What We Learned From the Frequent Hemodialysis Network Trials

By John T. Daugirdas, on behalf of the Frequent Hemodialysis Network Trial Group

Why the FHN trials were done

To understand why the Frequent Hemodialysis Network (FHN) Daily and Nocturnal Trials were initiated, one simply needs to look at the relationship between single-pool Kt/V (spKt/V), dialysis frequency and standard Kt/V (stKt/V), an equivalent kidney clearance, shown in Figure 1. As shown, the rather large separation (35 percent) between the values of spKt/V achieved in the randomized Hemodialysis Study (HEMO) groups was diminished to less than half of that amount when the doses were considered in terms of stKt/V (1, 2). A stKt/V in a person with a total body water volume of 35 L is roughly equivalent to a continuous clearance of 7 mL/min. Multiplying by 1.18, the difference in stKt/V of the two-dose arm, we get, for a patient of normative size, a comparison of an equivalent clearance of 7.0 versus 7.8 mL/min. In this regard, it was not surprising that the HEMO dose comparison was completely negative. As shown, by moving to a schedule of six treatments per week, one would be able to achieve stKt/V differences that would be potentially more meaningful, approaching 14 mL/min in the Daily Trial and 20 mL/min in the Nocturnal Trial (3). A second purpose of the FHN trials was to examine the effects of potentially better control of extracapillary volume that might be expected with a more frequent dialysis schedule.

What was surprising

Recruitment

We knew that we would not be able to randomize the 2000 or so patients required to examine “hard” outcomes of mortality and hospitalization. We therefore chose two intermediate outcome composites: 1) mortality, and in survivors, change in left ventricular (LV) mass; and 2) mortality, and in survivors, change in physical health composite scores. Our initial goal was to randomize 250 patients for each trial. What we did not anticipate was how difficult the recruitment would be for the Nocturnal Trial (4–6). We randomized 245 patients in the Daily Trial. For the Nocturnal Trial, the randomization target had to be reduced twice because of recruitment challenges. The recruitment target was reduced to 150 and then ultimately to 90. Ultimately in the Nocturnal Trial, 87 patients were randomized (4, 5).

Residual kidney function

Our two studies really examined different populations of dialysis patients: the daily in-center patients were largely prevalent patients who had long dialysis vintage and minimal residual renal function, whereas home nocturnal dialysis patients were largely incident patients new to dialysis with substantial urine volumes and residual renal function. To maintain generalizability and to facilitate recruitment, a higher amount of residual kidney function had to be allowed in the Nocturnal Trial compared with the Daily trial. It is possible that the inclusion of patients with substantial urine output combined with the small sample size in the Nocturnal Trial combined to limit the ability of that trial to detect a possible beneficial outcome.

LV mass: volume control and residual kidney function

In the Daily Trial, the co-primary outcomes, death or change in LV mass and death or change in self-reported physical health (based on the Physical Health Composite of the RAND-36 health survey), were improved in the group assigned to “daily” (six per week) dialysis (4). In the Nocturnal Trial, there was little signal for self-reported physical health, and a similar signal for effect of more frequent dialysis on LV mass, which was not statistically significant because of the smaller sample size (5). It can be argued that both of these outcomes were related to extracellu- lar fluid volume. Similarly, change in blood pres- sure was easily demonstrated in both trials (5–7).

We knew that echocardiographic assessment of LV hypertrophy (LVH), one of the co-primary outcomes, was unreliable in the situation of rapid shift in extracellular fluid, so we used magnetic resonance imaging. Still, given past experience, we anticipated that the majority of patients in both trials would have LVH. To our surprise, the incidence of LVH at baseline was only 34 percent in the Daily Trial and 28 percent in the Nocturnal Trial (8). Thus, for many of our patients, in terms of the primary outcome, we were looking for a fix for something that was not broken to begin with.

In analyzing our results, we found that even relatively small amounts of residual urea clearance or urine volume may have had a treatment-modifying effect; in patients with substantial residual kidney function, there was very little trend toward a benefi- cial effect of more frequent dialysis on LV mass. Another interesting finding was that in the conven- tional dialysis group, there appeared to be no progression of LVH overall during a 1- to 2-year follow-up period. If our conventional dialysis treatment was so poor, one might expect progres- sion of LVH with inadequate treatment. This was not seen, perhaps because of relatively good vol- ume control in the patients randomized to three treatments per week, perhaps because of intensified attention to this aspect of care in a trial setting.

Anemia and nutrition

We hypothesized that more frequent dialysis and increased removal of uric acid would improve anemia and nutrition. There was no evidence of benefits of the frequent dialysis interventions in either of these domains (9, 10).

Some adverse effects, one unexpected

We found an increase in vascular access proce- dures among patients randomized to frequent he- modialysis, although there was no difference in vascular access survival (11). Vascular access was a pre-specified outcome, and potential effects of frequent dialysis in this domain were anticipated. However, we did not anticipate that more frequent dialysis might have an adverse effect on residual kidney function, which was evident in the Nocturnal Trial. We did not observe a more rapid decline in residual kidney function in the Daily Trial, presumably because only patients with residual urea clearance below 3 mL/min/1.73 m² were eligible for enrollment, so it would have been more difficult to detect any change between treatment arms in terms of further decreases in residual function (12).

Prolongation of survival

As mentioned, neither of the two FHN trials had sufficient power to detect a change in survival. Still, at the outset of the trial, the investigators planned to examine the effects of frequent hemodialysis on death or non-access-related hospitalization occurring during each trial. In the FHN Daily Trial, when the mortal- ity analysis was extended beyond the initial 12-month trial period, a substantial, statistically significant benefit was seen among patients ran- domized to assignment to “daily” in-center he- modialysis. This difference in death rates was observed even though the majority of patients in the Daily Trial resumed a conventional schedule of three hemodialysis treatments per week after the 12-month study period (fewer than 1 patient in 6 continued with a schedule of four or more ses- sions per week in the 2 months after comple- tion of the 12-month intervention), whereas the majority of excess deaths in the conventional arm occurred after year 1 (13).

In the Nocturnal Trial, a substantial number of patients either continued on, or began, an extended, frequent nocturnal dialysis schedule at the conclusion of the 12-month study peri- od. Surprisingly, the group assigned to frequent nocturnal home treatments had a mortality rate that was substantially higher than the group as- signed to initially receive three treatments per week at home (14). Given the small sample sizes and other issues, the significance of these mor- tality results was unclear, but Bayesian analysis helped put them into perspective. In both tri- als, the survival rates of enrolled patients were very high, even in those patients randomized to conventional three treatments per week. Such an effect might call into question the generalizability of the results from these two trials, especially in the Nocturnal Trial, where excellent results in patients treated three times per week at home made it very difficult to detect any improvement. However, in the Daily Trial, the argument might turn in the opposite direction, i.e., that the in- clusion of sicker patients (those with more baseline LVH and also more anuric patients) might have magnified the benefits of frequent “daily”
dialysis.

Thus, overall, the data suggest both advantages and some potential disadvantages of more frequent hemodialysis (Figure 2). The FHN Trial results give some potential guidance regarding selection of patients who might benefit from more frequent schedules (pre-existing LVH or severe hypertension, low levels of residual kidney function). The results also suggest that change to a more frequent schedule in the hope of improving anemia management or nutrition is not likely to be successful. Despite our cautionary findings regarding a possible increase of vascular access events with frequent dialysis, whether or not more frequent dialysis adversely impacts the vascular access is far from being settled.

To me, personally, it was a great honor and privilege to participate in both the HEMO and the FHN trials from the outset with a most outstanding and dedicated group of investigators and support staff. The valuable results from these two trials speak for themselves, and they also emphasize the utility of, and need for, more randomized trials in the field of dialysis care.

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References

![Figure 1](image1.png)

**Figure 1**
Standard Kt/V (approximate) in the HEMO and FHN trials. A standard Kt/V of 2.0 corresponds to an equivalent continuous clearance of approximately 7 mL/min in a patient with a total body water of 35 L. Abbreviations: FHN = Frequent Hemodialysis Network; HEMO = Hemodialysis Study.

![Figure 2](image2.png)

**Figure 2**
Benefits vs. potential risks of more frequent dialysis, as determined from the Frequent Hemodialysis Network trials.