AJKD
Narrative Review

Intensive Hemodialysis and Treatment Complications and Tolerability

Jose A. Morfin, MD,[1] Richard J. Fluck, MA (Cantab), MBBS,[2] Eric D. Weinhandl, PhD, MS,[3] Sheru Kansal, MD,[4] Peter A. McCullough, MD, MPH,[5,6,7,8] and Paul Komenda, MD[9,10,11]

Hemodialysis (HD) treatment can be difficult to tolerate. Common complications are intradialytic hypotension (IDH) and long time to recovery after an HD session. IDH, as defined by nadir systolic blood pressure < 90 mm Hg and intradialytic decline > 30 mm Hg, occurs in almost 8% of HD sessions. IDH may be caused by aggressive ultrafiltration in response to interdialytic weight gain, can lead to myocardial stunning and cardiac arrhythmias, and is associated with increased risk for death. Long recovery time after a treatment session is also common. In DOPPS (Dialysis Outcomes and Practice Patterns Study), recovery time was 2 to 6 hours for 41% of HD patients and longer than 6 hours for 27%; recovery time was linearly associated with increased risks for death and hospitalization. Importantly, both decreases in blood pressure and feeling washed out or drained have been identified by patients as more important outcomes than death or hospitalization. Intensive HD likely reduces the likelihood of IDH. In the Frequent Hemodialysis Network trial, short daily and nocturnal schedules reduced the per-session probability of IDH by 20% and 68%, respectively, relative to 3 sessions per week. Due to lower ultrafiltration volume and/or rate, intensive HD may reduce intradialytic blood pressure variability. In a cross-sectional study, short daily and nocturnal schedules were associated with slower ultrafiltration and less dialysis-induced myocardial stunning than 3 sessions per week. In FREEDOM (Following Rehabilitation, Economics, and Everyday-Dialysis Outcome Measurements), a prospective cohort study of short daily HD, recovery time was reduced after 12 months from 8 hours to 1 hour, according to per-protocol analysis. Recovery time after nocturnal HD may be minutes. In conclusion, intensive HD can improve the tolerability of HD treatment by reducing the risk for IDH and decreasing recovery time after HD. These changes may improve the patient centeredness of end-stage renal disease care.
Am J Kidney Dis. 68(5)(suppl 1):S43-S50.

INDEX WORDS: Chronic kidney disease; daily dialysis; treatment tolerability; dialysis adequacy; end stage renal disease (ESRD); fatigue; Frequent Hemodialysis Network; home dialysis; intensive hemodialysis; intradialytic hypotension; nocturnal hemodialysis; organ stunning; recovery time; complications; short daily hemodialysis; ultrafiltration; review.

Long-term hemodialysis (HD) therapy, as it is usually prescribed in the United States, is inherently burdensome to patients. Conventional HD overwhelmingly involves 3 sessions per week, each 3 to 4 hours in duration.[1] Cumulatively, such time "on the machine" consumes 9 to 12 hours per week. However, because patients typically undergo HD in a health care facility, there is requisite travel before and after each session. In the DOPPS (Dialysis Outcomes and Practice Patterns Study), 2,140 US patients responded to the survey question, "How long does it take you to get to your dialysis unit or center (1 way)?" Among respondents, 47% reported 15 minutes or less, 33% reported 16 to 30 minutes, 17% reported 31 to 60 minutes, and 3% reported longer than 60 minutes.[2] From this distribution, it is reasonable to estimate that each dialysis session necessitates 45 minutes of travel, thus increasing the time that is devoted directly to dialysis therapy to 11 to 14 hours per week. Arguably as important as time on the machine is time that is consumed by recovering from a dialysis session. During recovery time, which is highly variable but may tend to range from 6 to 8 hours, physical and mental function may

From the [1]University of California, Davis, School of Medicine, Sacramento, CA; [2]Department of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; [3]Department of Pharmaceutical Care and Health Systems, College of Pharmacy, University of Minnesota, Minneapolis, MN; [4]Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; [5]Baylor University Medical Center; [6]Baylor Heart and Vascular Institute; [7]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas; [8]The Heart Hospital Baylor Plano, Plano, TX; [9]Section of Nephrology, Department of Medicine, and [10]Department of Community Health Sciences, University of Manitoba; and [11]Seven Oaks General Hospital Renal Program, Winnipeg, Canada.

Received February 16, 2016. Accepted in revised form May 25, 2016.
This article is part of a supplement that was developed with funding from NxStage Medical, Inc.
Address correspondence to Eric D. Weinhandl, PhD, MS, Department of Pharmaceutical Care and Health Systems, College of Pharmacy, University of Minnesota, Weaver-Densford Hall, 7th Fl, 308 Harvard St SE, Minneapolis, MN 55455. E-mail: wein0205@umn.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.05.021

be impaired.[3] With 18 hours per week devoted to recovery, cumulative time either directly or indirectly devoted to dialysis therapy is 29 to 32 hours per week. In tandem with any additional health care, including hospital admissions, clinic appointments, and pharmacy visits, long-term HD therapy is essentially a (permanent) full-time occupation, but with only 30% of effort devoted specifically to the task of dialyzing.

In light of this level of burden, it is plausible that interventions that can ease treatment itself or return some normalcy to the interdialytic interval would be appreciated by patients. Intensive HD, which is often prescribed in the home setting and/or during nighttime hours, may be an effective modality by which to accomplish such goals. In this review, we examine the poor tolerability of dialysis therapy, epidemiology and pathogenesis of intradialytic hypotension (IDH) and effects of intensive HD on the risk for IDH, epidemiology and pathogenesis of long recovery time after a dialysis session and the effects of intensive HD on recovery time, and the contrast of the prevailing concept of dialysis adequacy (urea clearance) with a countervailing concept of dialysis optimality, as represented by relative freedom from treatment complications and some oft-used medications. Accumulated evidence shows that intensive HD likely reduces the per-treatment risk for IDH and the length of recovery time. Although these effects do not necessarily portend improved clinical outcomes, they address some of the issues that are cited by patients as high priorities. The broader domains of blood pressure management and health-related quality of life—to which recovery time probably contributes—are further discussed in the accompanying reviews by Bakris et al[4] and Kraus et al,[5] respectively.

POOR TOLERABILITY OF DIALYSIS

Dialysis-Associated Symptoms

A wide array of symptoms during HD treatment is commonly reported. In a survey of 550 patients on conventional HD therapy, the most widely reported symptoms were fatigue (82%), IDH (76%), cramping (76%), postdialysis dizziness (63%), headache (54%), pruritus (52%), and back pain (51%). Nausea and vomiting were also reported in minorities of patients (Fig 1).[6]

Interestingly, some of these symptoms are related to outcomes that have been identified as important to patients and caregivers. In 12 focus groups, which included 58 adult dialysis patients and 24 caregivers, 68 outcomes were identified as important.[7] Each participant identified the 10 most important outcomes and ranked them from 10 (highest importance) to 1 (lowest importance). The most highly ranked outcomes among outcomes identified in 11 or 12 groups were fatigue and energy, resilience and coping, ability to travel, dialysis-free time, impact on family, ability to work, sleep, and decrease in blood pressure (mean rank scores of 4.5, 3.7, 3.6, 3.3, 3.2, 2.5, 2.3, and 2.0, respectively). Among symptoms, the most highly ranked outcomes were decrease in blood pressure, feeling washed out or drained, restless legs syndrome, and cramps (mean rank scores of 2.0, 1.6, 1.3, and 1.0, respectively). Feeling washed out or drained was ranked significantly more highly ($P = 0.01$) by in-center HD patients than home HD patients (mean rank score, 2.5 vs 0.2). For frame of reference, mean rank scores for mortality were 0.9 among patients and 3.6 among caregivers. Thus, patients generally valued mortality less than treatment complications.

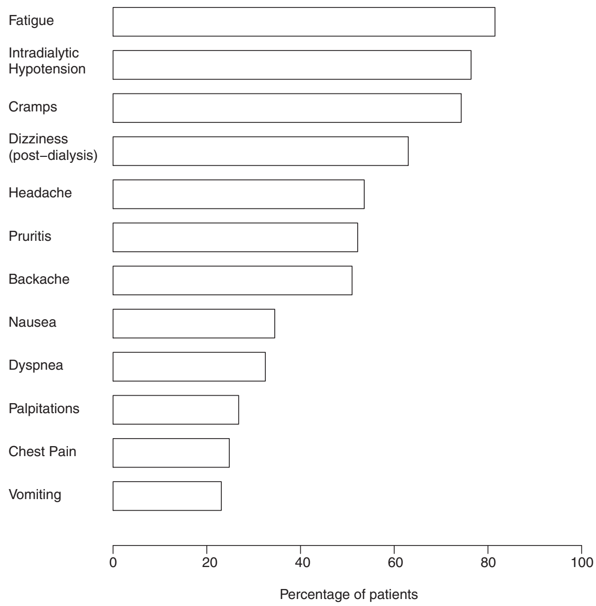

Figure 1. Prevalence of commonly reported symptoms in a cohort of 550 hemodialysis patients.[6]

Missed HD Sessions

Recurrence of dialysis-associated symptoms may encourage nonadherence to the HD prescription, including shortened or missed treatments. In a population study of a not-for-profit dialysis provider organization, the percentage of missed HD treatments among patients dialyzing on Monday, Wednesday, and Friday was 2.1%, and among patients dialyzing on Tuesday, Thursday, and Saturday, was 2.9%.[8] Corresponding percentages of shortened treatments were 14.9% and 16.4%, respectively. The percentages of missed and shortened treatments were each negatively associated with age. In an earlier single-center study, Rocco and Burkart[9] assessed reasons for shortened treatments, which occurred in 6.8% of sessions and resulted in an average loss of 32 minutes of treatment. The foremost reason for shortened treatments was cramping, followed by feeling “bad” or “sick.”

INTRADIALYTIC HYPOTENSION

Epidemiology

The incidence of IDH depends partially on the definition of IDH. In an analysis of blood pressure data from a large dialysis organization, the incidence of an intradialytic decline in systolic blood pressure (SBP) > 30 mm Hg and nadir SBP < 90 mm Hg was 7.5%, whereas the incidence of an intradialytic decline in SBP > 20 mm Hg and nadir SBP < 90 mm Hg was 8.5%. Incidences of nadir SBP < 90 mm Hg and between 90 and 99 mm Hg, regardless of intradialytic variation, were 9.7% and 12.3%, respectively.[10]

Clinical Significance

In the aforementioned study, multiple conceptions of IDH were associated with increased risk for death. For example, nadir SBP < 90 mm Hg was associated with 30% increased risk for death during a 1-year follow-up.[10] In another analysis in which IDH was defined as an intradialytic decline in SBP > 20 mm Hg and at least 2 responsive measures (eg, cessation of dialysis session or administration of saline solution), the incidence of IDH was significantly associated with increased risks for myocardial infarction, hospitalization for heart failure or fluid overload, and major adverse cardiac event (ie, myocardial infarction, stroke, or cardiovascular-related death).[11] The incidence of IDH has also been associated with increased risk for vascular access thrombosis.[12]

Pathogenesis

IDH is the consequence of an inadequate response to decreased intravascular volume when a large amount of fluid is quickly removed.[13,14] Ultrafiltration volume is typically plasma volume or greater, so maintenance of plasma volume during HD treatment requires mobilization of interstitial fluid. If the ultrafiltration rate exceeds the plasma refilling rate (eg, late in the dialysis session, when plasma refilling rate is lower[15]), hemodynamic instability and associated symptoms can occur. Impaired sympathetic activity may result in negative cardiac inotropy and inappropriate vasodilation, thus exaggerating IDH.

Aggressive ultrafiltration may be an iatrogenic factor in the pathogenesis of IDH. With the conventional HD schedule, especially after the 72-hour interval between consecutive dialysis sessions, achieving dry weight in 3 to 4 hours may be impossible without setting an aggressive ultrafiltration rate. There is mounting evidence that aggressive ultrafiltration provokes myocardial stunning, or subclinical myocardial ischemia, which can result in angina, arrhythmias, and hypotension and may lead to progressive cardiomyopathy. In a post hoc analysis of the Hemodialysis (HEMO) Study, adjusted hazard ratios (HRs) of all-cause and cardiovascular death for ultrafiltration rate ≥ 13 versus ≤10 mL/kg/h were 1.59 (95% confidence interval [CI], 1.29-1.96) and 1.71 (95% CI, 1.23-2.38), respectively.[16]

Effects of Intensive HD

Murashima et al[17] reported the experience of 12 patients who converted from conventional HD to short daily HD and remained on short daily HD therapy for at least 6 months. With conversion, median treatment time decreased from 3.5 to 2.5 hours per session and median ultrafiltration rate decreased from 11.0 to 6.9 mL/kg/h. After 6 months of follow-up, SBP was modestly lower, but diastolic blood pressure was unchanged. Conversion led to large reductions in intradialytic variability in SBP, diastolic blood pressure, and mean arterial pressure, for which measurements were taken every 30 minutes during dialysis treatment. Short daily HD was associated with a significantly lower incidence of IDH, according to NKF-KDOQI (National Kidney Foundation−Kidney Disease Outcomes Quality Initiative) criteria[18] of a decrease in SBP > 20 mm Hg or decrease in mean arterial pressure > 10 mm Hg (odds ratio, 0.39; 95% CI, 0.24-0.64). Likewise, short daily HD was associated with a significantly lower incidence of clinically significant IDH, as defined as SBP < 90 mm Hg or diastolic blood pressure < 55 mm Hg (odds ratio, 0.36; 95% CI, 0.16-0.81).

In the Frequent Hemodialysis Network (FHN) Daily Trial,[19,20] participants were randomly assigned to receive HD for either 6 short sessions (n = 125) or 3 conventional sessions (n = 120) per week. Participants undergoing intensive HD actually received 5.2 sessions per week, for an average of 2.6 hours per session, whereas those on the usual HD schedule received 2.9 sessions per week, for an average of 3.6 hours per session. Symptoms of IDH were assessed during a 1-week period of each month of follow-up. Symptoms of IDH were classified into 3 categories: those that led to lowering the ultrafiltration rate or reduced blood flow (level I); those that led to the administration of saline solution, but not to lowering the ultrafiltration rate (level II); and those that led to both the administration of saline solution and lowering the ultrafiltration rate (level III).[21] In the FHN Daily Trial (Fig 2), incidences of level I, II, and III IDH were 6.3%, 3.8%, and 3.5%, respectively, with conventional HD (cumulative incidence, 13.6%). In contrast, incidences of level I, II, and III IDH were 4.4%, 3.1%, and 3.3%, respectively, with short daily HD (cumulative incidence, 10.8%). The difference in

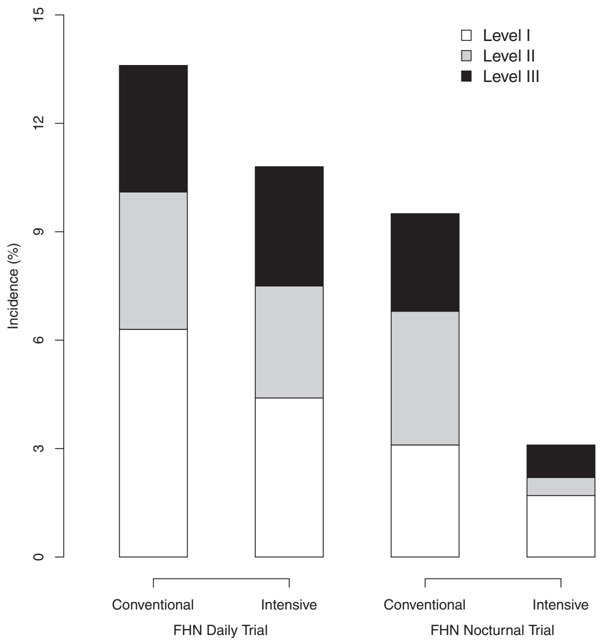

Figure 2. Incidences of levels I, II, and III intradialytic hypotension for intensive versus conventional hemodialysis in the Frequent Hemodialysis Network (FHN) Daily Trial and the FHN Nocturnal Trial.[21]

the cumulative incidence of IDH between treatment groups was significant ($P = 0.04$). Because of increased treatment frequency with short daily HD, the relative number of dialysis sessions with symptoms of level I IDH was 1.26 (95% CI, 0.89-1.77) for short daily HD versus conventional HD, whereas the relative number of sessions with symptoms of either level II or level III IDH was 1.53 (95% CI, 1.11-2.09). Notably, ultrafiltration rate was lower with short daily HD versus conventional HD after 2 months (treatment effect, −1.1 [95% CI, −2.1 to −0.1] mL/min) and again after 12 months (treatment effect, −0.6 [95% CI, −1.5 to 0.3] mL/min), although only the former was statistically significant. Interdialytic weight gain was ∼1 kg less with short daily HD versus conventional HD after both 2 and 12 months.

In the FHN Nocturnal Trial (Fig 2), participants were randomly assigned to receive home HD for either 6 nocturnal sessions (n = 45) or 3 conventional sessions (n = 42) per week. Patients on the nocturnal schedule actually received 5.2 sessions per week, for an average of 6.3 hours per session, whereas patients on the conventional schedule received 2.9 sessions per week, for an average of 4.3 hours per session. Incidences of level I, II, and III IDH were 3.1%, 3.7%, and 2.7%, respectively, with conventional HD (cumulative incidence, 9.4%). In contrast, incidences of level I, II, and III IDH were 1.7%, 0.5%, and 0.9%, respectively, with nocturnal HD (cumulative incidence, 3.1%). The difference in the cumulative incidence of IDH between treatment groups was significant ($P < 0.001$). Despite increased treatment frequency with nocturnal HD, the relative number of dialysis sessions with symptoms of level I IDH was 0.85 (95% CI, 0.33-2.17) for nocturnal HD versus conventional HD, whereas the relative number of sessions with symptoms of either level II or level III IDH was 0.35 (95% CI, 0.18-0.69). Ultrafiltration rates were significantly lower with nocturnal HD versus conventional HD after both 2 and 12 months (treatment effects of −4.2 [95% CI, −5.7 to −2.7] and −4.1 [95% CI, −5.4 to −2.8] mL/min, respectively).

Myocardial Stunning

Jefferies et al[22] conducted a cross-sectional study of 46 patients, with 12 on conventional HD therapy, 12 on short daily HD therapy in a facility, 12 on short daily HD therapy at home, and 10 on nocturnal HD therapy at home (mean session durations of 3.4, 2.4, 3.5, and 7.8 hours, respectively). Study participants were assessed during a single dialysis session and echocardiography was repeated before treatment, 15 minutes before the end of treatment (ie, at "peak stress"), and between 15 and 30 minutes after the end of treatment. Mean ultrafiltration volumes differed among groups. With conventional HD, mean ultrafiltration volume was 4.1 L, whereas for in-center short daily HD, home short daily HD, and home nocturnal HD, mean ultrafiltration volumes were 2.6, 1.0, and 1.1 L, respectively. Mean ultrafiltration rates likewise differed among groups. With conventional HD, mean ultrafiltration rate was 15.4 mL/kg/h, whereas for in-center short daily HD, home short daily HD, and home nocturnal HD, mean ultrafiltration rates were 13.5, 3.39, and 0.64 mL/kg/h, respectively.

In conventional HD patients, mean SBP decreased from 146 mm Hg before treatment to 105 mm Hg at peak stress, but then increased to 128 mm Hg after treatment. The mean difference between pretreatment and peak stress SBP was 42 mm Hg. In contrast, mean differences between pretreatment and peak stress SBP were 19 mm Hg with in-center short daily HD and 2 mm Hg with home short daily HD. With home nocturnal HD, the mean difference between pretreatment and peak stress SBP was −17 mm Hg because mean SBP increased from 143 mm Hg before treatment to 160 mm Hg at peak stress, before declining trivially to 159 mm Hg after treatment. Change in SBP between pretreatment and peak stress measurements was strongly correlated with both ultrafiltration volume and ultrafiltration rate (Pearson coefficients of 0.60 and 0.56, respectively).

Myocardial stunning was observed in all conventional HD patients and 92% of in-center short daily HD patients, but only 75% of home short daily HD patients and 50% of home nocturnal HD patients. Mean numbers of regional wall motion abnormalities were 4.8 ± 1.3 (standard deviation) for conventional HD and 4.6 ± 1.6 for in-center short daily HD, but only 3.3 ± 1.7 for home short daily HD and 3.0 ± 1.6 for home nocturnal HD. Differences in mean numbers of regional wall motion abnormalities were significant for the contrasts of home short daily HD and home nocturnal HD with conventional HD. Overall, ultrafiltration rate was positively correlated with the number of regional wall motion abnormalities (Pearson coefficient, 0.41).

RECOVERY TIME AFTER HD

Epidemiology

In the aforementioned survey regarding symptoms, ∼40% of patients had not recovered until at least bedtime.[6] In DOPPS, 6,040 patients were asked, "How long does it take you to recover from a dialysis session?" Recovery times were 2 to 6 hours in 41% of patients, 7 to 12 hours in 17% of patients, and longer than 12 hours in 10% of patients (Fig 3).[3]

Clinical Significance

In the aforementioned study, each 1-hour increment in postdialysis recovery time was associated with significantly increased risks for death (HR, 1.05; 95% CI, 1.03-1.07) and hospitalization (HR, 1.03; 95% CI, 1.02-1.04) after adjustment for demographic and clinical factors.[3] Longer recovery time was also associated with fewer activities of daily living and lower physical and mental health–related quality-of-life scores.

Pathogenesis

The exact causes of long recovery time are unknown.[23] Lindsay et al[24] validated the question, "How long does it take you to recover from a dialysis session?" Validation was performed in London Daily/Nocturnal Hemodialysis Study participants, including 11 participants on short daily HD therapy, 13 on nocturnal HD therapy, and 22 controls on conventional HD therapy. The test-retest correlation over 3-month intervals in patients on conventional HD therapy was extraordinarily high (Pearson coefficient, 0.962). Time to recovery was mostly highly correlated with fatigue at the end of the dialysis session (Pearson coefficient, 0.508). Time to recovery was also highly correlated with aching in arms and legs, difficulty concentrating, and importantly, dialysis stress, including hypotension, tingling extremities, muscle cramps, itching, and dizziness (Pearson coefficients of 0.357, 0.354, and 0.348, respectively).

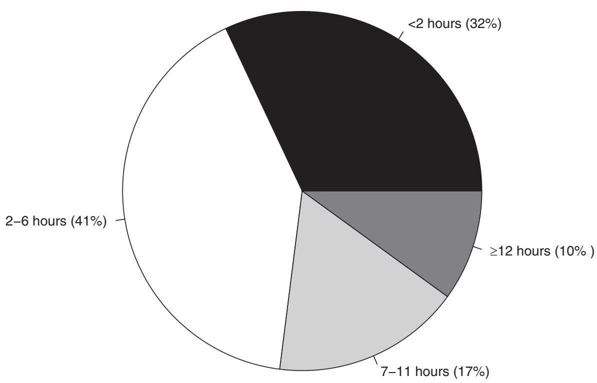

Figure 3. Distribution of postdialysis recovery time in the DOPPS (Dialysis Outcomes and Practice Patterns Study).[3]

Symptomatic recovery after HD may be related to myocardial stunning. Dubin et al[25] assessed the relationship between intradialytic left ventricular segmental wall motion abnormalities and postdialysis recovery time in a single-center study of 40 patients on conventional HD therapy. Patients were asked, "After most dialysis sessions, do you have fatigue for more than 2 hours?" An affirmative response to the question was classified as severe postdialysis fatigue. To assess segmental wall motion abnormalities, echocardiograms were collected immediately before a treatment session and during the last hour of the session, for 2 sessions per study participant. In each of the 16 myocardial segments, wall motion was scored as 1 point for normokinesis, 2 points for hypokinesis, 3 points for akinesis, and 4 points for dyskinesis. Segment-specific scores were summed for each echocardiogram. For each unique pair of patient and session, the difference between intradialytic and pretreatment summary scores was calculated, so that a positive score indicated worsening wall motion during treatment. Among the 40 study participants, the prevalence of severe postdialysis fatigue was 20%. However, 9 participants (23%) exhibited worsening wall motion during treatment, 27 (68%) exhibited unchanged wall motion, and 4 (10%) exhibited improved wall motion. The prevalence of severe postdialysis fatigue was 50% in patients with worsening wall motion during treatment, whereas the prevalence of severe postdialysis fatigue was only 16% in patients with unchanged or improved wall motion. After adjustment for depression, change in SBP during dialysis, and ultrafiltration volume, each 1-point increment in the summary score of segmental wall motion abnormalities was associated with a 1.9-fold (95% CI, 1.4- to 2.6-fold) increase in risk for severe postdialysis fatigue.

Effects of Intensive HD

In the London Daily/Nocturnal Hemodialysis Study, postdialysis recovery time in short daily HD patients decreased from 5.5 hours at baseline to 0.4 hour after 3 months of treatment, 1.1 hour after

6 months, and varied between 0.3 and 0.6 hour thereafter. In nocturnal HD patients, postdialysis recovery time decreased from 10.8 hours at baseline to 0.1 hour after 3 months of treatment, 0.3 hour after 6 months, and varied between 0.1 and 0.3 hour thereafter. However, in conventional HD patients, postdialysis recovery time was 6.0 hours at baseline and varied between 6.6 and 7.7 hours during the rest of follow-up.[24]

The Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) Study was a multicenter prospective cohort study of patients who initiated daily home HD treatment with the NxStage System One.[26] All study participants were adults with Medicare as their primary payer. Follow-up was 12 months. At baseline and again after 4 and 12 months of treatment, study participants were asked, "How long does it take you to recover from a dialysis session and resume your normal, usual activities?" In intention-to-treat analysis of recovery time, all participants were included and the last observation was carried forward, whereas in per-protocol analysis, only participants with complete follow-up were included.[27]

Mean postdialysis recovery time was longer in women versus men (12.1 vs 6.0 hours) and in study participants requiring assistance with daily activities versus not (21.2 vs 7.7 hours). In the intention-to-treat analysis, mean postdialysis recovery time decreased from 7.9 (95% CI, 6.4-9.4) hours at baseline to 4.0 (95% CI, 2.9-5.1) hours after 4 months and 4.0 (95% CI, 2.8-5.1) hours after 12 months (Fig 4). In the per-protocol analysis, the decline was more dramatic. Specifically, mean postdialysis recovery time decreased from 7.9 (95% CI, 6.0-9.9) hours at baseline to 1.0 (95% CI, 0.8-1.3) hour after 4 months and 1.1 (95% CI, 0.5-1.6) hour at 12 months (Fig 4). In both analyses, reductions were significant. In per-protocol analysis, the percentage of patients with recovery time less than 1 hour increased from 19% at baseline to 65% after 12 months.

DIALYSIS ADEQUACY VERSUS OPTIMALITY

Presently in the United States, particularly in the context of Medicare policy, the core metric of dialysis adequacy is single-pool Kt/V, which measures urea clearance during dialysis treatment. The utility of this metric has been vigorously debated. Regardless of arguments in support of and opposition to single-pool Kt/V, national data indicate that HD is almost universally adequate. Specifically, according to CROWNWeb data from December 2013, single-pool Kt/V was ≥1.2 in 97% of HD patients.[28] From the regulatory perspective, such a high percentage seems to be a major achievement. However, from the clinical perspective, that such an extreme rate of delivery of adequate dialysis could be accompanied by high rates of cardiovascular-related mortality and morbidity, frequent cases of IDH and shortened sessions, and long postdialysis recovery times suggests that ostensibly adequate dialysis is clearly different than "symptom-free" dialysis.

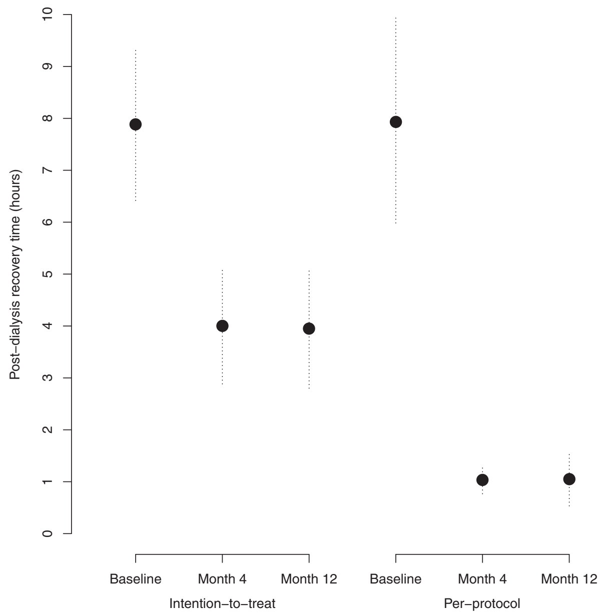

Figure 4. Mean postdialysis recovery time in intention-to-treat and per-protocol cohorts of the FREEDOM (Following Rehabilitation, Economics, and Everyday-Dialysis Outcome Measurements) Study.[28] Dashed bars span 1 standard deviation above and below the mean.

The countervailing picture of intensive HD on a nocturnal schedule, for example, paints a different picture. Pill burden is reduced because use of both antihypertensive medications and phosphate binders is significantly curtailed.[21,29] From a patient-centered perspective, dialysis treatment itself is less likely to be accompanied by treatment complications. The incidence of IDH is reduced, possibly because the ultrafiltration requirement—expressed as absolute volume, percentage of dry weight, or rate of fluid removal per unit of time—is lower than with intensive versus conventional HD. Recovery time likely shifts from hours to minutes, so that most of the time either directly or indirectly devoted to dialysis therapy is devoted to the task of dialyzing. Arguably, the defining characteristic of this conception of HD is relative freedom, from both dialysis-associated symptoms and pharmacologic interventions that in many patients are necessary to compensate for limited hours of dialysis therapy.

Meaningful reductions in the incidence of IDH and length of recovery time may be achieved with intensive HD, but at the expense of 2 to 3 additional HD sessions per week, increased risk for vascular access complications, and in the home setting, increased burden on care partners.[30-32] Moreover, lower risk for treatment complications with intensive HD may fail to translate to lower risks for mortality and morbidity. With extended follow-up of FHN Trial participants, short daily HD reduced the risk for death by 46%, relative to 3 sessions per week, but nocturnal HD increased risk by 288%, despite much lower ultrafiltration rates with nocturnal HD versus short daily HD.[33,34] Although neither trial was adequately powered to assess the effect of intensive HD on mortality risk, results of the trials suggest hypotheses regarding relative survival. Thus, the prescription of intensive HD (including a specific schedule) likely demands careful consideration of goals in the short run (eg, regarding burden of treatment complications) and the long run (eg, regarding expected time to death). In light of patient preference for outcomes other than mortality, patient-centered selection of dialytic modality and schedule might be anticipated to increase day-to-day quality of treatment, but not to maximize the expectation of remaining life.

Even with conventional HD, risk for treatment complications may be addressed. For example, risk for IDH may be reduced by altering dialysate composition (eg, calcium or sodium), cooling dialysate, or using biofeedback-controlled dialysis technology.[35] Midodrine is an effective vasopressor. To the extent that long recovery time is the consequence of aggressive ultrafiltration, recovery time may be reduced by limiting interdialytic weight gain, such as with dietary salt restriction.[36] Additional sessions and/or additional time per session may also be ordered on an as-needed basis. Evolving quality metrics regarding ultrafiltration will necessitate a variety of tactics.

CONCLUSIONS

In the narrow context of the usual HD schedule, the tolerability of long-term treatment is poor. Dialysis-associated symptoms, including IDH, are common and recovery from dialysis treatment can consume the balance of the day, resulting in deteriorated quality of life. Intensive HD may reduce the incidence of IDH and likely reduces postdialysis recovery time. Possibly mediating these effects is the diminished need for aggressive ultrafiltration, thereby resulting in lower incidence of myocardial stunning. Despite its potential risks (eg, vascular access complications), intensive HD embodies a shift in priorities from a mechanistic vision of adequate dialysis as a function of urea kinetics and life expectancy to a patient-centered vision of optimal dialysis as a function of relative freedom from treatment-related symptoms and the pills indicated for hypertension and hyperphosphatemia.

ACKNOWLEDGEMENTS

Support: The publication costs associated with this journal supplement were paid by NxStage Medical Inc. NxStage specified neither expectations nor restrictions regarding the content of this review. Furthermore, no employee of NxStage was involved in its writing. Dr Weinhandl has received compensation as an epidemiologist consultant to NxStage and his consulting agreement included an expectation of research and writing directed toward a journal supplement regarding intensive HD.

Financial Disclosure: All authors except Dr Weinhandl are members of the Chronic Therapy Scientific Advisory Board at NxStage and receive nominal compensation for their service. Drs McCullough and Komenda report no other financial relationships with a commercial entity producing health care–related products and/or services. Dr Morfin has received compensation as a physician consultant to NxStage and Satellite Healthcare. Drs Fluck and Kansal have received compensation as physician consultants to NxStage.

Peer Review: Evaluated by 2 external peer reviewers, the Deputy Editor, and the Editor-in-Chief.

REFERENCES

1. Arbor Research Collaborative for Health. The DOPPS Practice Monitor. http://www.dopps.org/DPM/. Accessed May 20, 2015.
2. Moist LM, Bragg-Gresham JL, Pisoni RL, et al. Travel time to dialysis as a predictor of health-related quality of life, adherence, and mortality: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2008;51(4):641-650.
3. Rayner HC, Zepel L, Fuller DS, et al. Recovery time, quality of life, and mortality in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2014;64(1):86-94.
4. Bakris GL, Burkart JM, Weinhandl ED, McCullough PA, Kraus MA. Intensive hemodialysis, blood pressure, and antihypertensive medication use. *Am J Kidney Dis*. 2016;68(5)(suppl 1):S15-S23.
5. Kraus MA, Fluck RJ, Weinhandl ED, et al. Intensive hemodialysis and health-related quality of life. *Am J Kidney Dis*. 2016;68(5)(suppl 1):S33-S42.
6. Caplin B, Kumar S, Davenport A. Patients' perspective of haemodialysis-associated symptoms. *Nephrol Dial Transplant*. 2011;26(8):2656-2663.
7. Urquhart-Secord R, Craig JC, Hemmelgarn B, et al. Patient and caregiver priorities for outcomes in hemodialysis: an international nominal group technique study. *Am J Kidney Dis*. 2016;68(3):444-454.
8. Obialo CI, Hunt WC, Bashir K, Zager PG. Relationship of missed and shortened hemodialysis treatments to hospitalization and mortality: observations from a US dialysis network. *Clin Kidney J*. 2012;5(4):315-319.
9. Rocco MV, Burkart JM. Prevalence of missed treatments and early sign-offs in hemodialysis patients. *J Am Soc Nephrol*. 1993;4(5):1178-1183.
10. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724-734.
11. Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol*. 2014;9(12):2124-2132.
12. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. *J Am Soc Nephrol*. 2011;22(8):1526-1533.

13. Palmer BF, Henrich WL. Recent advances in the prevention and management of intradialytic hypotension. *J Am Soc Nephrol*. 2008;19(1):8-11.
14. Chao C-T, Huang J-W, Yen C-J. Intradialytic hypotension and cardiac remodeling: a vicious cycle. *Biomed Res Int*. 2015;2015:724147.
15. Tabei K, Nagashima H, Imura O, Sakurai T, Asano Y. An index of plasma refilling in hemodialysis patients. *Nephron*. 1996;74(2):266-274.
16. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int*. 2011;79(2):250-257.
17. Murashima M, Kumar D, Doyle AM, Glickman JD. Comparison of intradialytic blood pressure variability between conventional thrice-weekly hemodialysis and short daily hemodialysis. *Hemodial Int*. 2010;14(3):270-277.
18. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. 2005;45(4 Suppl 3):S1-153.
19. FHN Trial Group; 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(24):2287-2300.
20. Rocco MV, Lockridge RS, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int*. 2011;80(10):1080-1091.
21. Kotanko P, Garg AX, Depner T, et al. Effects of frequent hemodialysis on blood pressure: results from the randomized frequent Hemodialysis Network trials. *Hemodial Int*. 2015;19(3):386-401.
22. Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol*. 2011;6(6):1326-1332.
23. Bossola M, Tazza L. Postdialysis fatigue: a frequent and debilitating symptom. *Semin Dial*. 2016;29(3):222-227.
24. Lindsay RM, Heidenheim PA, Nesrallah G, Garg AX, Suri R; Daily Hemodialysis Study Group London Health Sciences Centre. 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(5):952-959.
25. Dubin RF, Teerlink JR, Schiller NB, Alokozai D, Peralta CA, Johansen KL. Association of segmental wall motion abnormalities occurring during hemodialysis with post-dialysis fatigue. *Nephrol Dial Transplant*. 2013;28(10):2580-2585.
26. 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(2):310-320.
27. 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(3):531-539.
28. Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2015;66(1)(suppl 1):Svii, S1-S305.
29. Daugirdas JT, Chertow GM, Larive B, et al. Effects of frequent hemodialysis on measures of CKD mineral and bone disorder. *J Am Soc Nephrol*. 2012;23(4):727-738.
30. Suri RS, Larive B, Sherer S, et al. Risk of vascular access complications with frequent hemodialysis. *J Am Soc Nephrol*. 2013;24(3):498-505.
31. Suri RS, Larive B, Hall Y, et al. Effects of frequent hemodialysis on perceived caregiver burden in the Frequent Hemodialysis Network trials. *Clin J Am Soc Nephrol*. 2014;9(5):936-942.
32. Kraus MA, Kansal S, Copland M, et al. Intensive hemodialysis and potential risks with increasing treatment. *Am J Kidney Dis*. 2016;68(5)(suppl 1):S51-S58.
33. Chertow GM, Levin NW, Beck GJ, et al. Long-term effects of frequent in-center hemodialysis. *J Am Soc Nephrol*. 2016;27(6):1830-1836.
34. Rocco MV, Daugirdas JT, Greene T, et al. Long-term effects of frequent nocturnal hemodialysis on mortality: the Frequent Hemodialysis Network (FHN) Nocturnal Trial. *Am J Kidney Dis*. 2015;66(3):459-468.
35. Agarwal R. How can we prevent intradialytic hypotension? *Curr Opin Nephrol Hypertens*. 2012;21(6):593-599.
36. Shaldon S. Dietary salt restriction and drug-free treatment of hypertension in ESRD patients: a largely abandoned therapy. *Nephrol Dial Transplant*. 2002;17(7):1163-1165.