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ORIGINAL ARTICLE

Home Hemodialysis

Patient-reported outcomes from the investigational device exemption study of the Tablo hemodialysis system

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Abstract

Introduction: We recently completed an Investigational Device Exemption (IDE) study in which 30 patients were enrolled (13 patients previously on home hemodialysis (HHD) and 17 patients new to HHD) and treated with the Tablo Hemodialysis System (Outset Medical, Inc., San Jose, CA) for 8 weeks in-center and 8 weeks in-home with an interim 2–4 week transition period for home training.

Methods: In addition to assessments of urea kinetics, events related to safety, and operational issues (e.g., alarm resolution), we obtained data on several parameters of health-related quality of life, including time to recovery (TTR), the EQ-5D-5L (a well-validated measure of general health status), and the quality of sleep and related symptoms, to further assess the safety of HHD with Tablo. We compared results obtained during the in-center and in-home phases of the trial.

Results: Twenty-eight of 30 patients (93%) completed all trial periods. Adherence to the prescribed four treatments per week schedule was 96% in-center and 99% in-home. Median TTR was 1.5 hours (10th, 90th percentile range 0.17 to 12, mean TTR 3.68 ± 5.88 hours) during the in-center and 2 hours (10th, 90th percentile range 0 to 6.0, mean TTR 3.04 ± 5.14 hours) during the at-home phase (Wilcoxon signed rank $p = 0.57$). Median index values on the EQ-5D-5L were similar during the in-center (0.832, 10th, 90th percentile range 0.617 to 1, mean 0.817 ± 0.165) and in-home (0.826, 10th, 90th percentile range 0.603 to 1, mean 0.821 ± 0.163) trial phases (Wilcoxon signed rank $p = 0.36$). Patients reported feeling alert or well-rested with little difficulty falling or staying asleep or feeling tired and worn out when using Tablo in either environment.

Conclusion: When using Tablo in-home, patients reported similar TTR, general health status, and sleep quality and related symptoms compared to using Tablo in-center. (294 words).

Keywords: Clinical trial, home hemodialysis, health-related quality of life, time to recovery

INTRODUCTION

Over the past several decades, in-center hemodialysis has become the "default" dialytic modality for patients with end-stage kidney disease (ESKD), who are unable to undergo pre-emptive kidney transplantation. In the United States, roughly 1 in 10 patients receive peritoneal

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dialysis and fewer than 1 in 50 patients receive home hemodialysis (HHD), despite obvious advantages to patients vis-à-vis personal engagement, empowerment, flexibility, and vocational rehabilitation, and published observational data suggesting improved survival and health-related quality of life.[1, 2] The home setting also facilitates more frequent (>3 times per week) hemodialysis, which may improve health status and allow for liberalization of fluid intake and ease dietary restrictions. The recently released executive order (the Advancing American Kidney Health initiative https://www.whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health/) urged that 80% of new patients with ESKD be treated with kidney transplantation or home dialysis.

We recently completed an Investigational Device Exemption (IDE) study evaluating the safety and efficacy of a novel hemodialysis system (Tablo, Outset Medical, Inc., San Jose, CA) used both in-center and at home.[3] We assessed efficacy by achievement of a weekly standard $Kt/V_{urea} \geq 2.1$ during the in-center and in-home phases of the trial. We assessed safety primarily by determination of serious and non-serious adverse events. As complementary assessments of safety, we obtained patient-reported data on time-to-recovery (TTR), general health status (assessed using the EuroQoL 5-dimension 5-level, EQ-5D-5L), and sleep quality and related symptoms.

METHODS

Study design

The IDE trial was a prospective, multicenter, open label, cross-over trial comparing in-center and in-home hemodialysis performed using Tablo. The trial adhered to the principles outlined in the Declaration of Helsinki. Each participant served as his or her own control in terms of treatment phase comparisons. The original study protocol and amendments were approved by the United States Food and Drug Administration (FDA) and were registered on clinicaltrials.gov (NCT02460263). Participants remained in the trial for approximately 21 weeks during which time they were prescribed hemodialysis with Tablo four times per week. The trial consisted of four treatment phases during which Tablo was utilized: a run-in phase of one week in-center, an in-center phase of 32 treatments (approximately eight weeks) during which the dialysis staff managed the treatments, a transition phase of up to four weeks to train the patient or care partner to manage the dialysis, and a final in-home phase of 32 treatments (approximately eight weeks). Details of design and implementation of the IDE trial and the primary efficacy and safety results are published elsewhere.[3]

Briefly, patients from eight sites were enrolled in the trial after a HIPAA-compliant, IRB-approved consent form was signed. Inclusion criteria included adult patients (age 18 to 75 years) with end stage kidney disease (ESKD) treated with maintenance hemodialysis who consistently achieved a single pool $Kt/V_{urea} \geq 1.2$ and who were stable for at least three months with a vascular access providing a blood flow of at least 300 mL/min. Participants were expected to be able to adhere to the trial protocol including a willingness to do HHD and the ability to train on Tablo. Exclusion criteria included the inability to read English or Spanish, a persistent pre-dialysis systolic blood pressure below 100 mmHg or above 180 mmHg despite maximal therapy, New York Heart Association Class III or IV heart failure or an ejection fraction of less than 30%, and life expectancy of less than 12 months and/or presence of other ongoing serious illness, as determined by the site investigator.

Patient reported outcomes

We conducted assessments weekly throughout the trial. Questionnaires were completed by patients themselves. Within-patient results were averaged during the 8-week in-center and 8-week in-home periods.

Time-to-recovery (TTR)

We ascertained the TTR by asking a patient: "How long does it take you to recover from a dialysis session?" In the seminal study of Lindsay et al.,[4] the TTR proved to be reliable, valid, and responsive to change. In the Frequent Hemodialysis Network Daily Trial, more frequent hemodialysis yielded a nearly 90 min reduction in TTR relative to conventional hemodialysis.[5]

The Euro-QOL 5-dimension 5-level (EQ-5D-5L) questionnaire

With the EQ-5D-5L, health status is measured in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using a 5-level Likert scale. The EQ-5D-5L summary index is derived by applying a formula that attaches weights to each of the levels in each dimension. EQ-ED-5L index values range from states worse than dead (below zero) to 1 (full health), anchoring dead at zero. The EQ-5D-5L has been used in population health and clinical trials for more than two decades and across multiple populations,[6, 7] including patients with chronic kidney disease. Index values can be used to facilitate calculation of quality-adjusted life years (QALYs), a metric frequently applied

when comparing cost-effectiveness of healthcare interventions. EQ-5D-5L questionnaires obtained in patients receiving hemodialysis in Singapore, Spain, and Italy yielded index values of 0.621 (n = 163), 0.746 (n = 225), and 0.864 (n = 278), respectively.[8]

Sleep quality and related symptoms

Sleep assessment focused on sleep quality as well as the feeling of restfulness. Questions were generated from a review of established and previously validated sleep questionnaires.[10-14] We queried patients regarding the number of days/nights per week they (1) have trouble falling asleep; (2) wake up several times during the night; (3) have trouble staying asleep; (4) wake up feeling tired and worn out; (5) wake up feeling well-rested; (6) feel alert during daytime hours; and (7) feel well rested during the day. Categories were none, 1–2, 3–5, and 6–7 days/nights per week. For ease of graphical presentation and analysis, we collapsed these groups into 0–2 and 3 or more days/nights per week. We also asked patients to estimate the number of hours of sleep received on dialysis and non-dialysis days.

Statistical analysis

Given the limited sample size and relatively short treatment phases, we did not expect to observe statistically significant differences in patient-reported outcomes comparing results from the in-center to the in-home settings. We consider all inference tests to be exploratory. To compare within group changes in the TTR and EQ-5D-5L index value scores (and the estimated number of hours of sleep received), we used the Wilcoxon signed rank test. To compare categories of sleep quality and related symptoms, we used McNemar's test, collapsing categories into zero to 2 days per week and 3 or more days per week.

RESULTS

A total of 30 participants from eight centers were enrolled. Table 1 shows baseline demographic and clinical characteristics of the trial participants, stratified by whether they were new to HHD (n = 17) or established on HHD (n = 13). During the transition period, one participant died due to cardiac arrest during the interdialytic period. The event was deemed unrelated to dialysis and unrelated to Tablo. One participant withdrew consent before entering the in-home phase. The primary safety and efficacy outcomes have been previously published.[3] Briefly, adherence to the prescribed four treatments per week schedule was 96% in-center and 99% in-home.

Table 1 Baseline characteristics stratified by previous home hemodialysis experience

Patient characteristics	Established on HHD n = 13	New to HHD n = 17
Sex		
Male	8 (62%)	11 (65%)
Ethnicity		
Not Hispanic or Latino	9 (69%)	12 (71%)
Hispanic or Latino	3 (23%)	5 (29%)
Not Reported	1 (8%)	0 (0%)
Race		
White	8 (62%)	9 (53%)
Black or African American	5 (38%)	8 (47%)
Age		
Mean ± SD	49.8 ± 13.0	54.2 ± 10.4
Weight		
Mean ± SD	92.1 ± 16.5	95.2 ± 17.7
BMI		
Mean ± SD	32.6 ± 6.1	31.3 ± 4.2
Access		
Fistula	9 (69%)	14 (82)
Catheter	2 (15%)	2 (12)
Graft	2 (15%)	1 (6)
Comorbidities		
Coronary artery disease	6 (46%)	6 (35%)
Diabetes	6 (46%)	12 (71%)
Hypertension	13 (100%)	16 (94%)
Carotid artery disease	3 (23%)	3 (18%)
Peripheral artery disease	1 (8%)	4 (24%)
Arrhythmia	3 (23%)	3 (18%)
Tobacco use (current)	0 (0%)	4 (24%)
Tobacco use (former)	3 (23%)	4 (24%)

The average weekly standard Kt/V_{urea} for each individual participant was between 2.40 and 3.24 for the in-center phase and between 2.42 and 3.12 for the in-home phase. Ninety-four percent of treatments in-center and in-home achieved goal ultrafiltration. Adverse events were infrequent and comparable in-center (1.9% of sessions) and in-home (1.8% of sessions).

Time to recovery (TTR)

Median TTR was 1.5 hours (10th, 90th percentile range 0.17 to 12, mean 3.68 ± 5.88 hours) during the in-

center phase and 2 hours (10th, 90th percentile range 0 to 6.0, mean 3.04 ± 5.14 hours) during the in-home phase (Wilcoxon signed rank p = 0.57) (Figure 1). Among patients new to HHD, the mean TTR in-center and in-home were 3.68 ± 6.20 hours and 3.34 ± 6.08 hours, respectively (mean difference 9.1%). Among patients established on HHD, the mean TTR in-center and in-home were 3.69 ± 5.46 hours and 2.66 ± 3.63 hours, respectively (mean difference 27.9%).

The Euro-QOL 5-dimension 5-level (EQ-5D-5L) questionnaire

Median index values on the EQ-5D-5L were similar during the in-center (0.832, 10th, 90th percentile range 0.617 to 1, mean 0.817 ± 0.165) and in-home (0.826, 10th, 90th percentile range 0.603 to 1, mean 0.821 ± 0.163) phases of the trial (Wilcoxon signed rank p = 0.36). Figure 2 shows box plots of EQ-5D-5L scores on each of the five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and index values during the in-center and in-home phases. When stratified by new to HHD versus established HHD status, EQ-5D-5L index values were lower among patients new to HHD (in-center 0.751 ± 0.178 and in-home 0.751 ± 0.161) than among patients established on HHD (in-center 0.903 ± 0.095 and in-home 0.906 ± 0.119), as expected.

Sleep quality and related symptoms

Figure 3 shows the proportion of patients reporting the seven metrics of sleep quality and related symptoms during the in-center and in-home phases (comparing patient-reported symptoms 0–2 days versus 3 or more days per week). Patient counts for favorable statements were more prevalent and for unfavorable statements were less prevalent during the in-home phase; however, differences were not statistically significant. Participants reported slightly longer mean sleep duration during the in-home phase (8.31 ± 1.52 versus 8.11 ± 1.84 hours on non-dialysis days, and 7.67 ± 1.75 versus 7.06 ± 1.78 hours on dialysis days).

DISCUSSION

We recently reported the primary safety and efficacy results of an IDE study using Tablo, a novel hemodialysis system manufactured by Outset Medical, Inc. Thirty patients were enrolled and 28 (93%) completed the trial. Adherence was excellent, the frequency of adverse events was comparable during the in-center and in-home phases, and the trial met its primary efficacy endpoint (i.e., all participants achieved weekly standard Kt/Vurea ≥2.1).

As part of the IDE study, we explored several patient-reported outcomes (PROs) relevant to patients with ESKD contemplating HHD – specifically, time-to-

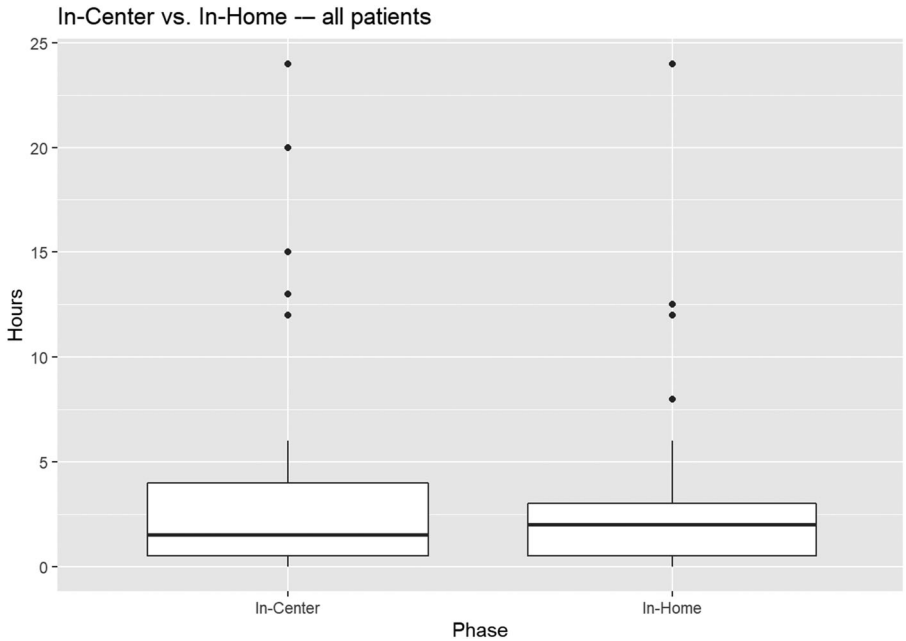

Figure 1 Box plot of time-to-recovery during the in-center and in-home phases of the trial.

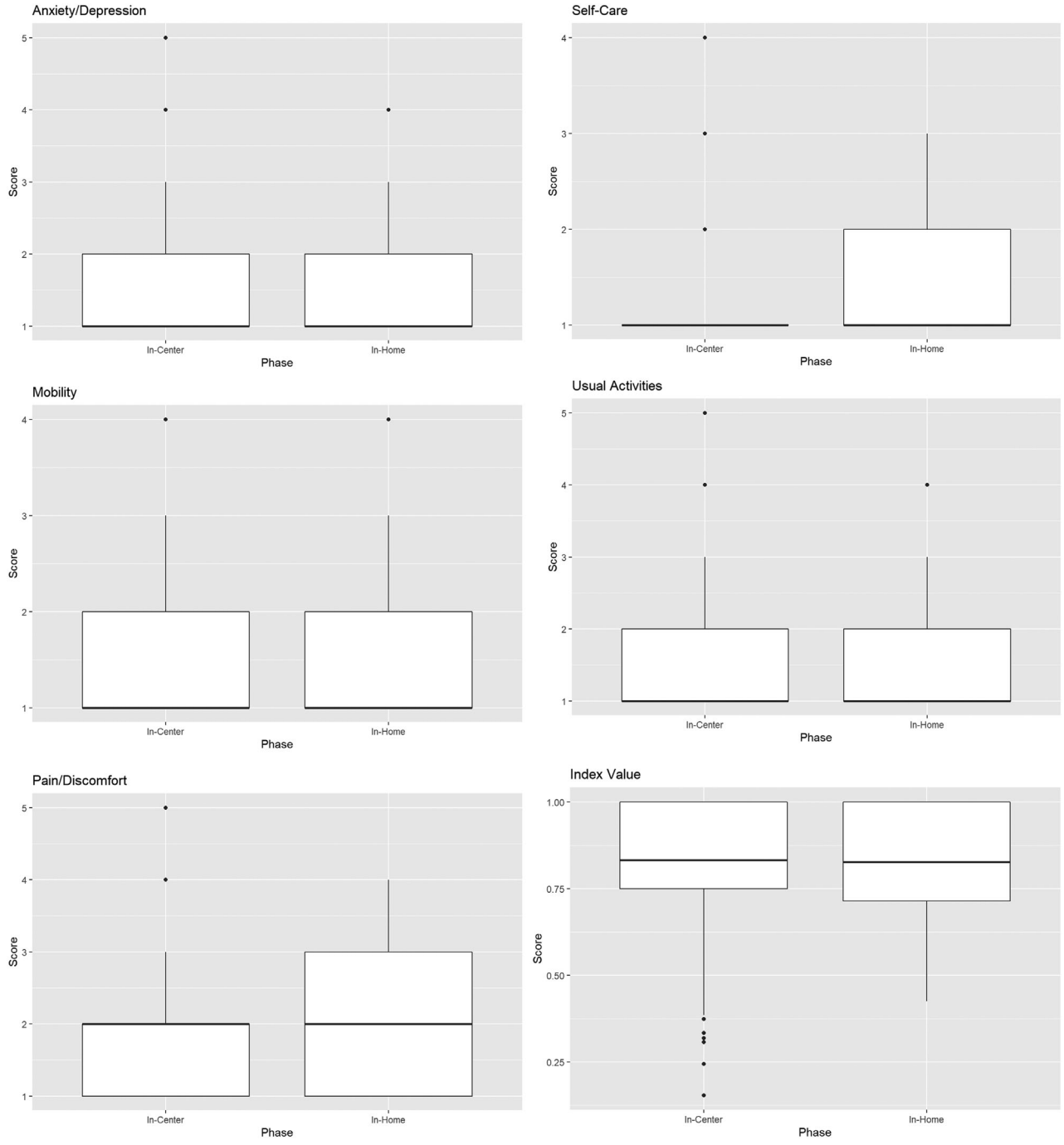

Figure 2 Box plots of each of the five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the index value of the EQ-5D-5L during the in-center and in-home phases of the trial.

recovery (TTR), sleep quality and related symptoms, and general health status. In view of the modest sample size and relatively short trial duration, we did not expect to observe significant within-patient differences when dialyzing in-center and in-home; nevertheless, we wanted to confirm that patients did not perceive any decrement in their health or well-being when transitioning to the home setting. We found that TTR was similar in both phases. There was no difference in health status as assessed by the EQ-5D-5L, although health status during the in-

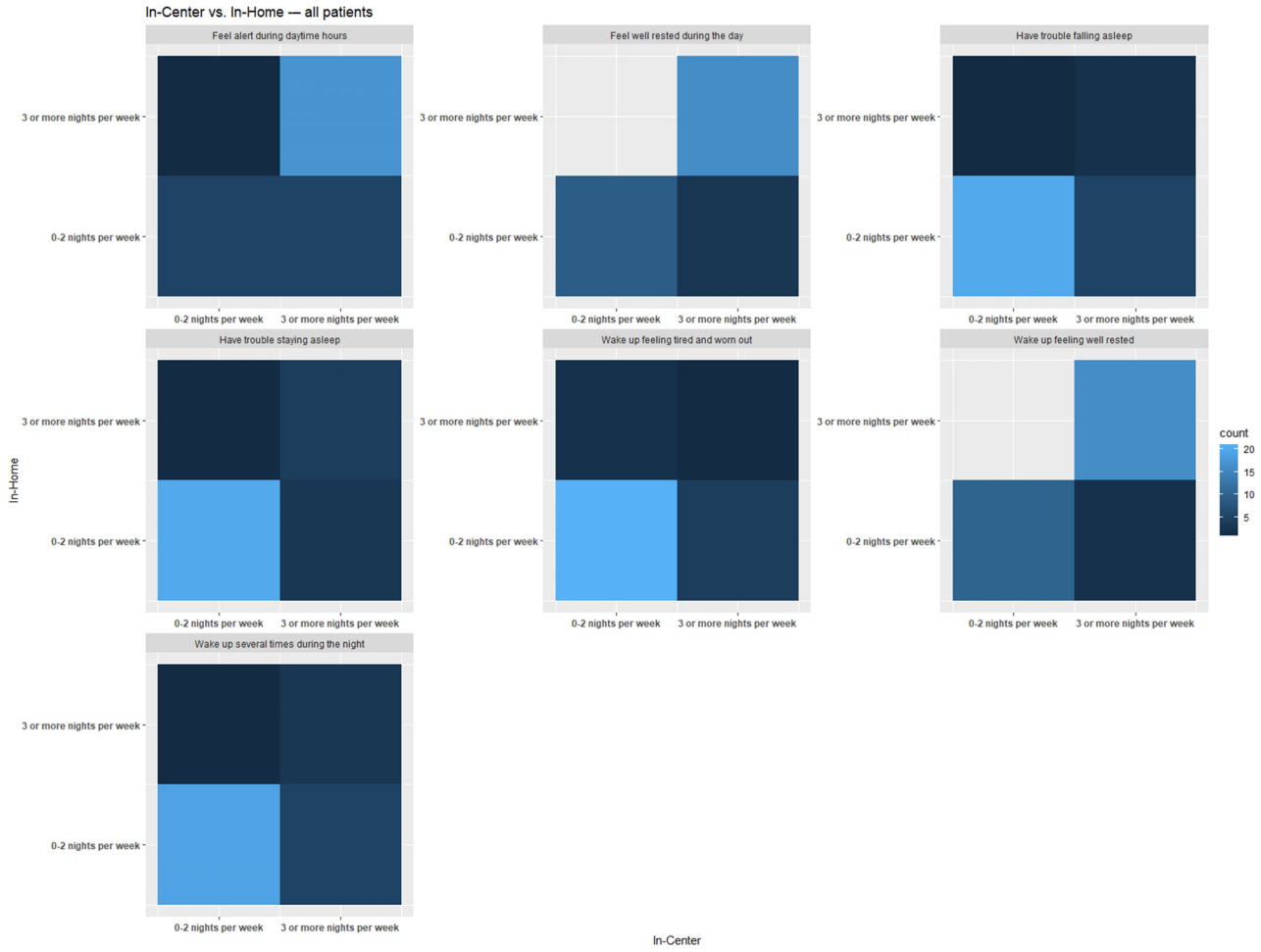

Figure 3 Proportion of patients scoring higher versus lower scores on seven metrics of sleep quality and related symptoms during the in-center and in-home phases of the trial. [Color figure can be viewed at wileyonlinelibrary.com]

center and in-home phases was superior among patients who were established on HHD compared to those new to HHD.

It is notable that the median TTR was relatively low during both study phases, which could reflect the provision of 4 times weekly therapy, or possibly, salutary effects of hemodialysis using the Tablo system and dialysate flows of 300 mL/min which may attenuate overly rapid solute shifts.

Home-based dialysis modalities (peritoneal dialysis (PD) and HHD) offer patients numerous advantages over in-center hemodialysis. Both home-based modalities offer patients much greater flexibility, particularly when fulfilling workplace and personal/family responsibilities. Some experts have advocated a "PD first" treatment strategy, which among several other benefits, abrogates the need for vascular access. While peritoneal dialysis is an effective modality for many patients, a fraction are ineligible owing to structural abnormalities within the peritoneum (e.g., adhesions related to prior abdominal surgery), and others may not tolerate the intraperitoneal administration of dextrose owing to poorly controlled diabetes mellitus or obesity. The mean Quételet (body mass) index of patients starting dialysis in the United States is 29.4 kg/m^2,[9] and the weight gain that sometimes accompanies PD can render patients ineligible for kidney transplantation, and may contribute to cardiovascular, pulmonary or other complications. Moreover, patients who initially thrive on PD may find themselves unable to adequately prevent uremic complications after residual kidney function declines. Home hemodialysis offers patients many of the same freedoms enjoyed with PD with greater efficiency of solute clearance. Conventional home hemodialysis systems can be burdensome to

patients and care partners owing to the need for 5–6 sessions per week and operational complexities. In the IDE, Tablo achieved an average weekly std Kt/V of 2.8 on 4 sessions per week.[3]

The study has several strengths. Retention and adherence were high. While the sample size was small, participants were diverse by age, sex, race/ethnicity, primary cause of kidney disease, dialysis vintage, and experience with home hemodialysis therapy. Health status measures were collected weekly; as such, time-averaged values during each study phase were more likely to reflect true patient experience and less prone to misclassification than in most other studies. There are some important limitations. We were not powered to detect meaningful differences across study phases. As designed, all participants were treated with the Tablo hemodialysis system in all study phases. Therefore, assessments of health status were not confounded by use of alternative hemodialysis systems. However, we could not determine whether there were differences in health status comparing Tablo to other home or conventional in-center hemodialysis equipment. Finally, the relatively small sample size and relatively short treatment periods preclude our ability to detect small changes in the health status measures we collected.

In summary, in an IDE study evaluating the use of the Tablo hemodialysis system at home, patients reported similar TTR, general health status, and sleep quality and related symptoms compared to using Tablo in-center. When considered in conjunction with high rates of retention and adherence and solute clearances above international clinical practice guideline targets, the use of Tablo could enable expansion of self-care and home hemodialysis, allowing patients, physicians, and dialysis providers to meet many of the challenges of the AAKH.

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