphorus in hemodialysis should take into account the length of the interdialytic interval preceding the time when the sample was drawn (IDIPS). Phosphorus continues

Table 5. Treatment effect on EPBD (g/d) in the Daily Trial

Dialysis Sessions per Week (*n*)	Observed Data (Mean ± SD) Patients with Complete Data[a]			Adjusted Means and Treatment Effects (±SEM or with 95% CIs)			
	Baseline	Month 4	Month 12	Month 4 Adjusted Mean Change ± SEM	Month 4 Treatment Effect (95% CI)	Month 12 Adjusted Mean Change ± SEM	Month 12 Treatment Effect (95% CI)
3	5.92±4.32	5.90±4.64	6.64±4.95	−0.12±0.35	−0.41	0.39±0.45	−1.35[b]
6	7.17±5.48	6.37±4.67	5.70±4.94	−0.53±0.34	(−1.31 to 0.49)	−0.96±0.43	(−2.50 to -0.20)

[a]Results provided for patients with nonmissing EPBD at baseline, follow-up month 4, and follow-up month 12.
[b]*P*=0.02.

Table 6. Treatment effect on EPBD (g/d) in the Nocturnal Trial

Dialysis Sessions per Week (*n*)	EPBD Range	Patients, *n* (%)[a]		
		Baseline	Month 4	Month 12
3	0	4 (10.5)	6 (15.8)	3 (7.9)
	0.01–2	6 (15.8)	8 (21.1)	8 (21.1)
	2.01–6	13 (34.2)	10 (26.3)	14 (36.8)
	>6	15 (39.4)	14 (36.8)	13 (34.2)
6	0	1 (2.7)	31 (83.8)	27 (73.0)
	0.01–2	11 (29.7)	1 (2.7)	1 (2.7)
	2.01–6	19 (51.4)	5 (13.5)	9 (24.3)
	>6	6 (16.2)	0 (0)	0 (0%)

[a]Results provided for patients with nonmissing EPBD at baseline, follow-up month 4, and follow-up month 12. The percentage of patients with 0 EPBD was significantly higher in the group receiving treatment six times per week compared with the group receiving treatments three times per week at month 4 and month 12 ($P<0.001$, Fisher's exact test).

to be ingested during the interdialytic interval, and studies have shown that, with a schedule of three times per week, Monday/Tuesday serum phosphorus concentrations, sampled after a 3-day interdialytic interval, typically are about 0.3 mg/dl higher than values sampled before a midweek session.[15,16] One of the strengths of this study was that a large sample of serum phosphorus and IDIPS values were available, allowing us to develop a model relating serum phosphorus to IDIPS. This model yielded results consistent with prior reports.[15,16] It must be emphasized that the lower IDIPS value with more frequent hemodialysis is responsible for a true, and not an artifactual reduction in mean predialysis serum phosphorus. Nevertheless, the mean IDIPS in the Nocturnal Trial participants receiving treatment six times per week was substantially longer than the average interdialytic interval over the week in which the serum phosphorus was sampled because of policies in several units to sample blood on Sunday night in participants being treated with nocturnal dialysis six times per week. For this reason, in the Nocturnal Trial, we probably underestimated the effect of treatment six times per week on the predialysis serum phosphorus.

It is noteworthy that despite improved control of hyperphosphatemia, we saw no major reductions in PTH; indeed, PTH was not reduced in the arm receiving treatment six times per week in the Daily Trial despite an increased dosage of activated vitamin D derivative. In fact, in the arm receiving treatment six times per week, the "tail" of participants with serum PTH levels >750 pg/ml was not reduced at month 12 and tended to be increased (Figure 4A), despite the increased dose of activated vitamin D derivative,. The probable explanation for the lack benefit of dialysis six times per week in the Daily Trial is that the relatively modest reduction in serum phosphorus was not sufficient to effect a material reduction in PTH. In addition, with the reduction in phosphorus binder dosing, the oral intake of calcium (and presumably calcium balance) was lower, which could also moderate the effect of better control of phosphorus on PTH. Moreover, moderate to severe secondary hyperparathyroidism is a progressive disease. In other words, without any change in therapy, secondary hyperparathyroidism tends to worsen over time.

In the Nocturnal Trial, baseline serum PTH concentrations were similar to those in the Daily Trial, despite a lower proportion of participants taking activated vitamin D derivatives, and the trend for lower weekly doses of activated vitamin D derivatives. After randomization, with the participants in both arms going home, the mean activated vitamin D derivative dose prescribed was reduced to a low level. The reduction in the dose of activated vitamin D derivatives did not yield a major effect on serum PTH, although other determinants of PTH were changing simultaneously. There was a trend for a relative reduction in serum PTH levels in participants assigned to therapy six times per week. This may have been due to the more substantial reduction in serum phosphorus achieved in this group. A higher dialysate calcium level (average approximately 3.0 mEq/L) was used by centers performing nocturnal dialysis six times per week. This was probably based on work of early adopters of nocturnal dialysis, which suggested that, unless a dialysate calcium of at least 3.0 mEq/L were used with such intensive treatment, calcium loss to the dialysate and associated hypocalcemia would stimulate serum PTH levels.[17]

Although direct comparisons of the Daily and Nocturnal Trials were not performed due to differences in design between the two studies, it is apparent that serum phosphorus control in the Daily Trial was not as "complete" as it was in the Nocturnal Trial. In contrast to results reported by Ayus *et al.*,[11] few participants randomized to the arm receiving treatment six times per week in the Daily Trial were able to be weaned completely off phosphorus binders. Hence, although "short daily" dialysis clearly improves the control of hyperphosphatemia, by lowering serum concentrations and reducing the dose of binders required, longer session lengths than those prescribed in the Daily Trial may be required to afford patients a fully liberal diet *vis-à-vis* protein/phosphorus and freedom from phosphorus binders. On the other hand, one may argue that use of a 6- to 8-hour session length given six nights per week is excessively long for ensuring adequate phosphorus control, given that 60% of nocturnal participants randomized to frequent dialysis who received more than 35 hours of dialysis per week required addition of phosphorus to the dialysate to prevent hypophosphatemia.

Strengths of this study include the trial design—a multicenter randomized clinical trial with broad diversity of participants in terms of age, sex, race/ethnicity, vintage, and primary cause of kidney disease. In our analyses of phosphorus control, we accounted for baseline concentrations and center-to-center and month-by-month differences in the timing of laboratory testing (the IDIPS). In so doing, we confirmed and quantified these effects. We applied the EPBD metric to accommodate between- and within-person differences in phosphorus binder class and dose. We used statistical methods that were conservative yet allowed us to include observations in which participants had some missing data elements or were censored altogether due to transplantation. There were some important limitations

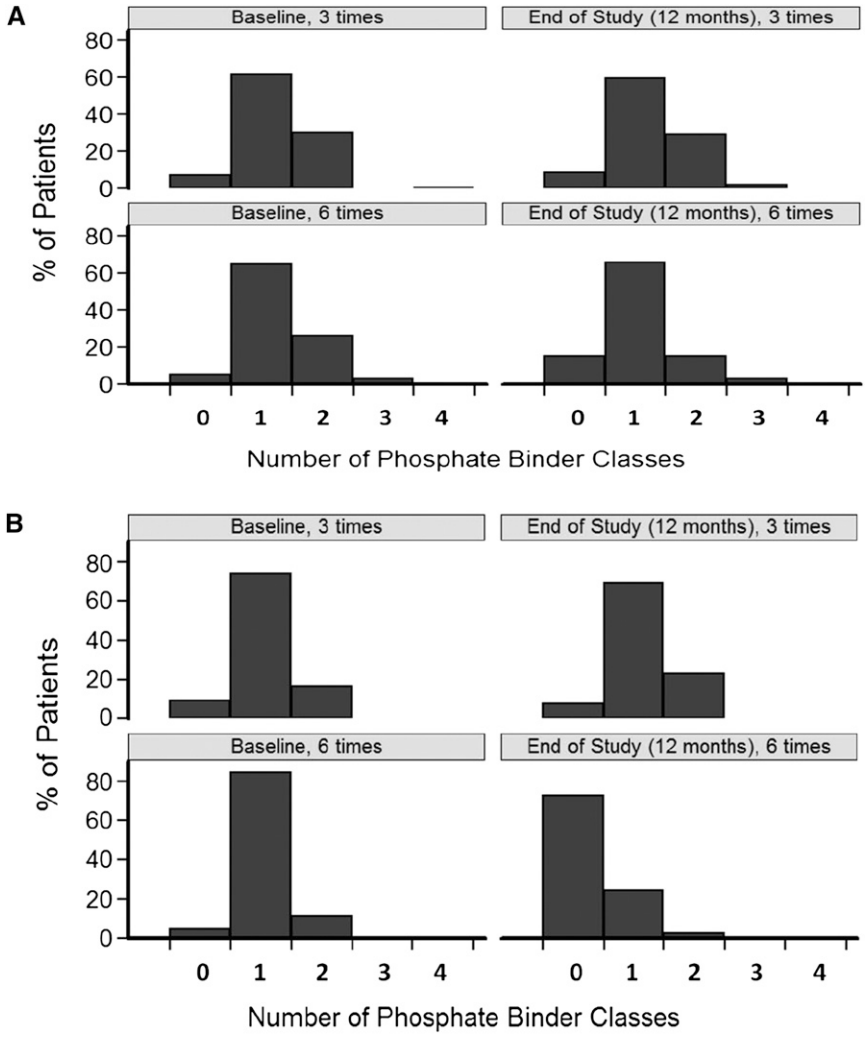

Figure 3. Number of different phosphorus binders taken at baseline and at the end of the study. Binders were grouped into six classes depending on whether they contained calcium carbonate, calcium acetate, sevelamer, lanthanum, aluminum, or magnesium plus calcium. (A) Participants in the Daily Trial. The top row depicts the control arm at baseline (left panel) and month 12 (right panel, and the bottom row depicts the six times per week arm at the same time points). (B) Participants in the Nocturnal Trial. The top row depicts the control arm at baseline (left panel) and month 12 (right panel, and the bottom row depicts the six times per week arm at the same time points).

as well. We did not collect detailed dietary records. Although the ePCR is a reasonable proxy for dietary protein intake, and dietary phosphorus and protein are moderately well correlated, there are numerous important dietary sources phosphorus (*e.g.*, dairy products, foods with phosphorus additives) about which we have no information. Moreover, although we believe that we captured the complexities of phosphorus binder prescription as well as possible, we were unable to confirm adherence to prescribed agents. Finally, we did not use a central laboratory for determination of phosphorus, calcium, PTH, or other laboratory studies. Use of dozens of laboratories almost certainly introduced some measurement error, although this would likely bias our overall results to the null.

In summary, hyperphosphatemia is among the laboratory abnormalities in patients on dialysis most consistently associated with mortality and major complications, including cardiovascular disease and fracture. Despite the use of high-flux, high-efficiency dialyzers, conventional hemodialysis rarely controls hyperphosphatemia. Frequent hemodialysis clearly facilitates control of hyperphosphatemia; frequent hemodialysis with extended session lengths could afford patients the option of more liberal diets and freedom from phosphorus binders. The optimum frequency and session length for hemodialysis patients with hyperphosphatemia remain to be determined. For now, more frequent hemodialysis and/or extended hemodialysis session length could be expected to improve phosphorus control in patients experiencing, or at risk for, important associated complications.

CONCISE METHODS

Study Design

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.[18] The FHN Nocturnal Trial was a similarly designed trial comparing the effects of frequent (six times per week) with conventional (three times per week) nocturnal hemodialysis.[18] The majority of participants in the Nocturnal Trial were receiving hemodialysis at home, with patients only receiving dialysis at night six times per week. Detailed description of study designs including randomization, specific inclusion and exclusion criteria, and data collection procedures of the FHN Daily and Nocturnal Trials have been previously described[18] and the primary results have been published (Daily Trial[19] and Nocturnal Trial[20]).

Study Population

Participants included those on maintenance hemodialysis who achieved mean equilibrated $Kt/V_{urea} > 1.0$ for the last two baseline hemodialysis sessions. Major exclusion criteria included age <13 years (Daily Trial) or <18 years (Nocturnal Trial), residual kidney function (mean of creatinine and urea clearance) >3 ml/min per 35 L (Daily Trial) or >10 ml/min per 1.73 m^2 (Nocturnal Trial), life expectancy <6 months, medical need for hemodialysis >3 times per week, history of poor adherence to hemodialysis, medical conditions preventing cardiac magnetic resonance imaging, inability to communicate in English or Spanish, and anticipated kidney transplant or relocation within 12 months. Informed

Table 7. Calcium and Vitamin D in the Daily and Nocturnal Trials

	Daily Trial, *n* (%)				Nocturnal Trial, *n* (%)			
	Baseline		12 Mo		Baseline		12 Mo	
	3 Sessions per Week	6 Sessions per Week	3 Sessions per Week	6 Sessions per Week	3 Sessions per Week	6 Sessions per Week	3 Sessions per Week	6 Sessions per Week
Prescribed elemental calcium dose (g/d)[a]								
0	46 (50.0)	59 (57.3)	48 (52.2)	66 (64.1)	10 (25.6)	13 (35.1)	12 (30.8)	31 (83.8)
>0–1000	15 (16.3)	16 (15.5)	12 (13.0)	12 (11.7)	8 (20.5)	9 (24.3)	9 (23.1)	3 (8.1)
1000–2500	24 (26.1)	20 (19.4)	24 (26.1)	18 (17.5)	18 (46.2)	13 (35.1)	15 (38.5)	3 (8.1)
>2500	7 (7.6)	8 (7.8)	8 (8.7)	7 (6.8)	3 (7.7)	2 (5.4)	3 (7.7)	0(0)
Total	92	103	92	103	39	37	39	37
Dialysate calcium (mEq/L)								
2.0–2.49	12 (12.9)	13 (12.5)	24 (25.8)	32 (30.8)	3 (7.7)	1 (2.7)	0 (0)	2 (5.4)
2.50–2.99	73 (78.5)	80 (76.9)	62 (66.7)	59 (56.7)	26 (66.7)	26 (70.3)	27 (69.2)	7 (18.9)
3.0–3.49	7 (7.5)	6 (5.8)	5 (5.4)	7 (6.7)	10 (25.6)	10 (27.0)	12 (30.8)	23 (62.2)
≥3.50	1 (1.1)	5 (4.8)	2 (2.2)	6 (5.8)	0 (0)	0 (0)	0 (0)	5 (13.5)
Total	93	104	93	104	39	37	39	37
Activated vitamin D derivative dose (μg/wk)								
0	19 (23.2)	21 (21.9)	18 (22.0)	19 (19.8)	29 (73.4)	21 (58.3)	36 (92.3)	33 (91.7)
>0–2.99	4 (4.9)	5 (5.2)	3 (3.7)	4 (4.2)	0 (0)	1 (2.8)	1 (2.6)	1 (2.8)
3.0–5.99	10 (12.2)	6 (6.3)	8 (9.8)	6 (6.2)	2 (5.1)	2 (5.6)	0 (0)	1 (2.8)
6.0–11.99	17 (20.7)	29 (30.2)	16 (19.5)	14 (14.6)	5 (12.8)	3 (8.3)	2 (5.1)	0 (0)
12.0–23.99	22 (26.8)	26 (27.1)	28 (34.1)	33 (34.4)	2 (5.1)	8 (22.2)	0 (0)	1 (2.8)
≥24.0	10 (12.2)	9 (9.4)	9 (11.0)	20 (20.8)	1 (2.6)	1 (2.8)	0 (0)	0 (0)
Total	82	96	82	96	39	36	39	36

[a]Prescribed elemental calcium dose with calcium-containing phosphorus binders.

consent was obtained from each participant. The trials were approved by the institutional review board at each participating study site.

Intervention, Control, and Adherence

After randomization in the Daily Trial, participants who were assigned to hemodialysis six times per week (n=125) had a target equilibrated Kt/Vn (where Vn=3.271×$V^{2/3}$) of 0.9 provided that the length of the session was between 1.5 and 2.75 hours.[21] Participants who were assigned to hemodialysis three times per week (n=120) continued their usual hemodialysis prescriptions, which included a minimum target equilibrated Kt/V_{urea} of 1.1 and a session length of 2.5–4.0 hours. After randomization in the Nocturnal Trial, participants were assigned to either hemodialysis three times per week (n=42) to a prescribed standard Kt/V_{urea} of >2.0 and a session length of ≥2.5 hours or to hemodialysis six times per week (n=45) to a standard Kt/V_{urea} of ≥4.0 for ≥6 hours per session.

Laboratory Measurements

All laboratory measurements were performed by local laboratories, including serum and dialysate calcium, serum phosphorus, and serum PTH. The PTH assays used included Bayer Advia Centaur (88 different testing laboratories [labs]), Diasorin IRMA (4 labs), DCP Immulite2000 (43 labs), Roche EPL 170 (20 labs), and Roche Elecsys (5 labs). The PTH assays used were all second-generation intact PTH assays, with normal values in nonuremics ranging from 6 to 14 pg/ml for the lower limit and from 65 to 80 pg/ml for the upper limit of normal. Blood was drawn either as serum or plasma, centrifuged, and then the refrigerated sample was sent to the local laboratory for analysis within 24 hours. With only rare exceptions, the PTH assay used and the method of sample collection and storage were not changed between values measure at baseline or throughout follow-up.

Outcomes

Mineral metabolism was one of nine prespecified domains selected for secondary analysis. We measured predialysis and postdialysis serum phosphorus concentrations monthly; the change in predialysis serum phosphorus from baseline to month 12 was the primary outcome within this domain. We also measured predialysis calcium and other routine laboratory studies monthly and PTH concentration and the prescribed amounts of phosphorus binders and vitamin D derivatives at baseline and at follow-up months 4, 8, and 12. To integrate data among participants using different phosphorus binders and/or combinations of binders, we calculated the EPBD as previously described.[14] We also calculated the proportion of participants with severe hyperphosphatemia (arbitrarily defined as P>8.0 mg/dl), and the proportion of participants who were taken off phosphorus binders by trial completion.

Statistical Analyses

Continuous variables were summarized using mean ± SD or median with 10th and 90th percentiles where data were skewed. Categorical variables were summarized using proportions. Descriptive summaries of changes in treatment-related variables are provided for the constant cohort with nonmissing values at baseline and at months 4 and 12 after randomization. To determine correlates of baseline predialysis serum phosphorus, we used a multiple linear regression

Table 8. Treatment effects on serum PTH (pg/ml) in the Daily and Nocturnal Trials

Trial	Sessions per Week (*n*)	Observed Patients with Complete Data (Median and 10th–90th Percentile Range)[a]			Adjusted Geometric Mean % Change and Treatment Effects (95% CI)			
		Baseline	3–5 Mo	10–12 Mo	3–5 Mo Adjusted Mean Change ± SEM	3–5 Mo Treatment Effect (95% CI)	10–12 Mo Adjusted Mean Change ± SEM	10–12 Mo Treatment Effect (95% CI)
Daily	3	282 (44, 846)	265 (54, 751)	258 (46, 832)	1.5 (−13.7 to 19.4)	7.5 (−13.2 to 33.2)	−7.9 (−24.8 to 12.8)	26.02[b] (−3.4 to 64.2)
	6	326 (94, 859)	350 (121, 1013)	369 (118, 972)	9.1 (−7.0 to 28.1)		16.0 (−4.0 to 40.0)	
Nocturnal	3	331 (112, 618)	220 (22, 1268)	268 (38, 1364)	−32.0 (−51.6 to −4.4)	0.3 (−37.5 to 61.0)	−11.4 (−39.2 to 28.9)	−38.23[c] (−63.4 to 4.2)
	6	296 (77, 650)	235 (25, 618)	233 (13, 672)	−31.8 (−51.1 to −4.8)		−45.3 (−62.2 to −20.8)	

[a]Results provided for patients with nonmissing serum PTH at baseline, month 4, and month 12.
[b]$P=0.09$.
[c]$P=0.07$.

analysis, controlling for clinical center and the interdialytic interval preceding the phosphorus measurement.

The effects of randomized treatment assignment on predialysis serum phosphorus were estimated with mixed-effects analyses, with covariate adjustment including a time interaction for the baseline phosphorus and clinical center for the Daily Trial, and baseline phosphorus in the Nocturnal Trial. The mixed-effects analysis for serum phosphoros incorporated the baseline and monthly measurements; we used a combined compound-symmetry first-order auto-regressive covariance matrix to account for correlations in measurements over time.[22] This analytic approach accounted for any nonmissing early phosphorus measurements in the analysis of changes to later time points in cases for participants who died or dropped out of the study during the follow-up period. Treatment effects were estimated for the mean change from baseline to the average predialysis serum phosphorus during months 3–5 and for the mean change from baseline to the average level during months 10–12. The same approach was used to evaluate treatment effects on predialysis serum calcium, ePCR, and enPCR (raw two-pool [equilibrated] PCR and PCR normalized to body water–estimated weight, respectively).

In the Daily Trial, we applied a mixed-effects analysis to EPBD at baseline and months 4, 8, and 12, using an unstructured covariance model to account for serial correlations in the measurements over time. The Fisher exact test was used to compare the proportion of participants with no prescribed EPBD between the Nocturnal Trial treatment groups.

The mixed-effects models for serum phosphorus were extended in both trials to investigate if the effect of six times per week compared with three times per week hemodialysis on serum phosphorus differed among participants with different levels of baseline GFR by adding an interaction term between treatment assignment and baseline GFR. Linear regression models with the same predictor variables were used to test for an interaction between baseline serum phosphorus concentrations and the treatment effect on change in serum phosphorus from baseline to months 10–12.

In a second extension of mixed-effects models, we related the monthly predialysis serum phosphorus to the interdialytic interval preceding the phosphorus measurements after controlling for factors potentially related to phosphorus generation and removal, including treatment assignment, visit month, age, diabetes, baseline GFR, the number of dialysis treatments within the week preceding the phosphorus measurement, the weekly treatment time, and interactions of the treatment assignment with both weekly treatment time and the number of treatments. The effect of the interdialytic interval was modeled as a quadratic regression.

We also compared the change in PTH over the study period by comparing the ratio of geometric means in the groups receiving treatment six times per week and the groups receiving treatment three times per week by applying adjusted mixed models to quarterly log-transformed PTH measurements as described above for EPBD in the Daily Trial.

All analyses were performed without formal adjustment for multiple comparisons using SAS software (version 9.2). Two-tailed $P<0.05$ was considered statistically significant.

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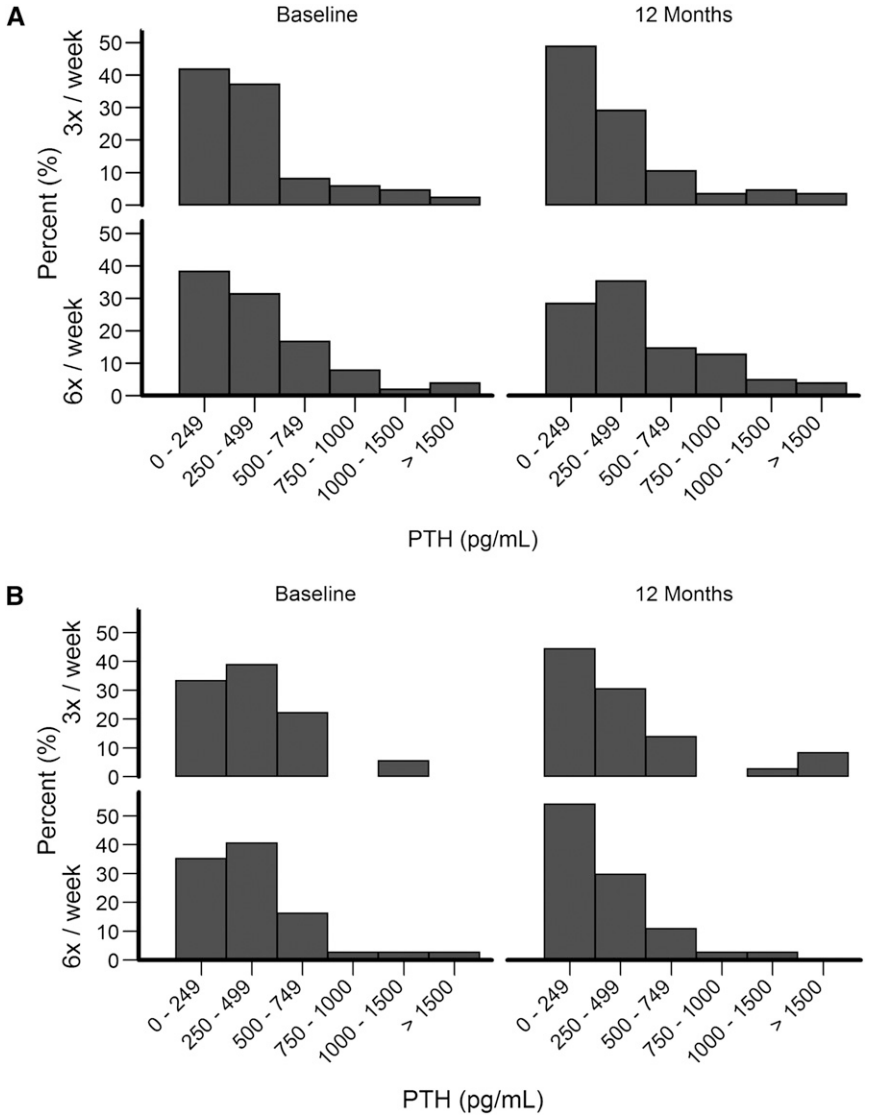

Figure 4. Serum PTH levels at baseline and month 12 of follow-up. Distribution of PTH in participants in the (A) Daily Trial and (B) Nocturnal Trial.

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Members of the FHN Trial Group are listed in references 19 and 20.

DISCLOSURES

None.

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