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At-home short daily hemodialysis improves the long-term health-related quality of life

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Patients with chronic kidney disease treated by in-center conventional hemodialysis (3 times per week) have significant impairments in health-related quality of life measures, which have been associated with increased morbidity and mortality. FREEDOM is an ongoing prospective cohort study measuring the potential benefits of at-home short daily (6 times per week) hemodialysis. In this interim report we examine the long-term effect of short daily hemodialysis on health-related quality of life, as measured by the SF-36 health survey. This was administered at baseline, 4 and 12 months after initiation of short daily hemodialysis to 291 participants (total cohort), of which 154 completed the 12-month follow-up (as-treated cohort). At the time of analysis, the mean age was 53 years, 66% were men, 58% had an AV fistula, 90% transitioned from in-center hemodialysis, and 45% had diabetes mellitus. In the total cohort analysis, both the physical- and mental-component summary scores improved over the 12-month period, as did all 8 individual domains of the SF-36. The as-treated cohort analysis showed similar improvements with the exception of the role-emotional domain. Significantly, in the as-treated cohort, the percentage of patients achieving a physical-component summary score at least equivalent to the general population more than doubled. Hence, at-home short daily hemodialysis is associated with long-term improvements in various physical and mental health-related quality of life measures.

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The impaired health-related quality of life (HRQOL) of patients with chronic kidney disease treated by conventional three times weekly hemodialysis (HD) is well documented[1–6] and has been an area of major concern for patients, their families, and nephrologists. The Center for Medicare and Medicaid Services now mandates that dialysis facilities in the United States perform an annual measurement of HRQOL for dialysis patients, preferentially using the Kidney Disease Quality of Life-36 (KDQOL-36) questionnaire with additional instruments as clinically indicated (http://www.cms.hhs.gov/cpmproject). A major challenge for nephrologists is how to respond to these quality of life measurements, and what strategies, if any, can be implemented to improve the lives of dialysis patients.

This is an area that has been attracting much interest recently, as there is increasing recognition of the importance of HRQOL measurements.[1–6] Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that reduced scores in patients undergoing in-center three times weekly HD using generic HRQOL instruments, such as the Short Form-36 (SF-36) health survey, are associated with significantly higher hospitalization rates and mortality.[1] Specifically, the physical-component summary (PCS) and mental-component summary (MCS) scores of the SF-36 were associated with a 25 and 13% risk increase in mortality per 10-point drop, respectively. The corresponding hospitalization risk increase was 15 and 6%, respectively.[1] These important observations were substantiated by a more recent study with very similar findings examining outcomes in over 40,000 patients.[6]

Improvement in a variety of HRQOL measures has been observed in several small studies among patients receiving more frequent (more than three times weekly) HD.[4,7–9] These preliminary findings have, to some extent, been confirmed in more recent, larger cohort studies as well as in randomized controlled trials. In the Frequent Hemodialysis Network (FHN) trial, patients randomized to in-center short daily HD prescribed six times per week experienced significant

improvement in the physical-health composite (PHC) score of the RAND 36-item health survey[10] compared with those maintained on in-center three times weekly HD. Indeed, at 12 months, the frequent HD-treated group reported an increase in the adjusted mean PHC score of 3.3 points, compared to a change of only 0.2 in the conventional HD-treated group.[11]

The FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study is an ongoing US-based observational study examining the potential clinical and economic benefits of at-home short daily HD.[12] We have previously demonstrated that short daily HD is associated with a sustained improvement in depressive symptoms, quality of sleep, prevalence and severity of restless legs symptoms, and post-dialysis recovery time.[12,13] In this interim report, as part of an *a priori* planned analysis, we examine the long-term effect of short daily HD on HRQOL, as measured by the SF-36 health survey.

RESULTS

Derivation of the cohort

Between 23 January 2006 and 31 December 2009, a total of 312 study participants were enrolled from 33 sites, of which 13 participants were excluded due to consent withdrawal or study ineligibility. Of the remaining 299 participants, 291 completed the SF-36 health survey at enrollment. Of the 291 participants included in this analysis, 137 discontinued study therapy before 12 months, of which 74 occurred before 4 months. Reasons for study discontinuation included kidney transplantation ($n=14$), transfer out of participating dialysis center ($n=7$), death ($n=13$), modality change/return to in-center dialysis ($n=63$), off short daily HD for >6 weeks ($n=12$), recovery of kidney function ($n=2$), non-compliance ($n=3$), and other ($n=23$). The remaining 154 participants completed 12 months of follow-up, and constituted the as-treated cohort.

Characteristics of the cohort

Table 1 displays the enrollment characteristics of the total cohort (291 participants) included in this report, stratified by the baseline PCS and MCS score tertiles. Mean age was 53 years, 66% were men, 70% were white, 45% were diabetic, 90% had hypertension, 27% had a history of congestive heart failure, and 58% had an arteriovenous fistula. Mean duration of dialysis was 3.6 years, and residual urine volume 365 ml/day. Overall, 5% of participants required assistance with daily activities, and 3% were unable to ambulate. In terms of psychotropic drugs, 19% of participants were prescribed anxiolytics/muscle relaxants, 16% hypnotics, 37% analgesics, and 25% anti-depressants. Participants in the upper baseline PCS score tertile were younger ($P=0.007$) and healthier, as evidenced by a lower body mass index ($P=0.02$), a lower prevalence of comorbidities (e.g., diabetes, and heart failure), a higher prevalence of arteriovenous fistula use ($P=0.003$), a higher serum creatinine ($P<0.001$) and albumin ($P=0.002$), a lower requirement for assistance with daily activities ($P<0.003$), and a higher ability to ambulate ($P=0.002$). By contrast, participants in the upper baseline MCS score tertile were older ($P=0.007$), and had a lower prevalence of anti-depressant use ($P=0.02$) and lower serum phosphorus ($P=0.03$).

There were no significant differences in the baseline characteristics between patients who dropped out before 12 months and those who completed 12 months of follow-up, with the exception of a lower serum creatinine (8.3 ± 3.6 vs. 9.3 ± 3.8 mg/dl; $P=0.04$) and albumin (3.7 ± 0.5 vs. 3.9 ± 0.4 g/dl; $P=0.007$), and a higher prescription of analgesics (44 vs. 32%; $P=0.04$) among patients who dropped out compared with those who did not (Supplementary Table online). Participants who discontinued the study before month-12 had significantly lower baseline MCS scores compared with those who completed 12 months (43 ± 13 vs. 49 ± 12; $P<0.001$). Although the baseline mean PCS score was not significantly different between the two groups (34 ± 10 vs. 35 ± 11; $P=0.6$), those who discontinued the study before month-12 had lower scores on most of the individual SF-36 domains, including role physical ($P=0.05$), bodily pain ($P=0.07$), general health ($P=0.03$), vitality ($P=0.03$), role emotional ($P<0.001$), mental health ($P<0.001$), and social functioning ($P=0.02$).

Short daily HD treatment characteristics

For the total cohort, the mean training period required to transition to short daily HD was 26 ± 34 days. The initial prescribed dialysate volume was 21 ± 4 l/session, with a prescribed blood flow rate of 462 ± 59 ml/min, and a flow fraction ((blood-to-dialysate flow rate ratio) $\times$ 100) of 33 ± 3%. The dialysate lactate concentration was 43 ± 3 mEq/l. There were no differences in these parameters among patients who completed 12 months of follow-up and those who did not (data not shown).

Effect of short daily HD on the SF-36 health survey

As shown in Figure 1, short daily HD resulted in a sustained improvement in the PCS score at 4 and 12 months (global $P<0.0001$), after adjustment for the use of psychotropic medications. Indeed, in the as-treated cohort (Figure 1a), the adjusted mean PCS score increased by 4 points at month-4 ($P<0.0001$) and month-12 ($P<0.0001$) compared with baseline. These findings were attenuated but remained robust in the total cohort (Figure 1b) with an adjusted mean PCS score increase of 3 points at month-4 ($P<0.0001$), and 4 points at month-12 ($P<0.0001$). Similarly, over the 12-month period, there was significant improvement in the mean adjusted scores of all six PCS domains in the as-treated cohort (Figure 1a), including scales related to physical functioning ($P<0.001$), role physical ($P<0.0001$), bodily pain ($P=0.04$), general health ($P<0.0001$), vitality ($P<0.0001$), and social functioning ($P<0.0001$). Results were similar for all six PCS domains in the total cohort (Figure 1b). In a sensitivity analysis adjusting for the number of participants per study site, the change in the PCS score remained significant, with an improvement in the mean score

Table 1 | Characteristics of the study cohort stratified by the baseline tertiles of the PCS and MCS scores

Characteristic	All participants (*n*=291)	Baseline PCS score				Baseline MCS score			
		1st Tertile (<29) (*n*=97)	2nd Tertile (29–39) (*n*=97)	3rd Tertile (>39) (*n*=97)	Global *P*-value	1st Tertile (<41) (*n*=97)	2nd Tertile (41–54) (*n*=97)	3rd Tertile (>54) (*n*=97)	Global *P*-value
Age, years	53 ± 15	55 ± 13	54 ± 14	49 ± 18	0.007	50 ± 14	52 ± 16	57 ± 15	0.007
Men	192 (66)	56 (58)	65 (68)	71 (73)	0.07	70 (72)	54 (56)	68 (70)	0.04
Race					0.5				0.08
White	200 (70)	71 (73)	68 (72)	61 (64)		68 (70)	60 (63)	72 (76)	
Black	78 (27)	22 (22)	24 (25)	32 (34)		23 (24)	33 (35)	22 (23)	
Other	9 (3)	4 (4)	3 (3)	2 (2)		6 (6)	2 (2)	1 (1)	
Prior renal replacement therapy					0.6				0.4
Hemodialysis	261 (90)	88 (91)	87 (91)	86 (90)		85 (88)	88 (92)	88 (92)	
New to dialysis	14 (5)	4 (4)	3 (3)	7 (7)		8 (8)	3 (3)	3 (3)	
Kidney transplant	5 (2)	2 (2)	3 (3)	0 (0)		1 (1)	1 (1)	3 (3)	
Peritoneal dialysis	9 (3)	3 (3)	3 (3)	3 (3)		3 (3)	4 (4)	2 (2)	
Duration of dialysis, years	3.6 ± 4.1	3.1 ± 3.7	3.2 ± 4.1	4.3 ± 4.4	0.2	3.8 ± 5.0	3.2 ± 3.3	3.7 ± 3.9	0.6
Body mass index, kg/m^2	29 ± 8	31 ± 9	29 ± 8	28 ± 6	0.02	29 ± 8	29 ± 7	29 ± 8	1.0
Residual urine volume, ml/day	365 ± 587	325 ± 512	467 ± 684	301 ± 540	0.2	354 ± 630	312 ± 526	433 ± 607	0.4
Vascular access type, %					0.003				0.1
Arteriovenous fistula	167 (58)	47 (49)	52 (54)	68 (70)		49 (51)	57 (59)	61 (63)	
Arteriovenous graft	41 (14)	11 (11)	16 (17)	14 (14)		11 (11)	16 (17)	14 (14)	
Central venous catheter	82 (28)	39 (40)	28 (29)	15 (16)		37 (38)	23 (24)	14 (14)	
Comorbid conditions									
Hypertension	261 (90)	85 (88)	88 (91)	88 (91)	0.7	93 (96)	85 (88)	83 (86)	0.04
Diabetes mellitus	131 (45)	61 (63)	41 (42)	29 (30)	<0.001	47 (49)	37 (38)	47 (49)	0.2
Diabetic retinopathy	43 (15)	20 (21)	14 (14)	9 (9)	0.08	14 (14)	10 (10)	19 (20)	0.2
Congestive heart failure	77 (27)	41 (42)	19 (20)	17 (18)	<0.001	29 (30)	21 (22)	27 (28)	0.4
Other cardiovascular disease	70 (24)	33 (34)	22 (23)	15 (16)	0.01	25 (26)	15 (16)	30 (31)	0.04
Cerebrovascular disease	29 (10)	12 (12)	9 (9)	8 (8)	0.6	11 (11)	6 (6)	12 (12)	0.3
Atherosclerotic heart disease	51 (18)	19 (20)	19 (20)	13 (13)	0.4	16 (17)	16 (17)	19 (20)	0.8
Peripheral vascular disease	38 (13)	19 (20)	8 (8)	11 (11)	0.05	15 (16)	8 (8)	15 (16)	0.2
Chronic obstructive lung disease	24 (8)	12 (12)	8 (8)	4 (4)	0.1	10 (10)	5 (5)	9 (9)	0.4
Cancer	31 (11)	15 (16)	8 (8)	8 (8)	0.2	9 (9)	12 (12)	10 (10)	0.8
Current smoker	37 (13)	17 (18)	12 (12)	8 (8)	0.2	14 (14)	11 (11)	12 (12)	0.8
Assistance with daily activities	13 (5)	10 (10)	2 (2)	1 (1)	0.003	7 (7)	4 (4)	2 (2)	0.2
Inability to ambulate	9 (3)	8 (8)	0 (0)	1 (1)	0.002	3 (3)	2 (2)	4 (4)	0.7
Selected prescribed medications									
Anxiolytics	54 (19)	25 (26)	20 (21)	9 (10)	0.01	21 (22)	21 (22)	12 (13)	0.1
Hypnotics	45 (16)	17 (18)	19 (20)	9 (10)	0.1	21 (22)	13 (14)	11 (12)	0.1
Analgesics	106 (37)	52 (55)	35 (36)	19 (20)	<0.001	37 (39)	38 (40)	31 (32)	0.5
Anti-depressants	72 (25)	33 (35)	23 (24)	16 (17)	0.02	26 (28)	31 (33)	15 (16)	0.02

Table 1 Continued on the following page

Table 1 | Continued

Characteristic	All participants (*n*=291)	Baseline PCS score				Baseline MCS score			
		1st Tertile (<29) (*n*=97)	2nd Tertile (29–39) (*n*=97)	3rd Tertile (>39) (*n*=97)	Global *P*-value	1st Tertile (<41) (*n*=97)	2nd Tertile (41–54) (*n*=97)	3rd Tertile (>54) (*n*=97)	Global *P*-value
Selected laboratory values									
Hemoglobin, g/dl	11.7 ± 1.3	11.7 ± 1.2	11.6 ± 1.2	11.9 ± 1.3	0.2	11.6 ± 1.5	11.8 ± 1.1	11.8 ± 1.1	0.4
Serum ferritin, ng/ml	523 ± 318	485 ± 301	467 ± 306	612 ± 328	0.005	487 ± 277	558 ± 346	521 ± 324	0.4
Transferrin saturation, %	28 ± 10	26 ± 9	27 ± 9	30 ± 11	0.1	27 ± 9	29 ± 12	28 ± 9	0.4
Serum calcium, mg/dl	9.4 ± 0.7	9.5 ± 0.6	9.4 ± 0.8	9.4 ± 0.6	0.8	9.4 ± 0.7	9.3 ± 0.7	9.5 ± 0.6	0.2
Serum phosphorus, mg/dl	5.6 ± 1.5	5.5 ± 1.4	5.9 ± 1.6	5.5 ± 1.5	0.2	6.0 ± 1.8	5.6 ± 1.2	5.4 ± 1.4	0.03
Serum calcium-phosphorus product, mg^2/dl^2	53 ± 14	51 ± 14	56 ± 14	52 ± 14	0.1	55 ± 16	52 ± 13	52 ± 14	0.4
Serum intact PTH, pg/ml	462 ± 437	518 ± 475	470 ± 417	405 ± 414	0.3	510 ± 514	493 ± 429	390 ± 358	0.2
Serum urea nitrogen, mg/dl	57 ± 17	55 ± 16	56 ± 16	60 ± 18	0.2	57 ± 17	57 ± 17	57 ± 16	1.0
Serum creatinine, mg/dl	8.9 ± 3.7	7.5 ± 3.4	8.7 ± 3.3	10.3 ± 4.0	<0.001	9.0 ± 4.1	8.9 ± 3.8	8.7 ± 3.4	0.8
Serum albumin, g/dl	3.8 ± 0.4	3.7 ± 0.5	3.8 ± 0.4	3.9 ± 0.4	0.002	3.7 ± 0.5	3.8 ± 0.5	3.9 ± 0.3	0.1
Serum potassium, mEq/l	4.8 ± 0.6	4.7 ± 0.7	4.8 ± 0.6	4.8 ± 0.6	0.4	4.7 ± 0.7	4.8 ± 0.6	4.9 ± 0.6	0.2

Abbreviations: MCS, mental-component summary; PCS, physical-component summary; PTH, parathyroid hormone.
Data are presented as mean ± standard deviation or number (percentage). The serum calcium is corrected for the serum albumin.

by four (95% confidence interval 2, 5) points at 4 and 12 months, respectively ($P<0.0001$).

Although short daily HD resulted in a sustained improvement in the MCS score over the study course in both the as-treated (Figure 1a, global $P=0.02$) and total (Figure 1b, global $P=0.0001$) cohort, the increase was less than that observed for the PCS scores. In the as-treated cohort, the adjusted mean MCS score increased by only 2 points at month-4 ($P=0.005$) and month-12 ($P=0.08$), compared with the baseline value of 50. A similar trend was observed in the total cohort, with scores increasing by 3 points at month-4 ($P=0.005$) and 2 points at month-12 ($P=0.08$). In both analyses, among the two MCS-specific domains, the adjusted mean mental health score significantly improved by 4–6 points at month-4 ($P<0.01$) and by 4 points at month-12 ($P=0.01$), whereas the role-emotional scale displayed no significant improvement.

In the as-treated cohort, the proportion of participants with a PCS score $\geqslant 50$ (a cut-off representing the mean score observed in the general US population) more than doubled, increasing from 9% at baseline to 21% at month-12 ($P<0.001$; Figure 2a). However, the percentage of participants with an MCS score $\geqslant 50$ did not significantly change over the 12-month period ($P=0.2$; Figure 2b). In the total cohort, the proportion of participants with a PCS score $\geqslant 50$ increased from 8% at baseline to 20% at month-4 ($P<0.001$) and 24% at month-12 ($P<0.001$; Figure 2a). However, the percentage of participants with an MCS score of $\geqslant 50$ increased from 47% at baseline to 57% at month-4 ($P=0.03$) and 64% at month-12 ($P=0.001$; Figure 2b).

Figure 3 displays the 12-month change in the adjusted mean PCS score, stratified by baseline PCS tertiles. In the as-treated and total cohort, participants in the lowest baseline PCS tertile group (<30 and <29 for the as-treated and total cohort, respectively), suggestive of the poorest physical health, experienced the greatest improvement in the adjusted mean PCS score. Indeed, in tertile-1, the PCS score improved by 6–7 points ($P<0.001$) at month-12, compared with only a 4-point improvement in tertile-2 ($P\leqslant 0.03$). Tertile-3 experienced no further improvement in PCS score. In a separate sensitivity analysis aimed at examining change in the PCS score after adjustment for number of comorbidities or the baseline PCS score, the 12-month adjusted mean PCS score improvement remained significant in both the as-treated and total cohort (data not shown).

DISCUSSION

One of the major challenges for nephrologists is developing strategies to manage the impaired HRQOL measures reported by dialysis patients. Although these impairments are well documented, how to systematically address and improve the HRQOL in dialysis patients has received far too little attention. The present study reports on the interim results of the FREEDOM using data from the SF-36 health survey in patients completing 4 and 12 months of at-home short daily (six times per week) HD with a targeted standard

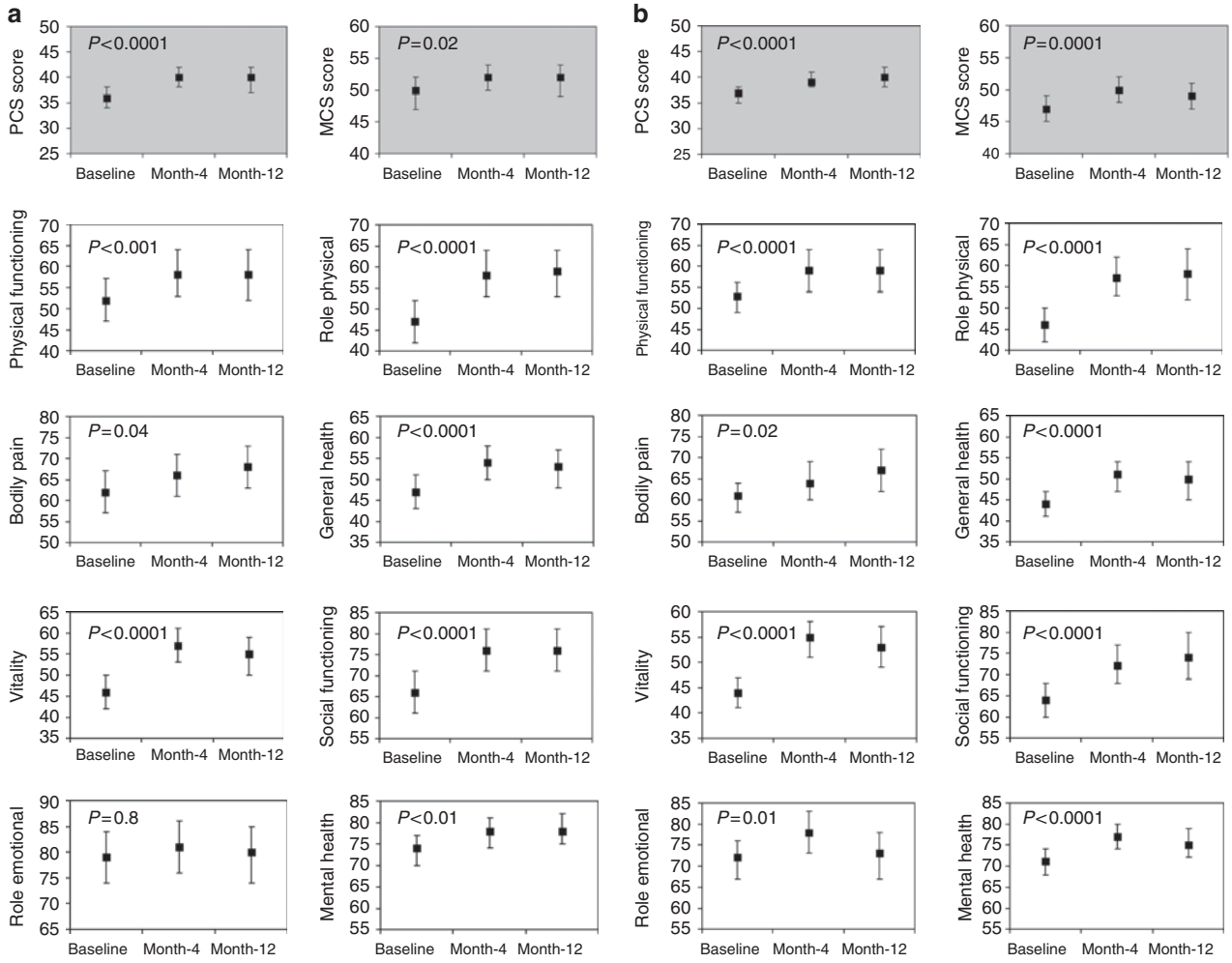

Figure 1 | Effect of short daily hemodialysis on the SF-36 health survey (eight domains and two summary measures) at 4 and 12 months. The results are displayed for the as-treated cohort (**a**; $n = 154$) and the total cohort (**b**; $n = 291$). The data are presented as adjusted mean (95% confidence interval) derived from a random-effects mixed model. Adjustment variables include use of anxiolytics, hypnotics, anti-depressants, and analgesics (at any time both for the as-treated and total cohort), time, and dropout (for the analysis of the total cohort only). PCS denotes physical-component summary; and MCS, mental-component summary. For each domain and summary measures, the global score statistic *P*-value is reported.

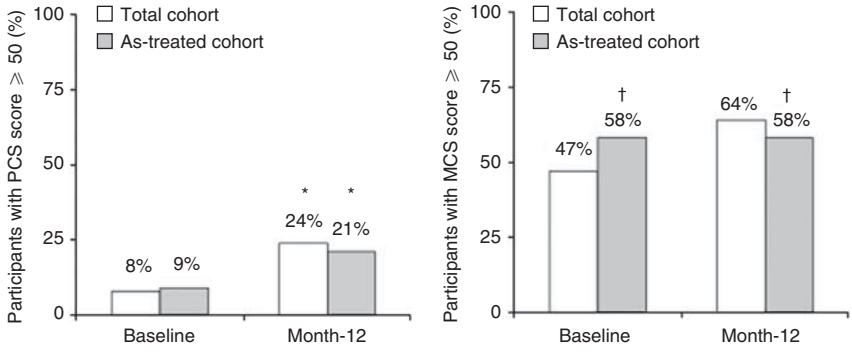

Figure 2 | Percentage of study participants with mean physical-component summary (PCS) + mental-component summary (MCS) score ⩾50. Percentage of study participants with PCS (**a**) and MCS (**b**) score ⩾50 (normal mean score for US population) at baseline and after 12 months of short daily hemodialysis in the as-treated ($n = 154$) and total ($n = 291$) cohort. The *P*-values are derived from the McNemar test. *$P < 0.001$ vs. baseline; †$P = 0.001$ vs. baseline.

Kt/V_{urea} of 2.0. Psychometric studies performed in dialysis patients have shown the widely used SF-36 health survey to be a reliable and valid measure of HRQOL.[14] It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has been useful in comparing the relative burden of diseases, and differentiating

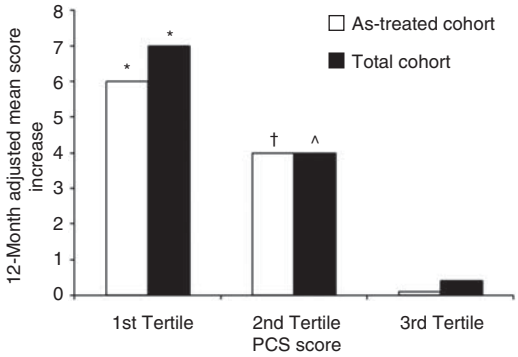

Figure 3 | Twelve-month change in the adjusted mean physical-component summary (PCS) score according to the baseline PCS tertiles. The results are displayed for the as-treated ($n = 154$) and total cohort ($n = 291$). The data are derived from a random-effects mixed model, and adjustment variables include use of anxiolytics, hypnotics, anti-depressants, and analgesics (at any time both for the as-treated and total cohort), time, and dropout (for the analysis of the total cohort only). *$P < 0.001$; †$P = 0.03$; ^$P = 0.01$.

the health benefits produced by a wide range of treatment strategies.[15]

To our knowledge, the FREEDOM study is the largest prospective cohort study of short daily HD delivered at home. In the present interim report, this study demonstrates that over a 12-month period, the initiation of at-home short daily HD, primarily in a prevalent HD population, results in broad and sustained improvement in the majority of the SF-36 scores. The increases were most dramatic for the physical domains, including the PCS and the six domains that contribute to the PCS score. These improvements were observed after adjustment for the use of several psychotropic drugs, including hypnotics, anxiolytics, anti-depressants, and analgesics. A switch to short daily HD resulted in a clinically meaningful PCS score improvement of 4 points, which was consistent with our hypothesized effect estimate,[12] and was independent of comorbidities. Furthermore, the greatest improvement in the PCS score was observed in the lowest baseline PCS tertile group (score of less than 29 to 30), where there was a gain of 6–7 points in both the as-treated and total cohort. In addition, the proportion of patients reporting PCS scores of 50 or greater (50 being the average value observed in the general US population) more than doubled over the 12-month study period, suggesting an overall improvement in physical health. The study findings are important, as dialysis patients with reduced PCS scores have worse clinical outcomes, with regard to mortality and hospitalization rates.[1,6] Despite the strong association of PCS scores with adverse outcomes, few studies have examined strategies to improve these measures as a potential means to enhance patient survival. Thus, the findings in this study are particularly important, and the sustained improvement at 12 months of a statistically significant 4-point increase in mean PCS score is especially noteworthy.

Changes in the mental and emotional domains of the SF-36 were noted as well, but the changes were not as impressive as for the physical domains. Indeed, compared with baseline values, the MCS scores significantly improved at month-4, but not at month-12, although the global *P*-value for the trend analysis was significant. Of note, the baseline MCS score of the group that completed the 12-month follow-up period (mean score of 50) was the same as that observed in the general US population.[15] Significant increases, however, were observed in four of the five domains that contribute to the MCS score at both 4 and 12 months. Furthermore, previous data from the FREEDOM study indicated significant improvement in depression scores,[16] suggesting a positive emotional impact of treatment change with more frequent home HD.

Studies that have looked at the changes that occur in HRQOL measures with institution of short daily HD have generally shown an improvement in a variety of selected domains. However, many of these studies have been limited by small sample sizes, lack of control groups, and the variability in the delivered dose of dialysis. The results of the FHN trial are, therefore, of particular interest.[11] In this controlled trial, patients randomized to in-center short daily HD (prescribed six times per week, with an achieved standard Kt/V_{urea} of 3.6), as compared with patients on conventional three times weekly in-center HD, were noted to have significant improvements at 12-months in the RAND-36 PHC score. Although the scoring of the PHC and PCS is slightly different, it is noteworthy that the increment of the PHC in the FHN trial and the PCS in this study were of similar magnitude (about 3–4 points). However, it is important to note that the treatments in the two studies were different—the FHN trial treated patients in dialysis centers with a standardized Kt/V_{urea} of 3.6, whereas the FREEDOM study treated patients at home with a standardized Kt/V_{urea} of 2.0–2.1.

How should clinicians interpret the changes in the HRQOL scores with the modification in the dialysis treatment regimen? There is considerable controversy concerning what constitutes a 'meaningful' change in HRQOL scores. Some investigators find this concept problematic and have suggested that an improvement in patient reported quality of life, of whatever magnitude, may be important for the individual.[17,18] It is important to note that in our initial paper describing the methodology of the FREEDOM study,[12] we indicated that we were focusing attention on a 3–5 point increase in the PCS score based on previously published data. An interesting observation in this study is that patients who did not complete the study, compared to those who did, scored lower on MCS and various individual SF-36 domain scores. This is an area that deserves further exploration. We can only speculate as to whether patients with lower scores are at greater risk for daily HD technique failure, and therefore might require targeted interventions and closer monitoring by health-care providers to help mitigate this risk.

Strengths of this interim analysis include a large number of participants recruited from 36 sites, the use of a well recognized, validated survey to assess physical and mental

HRQOL, and the 12-month follow-up. The results remained robust in both the as-treated and total cohort. It should be emphasized that this study extends previous observations from the FREEDOM study documenting significant improvements in several other HRQOL indicators, including depressive symptoms, post-dialysis recovery time, restless legs symptoms, and sleep disturbances.[13,16]

Study limitations include selection biases that are evident by the recruitment of a relatively younger patient population when compared with the typical US dialysis population. However, 28% of patients had a central venous catheter for vascular access, 45% were diabetic, and 27% had a history of heart failure, suggesting that the cohort was not necessarily healthier. Although the study experienced a high attrition rate, characteristics of the participants who dropped out did not differ from those who completed 12 months of follow-up with the exception of poorer nutritional biochemical markers and lower MCS scores. Although the absence of a control group is an important limitation, it should be emphasized that the observed improvement persisted beyond 4 months, arguing against the potential for regression to the mean. To what extent the improvement in HRQOL is the consequence of more frequent HD, as opposed to the location of the therapy in the home setting, cannot be ascertained from this study, although the FHN trial, which was conducted in-center, also demonstrated significant improvements in the PHC scores. Finally, although the as-treated and total cohorts were similar on the measured characteristics, some potentially important unmeasured characteristics are not accounted for including differences in psychosocial support and commitment of the family caregiver.

In conclusion, the present interim report of the FREEDOM study demonstrates that initiation of short daily HD at home is associated with significant and clinically meaningful improvement in HRQOL, as measured by the SF-36 health survey. Whether these changes are associated with a decline in hospitalizations or an improvement in survival remains to be determined.

MATERIALS AND METHODS

Study design and setting

This was a multi-center, prospective, cohort study of at-home short daily HD with a planned 12-month follow-up (ClinicalTrials.gov identifier, NCT00288613).[12] Eligible patients were adults (age $\geqslant$18 years) with end-stage renal disease requiring dialysis who were being initiated on short daily HD (prescribed six times per week) at home and who had Medicare as their primary insurance payer. Exclusion criteria included current use of the device, prior enrollment in the study, current enrollment in an investigational drug or device trial that might impact the outcome measures, and low likelihood of surviving the first 4–6 weeks encompassing the training period. Written informed consent was obtained from all study participants. A central or local institutional review board approved the study protocol.

Short daily HD prescription

Short daily HD was delivered using the NxStage System One cycler (NxStage Medical, Lawrence, MA, www.nxstage.com). This device incorporates a high-flux polyethersulfone dialyzer and relies on an inverse dialysate-to-blood flow rate ratio of 1-to-3 compared with a conventional dialysis machine, which uses a 2-to-1 ratio. Lactate-based dialysate was delivered either in premixed, sterile, non-pyrogenic dialysate fluid bags or through an ultrapure water purification system (PureFlow SL, NxStage Medical). The initial prescription targeted a single pool Kt/V_{urea} of 0.45–0.50, based on six treatments per week, using the Daugirdas 2nd generation equation.[19] This corresponded to a weekly standard Kt/V_{urea} of 2.0–2.2, meeting or exceeding the recommended threshold of 2.0.[20]

Data collection

At enrollment, data collection included demographic information, comorbid conditions, duration of dialysis, dialysis prescription parameters (including Kt/V_{urea}), vascular access type, prior renal replacement therapy, and laboratory data (average of three recordings). A 24-hour timed urine collection was also obtained to assess residual urine volume. Data on prescribed psychotropic medications, including the use of anxiolytics, hypnotics, anti-depressants, and opioid analgesics, were collected at enrollment, and at 4 and 12 months. A variety of HRQOL surveys were also obtained over the course of the study, which have previously been reported.[13,16]

Self-administration and scoring of the SF-36 health survey

HRQOL was assessed at enrollment and at 4 and 12 months of follow-up by self-administering the SF-36 health survey (Medical Outcomes Trust, Boston, MA). This multipurpose self-reported measure of HRQOL has been widely used, and validated for use in both the general population and dialysis patients.[14,21,22]

The SF-36 comprises 36 questions and yields an 8-scale profile that is integrated into two summary measures, the PCS and MCS.[15,22] The PCS includes dimensions of the physical functioning, role-physical, bodily pain, and general health scales, as well as elements of the vitality and social functioning scales. The MCS is comprised of the role-emotional, and mental health scales, and also includes elements of the general health, vitality, and social functioning scales.[15,22] The survey results were scored using version 2 of the SF-36 health survey software (SF-36v2 Health Survey). Aggregate PCS and MCS scales are standardized to have a mean $\pm$ standard deviation of 50 ± 10 in the average US population.[15] Normalization of the PCS and MCS scores over the study period was defined by a score of greater than 50.

Statistical analysis

Continuous variables are presented as mean ($\pm$ standard deviation) or median (with interquartile range), and categorical variables as number (with percentage). For this analysis, an *a priori* sample size calculation was performed to assess the change in the PCS score at the 12-month time point to achieve 80% power for a two-sided test with type-I error of 0.05, assuming a drop out rate of 30%.[12] A minimum sample size of 153 was calculated based on a mean ($\pm$ standard deviation) PCS score improvement of 4 ± 10 units.[21,23]

Baseline characteristics were compared using the unpaired *t*-test or χ^2-test. For variables measured over 2 time points, comparisons were made by paired *t*-test or signed rank test, as appropriate and the McNemar test (test of symmetry).

Analyses were performed on the as-treated and total cohort to examine the effect of short daily HD on SF-36 scores, including the PCS, MCS, and the eight individual domains. The as-treated cohort was restricted to study participants who completed 12 months of

follow-up. The total cohort included all participants irrespective of early study discontinuation. For this conservative analysis, we applied a pattern-mixture model,[24] whereby an indicator variable (dropout = 1, 12-month study completion = 0) was introduced with the assumption that study participants who dropped out had different outcomes by a constant amount compared with those who completed the study. As an estimate of missing data pattern, the proportion of dropout of this study sample (0.47, 137/291) was used, and then the predicted means were obtained by averaging this over the dropout pattern.

For both analyses, we used mixed models to examine improvements in summary and individual SF-36 scores over 12 months, and included use of anxiolytics, hypnotics, anti-depressants, and analgesics as fixed factors, and each subject's intercept and slopes due to time as random factors. These analyses were adjusted for the use of psychotropic drugs to account for the potential confounding effect of these drugs on changes in the individual and summary components of the SF-36 health survey. In sensitivity analyses examining changes in the PCS score, the models were adjusted for the baseline PCS score, number of comorbidities, or number of participants per study site (<5, 5–10, and >10 participants).

The results are displayed as adjusted means with 95% confidence interval. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Differences were considered statistically significant at $P<0.05$.

DISCLOSURE

The following authors are members of the NxStage Scientific Advisory Board that oversees the FREEDOM study: JM Burkart, FOF, BLJ, MAK, BWM, and BS.

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SUPPLEMENTARY MATERIAL

Table. Characteristics of the study cohort according to completers vs. non-completers of 12-month follow-up.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Mapes DL, Lopes AA, Satayathum S *et al.* Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 2003; **64**: 339–349.
2. Lowrie EG, Curtin RB, LePain N *et al.* Medical outcomes study short form-36: a consistent and powerful predictor of morbidity and mortality in dialysis patients. *Am J Kidney Dis* 2003; **41**: 1286–1292.
3. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. *Kidney Int* 2009; **76**: 946–952.
4. Reynolds JT, Homel P, Cantey L *et al.* A one-year trial of in-center daily hemodialysis with an emphasis on quality of life. *Blood Purif* 2004; **22**: 320–328.
5. DeOreo PB. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *Am J Kidney Dis* 1997; **30**: 204–212.
6. Lacson Jr E, Xu J, Lin SF *et al.* A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients. *Clin J Am Soc Nephrol* 2010; **5**: 252–260.
7. Lindsay RM. The London, Ontario, Daily/Nocturnal Hemodialysis Study. *Semin Dial* 2004; **17**: 85–91.
8. Kooistra MP, Vos J, Koomans HA *et al.* Daily home haemodialysis in The Netherlands: effects on metabolic control, haemodynamics, and quality of life. *Nephrol Dial Transplant* 1998; **13**: 2853–2860.
9. Lindsay RM, Heidenheim PA, Nesrallah G *et al.* Minutes to recovery after a hemodialysis session: a simple health-related quality of life question that is reliable, valid, and sensitive to change. *Clin J Am Soc Nephrol* 2006; **1**: 952–959.
10. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med* 2001; **33**: 350–357.
11. Chertow GM, Levin NW, Beck GJ *et al.* In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010; **363**: 2287–2300.
12. Jaber BL, Finkelstein FO, Glickman JD *et al.* Scope and design of the Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) study. *Am J Kidney Dis* 2009; **53**: 310–320.
13. Jaber BL, Schiller B, Burkart JM *et al.* Impact of short daily hemodialysis on restless legs symptoms and sleep disturbances. *Clin J Am Soc Nephrol* 2011; **6**: 1049–1056.
14. Yarlas AS, White MK, Yang M *et al.* Measuring the health status burden in hemodialysis patients using the SF-36(R) health survey. *Qual Life Res* 2011; **20**: 383–389.
15. Ware J, Snow K, Kosinski M *et al. MOS SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: Health Institute, 1993.
16. Jaber BL, Lee Y, Collins AJ *et al.* Effect of daily hemodialysis on depressive symptoms and postdialysis recovery time: interim report from the FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study. *Am J Kidney Dis* 2010; **56**: 531–539.
17. Hayes RD, Wooley JM. The concept of clinically meaningful difference in health-related quality of life research. *Pharmacoeconomics* 2000; **18**: 419.
18. Samsa G, Edelman D, Rothman ML *et al.* Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999; **15**: 141–155.
19. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993; **4**: 1205–1213.
20. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. *Am J Kidney Dis* 2006; **48**(suppl 1): S1–S322.
21. Troidle L, Hotchkiss M, Finkelstein F. A thrice weekly in-center nocturnal hemodialysis program. *Adv Chronic Kidney Dis* 2007; **14**: 244–248.
22. Ware Jr JE. SF-36 health survey update. *Spine* 2000; **25**: 3130–3139.
23. Jaber BL, Zimmerman DL, Teehan GS *et al.* Daily hemofiltration for end-stage renal disease: a feasibility and efficacy trial. *Blood Purif* 2004; **22**: 481–489.
24. Hedeker D, Gibbons R. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods* 1997; **2**: 64–78.

Appendix

FREEDOM Study Group

The following FREEDOM Study investigators enrolled at least one subject as of 31 December 2009: Mirel Abramovici, MD (Renal Center of Westwood, Westwood, NJ); Sujatha Addagatla, MD (Apollo Healthcare, Niagara Falls, NY); George Aronoff, MD (University of Louisville, Louisville, KY); John Burkart, MD (Wake Forest University/Piedmont Dialysis, Winston-Salem, NC); Prakas D'Cunha, MD (Renal Advantage Inc., Palm Harbor, FL); Rachid Daoui, MD (Hortense & Louis Rubin Dialysis Center, Clifton Park, NY); William Elliott, MD (DaVita Bluemound Dialysis, Wauwatosa, WI); Claude Galphin, MD (Nephrology Associates, Chattanooga, TN); Todd Gehr, MD (Virginia Commonwealth University/Renal Advantage Inc., Richmond, VA); Martin Gelman, MD (Personal Dialysis, Inc., Brighton, MA); Michael S Gersch, MD (Arkansas Nephrology Research Associates, Hot Springs, AR); Tim Govaerts, MD (Dialysis Center of Lincoln, Lincoln, NE); Troy Plumb, MD (University of Nebraska/Renal Advantage Inc., Omaha, NE);

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