Dialysis frequency versus dialysis time, that is the question

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We reviewed a number of prospective randomized and multiple retrospective cohort studies of different dialysis prescriptions: longer dialysis time, at a frequency of at least three times a week, or a frequency of daily hemodialysis with a shorter dialysis time. Interestingly, the retrospective analyses have generally found significant survival benefits in the intensive dialysis groups, whereas more modest effects were observed in the prospective randomized controlled trials. The reason for this discrepancy may be related to the retrospective nature of the studies and possible selection bias; for example, the patients who were prescribed more frequent dialysis may have had more difficulties with volume control or high blood pressure. In contrast, the randomized controlled trials of increased dialysis frequency, which have shown indirect and modest benefits in complex coprimary end points, have small sample sizes and are plagued with difficulties in recruitment and compliance with the randomly allocated more frequent dialysis. This review, which attempts to balance the potential benefits of more frequent dialysis with the burden on the patient’s lifestyle, an increased risk of access malfunction, as well as societal costs of such intensive dialysis prescriptions, concludes in favor of the conventional three times per week dialysis (at a minimum) but at longer dialysis times than is currently prescribed based on the \( \text{Kt/V}_{\text{urea}} \) metric alone.

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Several retrospective cohort studies as well as a few prospective randomized studies have assessed the impact of changes in dialysis treatment time (TT) or dialysis frequency. The major impetus for such studies stems from the fact that the mortality and morbidity of ESRD patients undergoing hemodialysis (HD), particularly in the United States, has been unacceptably high. According to the 2012 US Renal Data System (USRDS) report, only 30% of the patients who start dialysis in the United States are still alive at 5 years, and the adjusted mortality rate in prevalent dialysis patients 65 years or older is twice as high as that of patients with cancer, and six times as high as that of the general Medicare population.¹ Comparison by DOPPS (Dialysis Outcome and Practice Patterns Study) of similar outcomes of the dialysis population in other countries, such as Japan or specific European countries where mortality rates are significantly lower, have indicated that such a high disease burden is not necessarily intrinsic to the disease process or its treatment by HD; such comparative analyses highlighted a number of modifiable parameters in the dialysis prescription, such as longer dialysis time that, if implemented in the United States, may improve patient outcomes.²

One of the earliest observational studies that highlighted the improved survival from longer dialysis times but at a frequency of three times a week came from the Tassin experience where HD had been provided three times a week for 8 h using in-center dialysis. Such longer TTs (accompanied by a strong emphasis on salt restriction) resulted in a standardized mortality rate of less than half that of concurrent patients from USRDS data.³ In contrast to the focus on dialysis session length but at a frequency of three times per week, dialysis frequency (daily or 6 days per week) has been the focus of several small studies in the United States. Kjellstrand et al.⁴ highlighted the > 25% (hazard ratio (HR) = 0.73) reduction in mortality of 150 patients who were prescribed daily in-center dialysis when compared with matched USRDS HD patients and an even greater reduction in mortality (HR = 0.5) when 265 patients were dialyzed daily at home. Similarly, Blagg et al.⁵ and Johansen et al.⁶ found that patients receiving short daily or nocturnal HD at home had a significantly lower mortality rate (HR = 0.39 and 0.64, respectively) when compared with patients receiving conventional HD in-center, matched by propensity score; such retrospective studies provided the impetus to explore
longer dialysis time and more frequent dialysis as prescription tools to improve the survival of HD patients in the United States.

**RANDOMIZED CONTROLLED TRIALS OF DIALYSIS PRESCRIPTION—CONSTANT FREQUENCY**

The National Cooperative Dialysis Study (NCDS) and the Hemodialysis Study Group (HEMO) were some of the earlier prospective randomized controlled trials to address dialysis prescriptions. Both studies attempted to examine the impact of different dialysis doses on hospitalization (NDCS) and on mortality (HEMO); both studies maintained the frequency of dialysis at three times per week and randomized patients to different doses of dialysis, using urea as the surrogate molecule.

NCDS, which was powered to detect the impact of dialysis dose on hospitalization, focused on ‘time-average concentration of urea’ (TAC$_{\text{urea}}$) and concluded that lower TAC$_{\text{urea}}$ was associated with lower hospitalization. Although NCDS included dialysis time as one of the two main intent-to-treat interventions (in the two longer dialysis time groups, mean session length was 4.3 h, compared with 3.2 h for the shorter dialysis session), the magnitude of the time effect was large, but fell just short of achieving the ‘classical’ statistical significance ($P = 0.06$). As stated by Chertow, ‘in retrospect, one might argue that the NCDS session length was the most significant (i.e., important) ‘nonsignificant’ (statistically) effect in the history of dialysis research.’ In a reanalysis of the NCDS, the TAC$_{\text{urea}}$ concept was later modified to analyze the data in terms of Kt/V (again with K and V determined only by urea) and concluded that the optimal dose of dialysis was achieved when Kt/V$_{\text{urea}}$ is $\geq 1.0$ (single pool). This reanalysis of the NCDS study did not consider dialysis time as an independent factor.

The singular focus on Kt/V gained wide acceptance in the late 1980s and resulted in a trend in which patients were dialyzed at higher blood flows, using larger surface area dialyzers to reach the minimum Kt/V in the shortest possible time. This coincided with a consistently high mortality rate in the United States, which in the early 1990s reached an annual mortality rate close to 30% and led to the planning of the HEMO study in the late 1990s.

The HEMO study attempted to compare two doses of dialysis, defined by Kt/V$_{\text{urea}}$ in 1846 patients, still keeping the dialysis frequency at three times a week. The HEMO study also attempted to define the impact of different dialysis membranes by comparing the use of high-flux and low-flux dialysis membranes, defined by their clearance of β2 microglobulin. Although in the initial ‘intent-to-treat’ analysis of the HEMO results there was no statistical difference in the mortality of patients randomized to any of the assigned therapies, in retrospect, the relatively small difference in Kt/V (20% higher in the ‘high’ Kt/V group, compared with the standard Kt/V group) and a relatively small difference in dialysis time (approximately 30 min per session longer in the high Kt/V group) may explain these negative results. One important consideration in the HEMO study is that the exclusion criterion of ‘eKt/V of 1.3 not achieved in 4.5 h’ practically excluded all patients over 100 kg and thus 97% of randomized patients weighed $< 100$ kg; indeed, the average weight of patients in the HEMO study was 69.2 kg and the average age was 57.6 years, both considerably less than those of the prevalent patients on dialysis at the time.

Nevertheless, these findings led many nephrologists to conclude that there is no benefit of increasing the dialysis dose or dialysis time for patients receiving HD three times a week.

Post-hoc analysis of the HEMO study, using an as-treated model, concluded that patients randomized to the high-flux group had statistically significant reductions in both the risk of death from cardiac causes and in the combined outcome of first hospitalization for cardiac causes and/or death, and suggested that dialysis time had a marked effect on survival particularly in the high-dose arm of the study. Although these post-hoc results were interpreted as strongly biased (dose-targeting bias), they also pointed out the possibility that total weekly dialysis time, independent of Kt/V$_{\text{urea}}$ may be a critical factor in patient outcomes.

**FHN TRIAL: RANDOMIZED CONTROLLED TRIAL OF DIFFERENT DIALYSIS FREQUENCIES**

Several investigators concluded that, to determine whether still higher doses of dialysis or longer dialysis time may result in improved patient outcomes, patients will need to receive HD more than three times per week and/or for much greater duration than the minimum time to achieve a Kt/V$_{\text{urea}}$ of $\geq 1.0$. These preliminary conclusions were the basis of the prospective randomized Frequent Hemodialysis Network trial (FHN).

There were two components of the FHN trial: in the first, patients were randomly assigned to undergo HD either six times per week or three times per week for 52 weeks. The ‘intent-to-treat’ FHN trial highlighted that in the six times per week dialysis there were significant improvements in both coprimary composite outcomes (death or change in left ventricular mass and, separately, death and/or change in physical health composite score), but, importantly, because of the relatively small number of patients in each arm (approximately 120), there was no difference in death or hospitalization (unrelated to vascular access) (HR = 0.93, $P = 0.71$) between the two groups, and the major difference was in the relatively modest reduction in left ventricular mass among the survivors of the daily HD group.

There were also no significant effects of frequent HD on cognitive performance, self-reported depression, serum albumin concentration, or the use of erythropoietin-stimulating agents.

The second component of the FHN trial was to compare daily nocturnal (6–8 h) home HD to conventional three times weekly home HD. This component of the FHN trial also suffered from a slow and difficult recruiting process, which resulted in only 87 patients to be randomized and was thus significantly underpowered. Therefore, although the
delivered dose was much higher in the nocturnal FHN arm, there was no statistical difference in the same two predefined coprimary outcomes described above. Finally, although both parts of the FHN study were ‘prospective, randomized’, the participants in the study were younger and weighed less than average than patients in the United States (e.g., 50.4 years old in the FHN study, compared with 62.8-year-old incident patients in the United States).1,13

**NON-RANDOMIZED RETROSPECTIVE COHORT TRIALS**

These results of the FHN trial are in contrast to those of several retrospective clinical studies reported by several other investigators. In a recent analysis by the International Quotidian Dialysis Registry (IQDR) in 2012, Nesrallah et al.16 compared the outcomes of >300 patients who were receiving intensive home dialysis (4.8 sessions per week, with a mean TT of 7.4 h per session) with those of 1388 patients who were in the conventional dialysis group (three sessions per week, with a mean TT of 3.9 h per session). Comparing patient outcomes, the HR of mortality in the intensive dialysis group was close to half (HR = 0.55) compared with the conventional dialysis group. Such improved patient outcomes have led Kjellstrand et al. and Paul17 to conclude that intensive HD results in a probability of survival that is similar between patients on intensive dialysis and those who have undergone deceased donor transplantation.

A similar retrospective study by Lacson et al.18 evaluated nearly 1000 patients undergoing in-center nocturnal dialysis three times weekly (7.85 h per treatment) compared with patients dialyzed with conventional dialysis (3.75 h per treatment). The authors concluded that these longer dialysis times were associated with a 25% reduction in the risk of death (HR 0.75, P < 0.004) when compared with patients in the conventional arm, after matching and adjusting for several variables using a propensity score. More recently, using propensity matching and USRDS data, Weinhandl et al.,19 also found 13% lower mortality in patients undergoing daily home dialysis compared with three times a week in-center HD patients. Thus, these three retrospective cohort studies and the accompanying editorials concluded that there is a strong association between longer HD TT (at a minimum frequency of three times per week) and improved survival.20,21

**WHY THE DIFFERENCE IN RESULTS BETWEEN THE FHN AND RETROSPECTIVE STUDIES?**

Although the prospective randomized FHN trial was positive in favor of more intensive dialysis, these results were certainly less marked than the results of the retrospective observational studies. It is perhaps worthwhile to speculate on the reasons for this disparity.

The most important, in our consideration, was that the FHN trial required patients to be ‘blindly’ randomized to either arm of the study. Several observations point to the reluctance of patients to participate in the FHN trial, including the 4-year recruitment period where over 6000 patients were screened but only 245 patients were randomized.13,22 Thus, <4% of the screened patients actually agreed to participate in the study.22 Even in those patients who were finally randomized, the acceptance of daily dialysis was relatively poor.12 This is confirmed by the large disparity in treatment attendance, which was statistically significant between the two groups (77.7% for frequent vs. 94.9% for conventional, P < 0.001).13 Thus, one of the major differences between the FHN studies and the retrospective studies may well be the acceptance (or resistance) of patients to undergo more intensive dialysis. A comparative review of the benefits and barriers of intensive dialysis, which may also influence a patient’s decision to participate in trials of intensive HD, was recently provided by Chan and colleagues.23

Another important consideration in the interpretation of the FHN trial is that in both randomized groups (short daily and conventional) the rate of fluid ultrafiltration (UFR) was very similar at approximately 10–11 ml/kg/h, a critical factor that will be discussed in more detail later.13 Although there was a statistical difference in the composite end point of ‘mortality and change in left ventricular mass’, patients assigned to frequent HD are also more likely to undergo vascular access interventions (HR = 1.71).24

It is possible therefore that the contrast between the modest difference in the coprimary outcome seen in the FHN trial (but no statistical difference in the mortality end point) and the larger difference in mortality outcomes observed in retrospective cohort studies lies in the manner in which patients were asked to participate in such studies. One presumes that the patients in the retrospective studies were educated on the advantages of more HD, either because the patients had an underlying indication for longer or more frequent dialysis (e.g., large interdialytic weight gains) leading to results in favor of more HD, but which may be affected by a bias by indication, or because of the strong conviction and recommendation of their nephrologist. Thus, the patient’s willingness to undergo the intervention along with the associated lifestyle changes is an important but difficult-to-quantitate factor in the outcome of patients facing complex therapies.

Another possible explanation for the difference in the conclusions regarding the effectiveness of frequent dialysis between the FHN trial and the retrospective cohort studies is the length of follow-up. In the FHN trial, participation was limited to 1 year, whereas the Kaplan–Meier analysis of the retrospective cohort by the IQDR indicated that the percentage survival between the conventional and intensive HD begins to diverge after 1 year.16 Potentially, the duration of participation in the FHN trial may have been too short to show a difference in mortality alone. Finally, although propensity matching or risk adjustments are partially successful in minimizing such bias, these statistical adjustments may not fully account for the differences in severity of the comorbidities or other unmeasured variations, and may also result in biased conclusions from such retrospective studies.12
Unfortunately, to further confuse the issue of dialysis time or dialysis frequency, the same investigators who highlighted the survival advantages of intensive nocturnal home dialysis discussed above (IQDR)\textsuperscript{16} have recently published a comparison of a multinational cohort study of in-center short daily HD (weekly TT 15.7 h) compared with contemporaneous patients receiving conventional (three times weekly) dialysis. Using propensity score-based matching, these investigators concluded that patients receiving short daily HD had a significantly higher mortality (HR = 1.6) compared with those receiving conventional HD.\textsuperscript{25} The mortality difference was seen in matched and unmatched adjusted analyses and was qualitatively similar across the subgroups analyzed.\textsuperscript{25} A critique of this retrospective study and its conclusions followed shortly.\textsuperscript{26}

**SO, WHAT IS THE ANSWER: DIALYSIS FREQUENCY OR DIALYSIS TIME?**

The review of the above studies does not provide a clear answer to this question. However, it would be reasonable to conclude that longer dialysis times, preferably nocturnal for 6–7 h, provided at a minimum of three times a week (or more often if it is provided at home) appears to be the dialytic therapy with the most favorable balance between benefits, risks, and lifestyle burden, and may be the therapy that is more readily accepted by patients in the long term. In the post-hoc reanalysis of patients randomized to the high-dose arm in both the NCDS and the HEMO study (both at a frequency of three times per week), an increase in dialysis time during follow-up (in an ‘as-treated’ analysis) was associated with a marked improvement in survival, whereas shorter dialysis time was associated with increased mortality risk.\textsuperscript{27} Both the nocturnal (three times a week in-center) dialysis study by Lacson and the frequent (three to seven times per week) home IQDR dialysis study that basically analyzed ‘as-treated’ patients highlighted significant survival advantages for the patients who accepted longer dialysis time, particularly in home dialysis patients, where the advantages of a reliable, self-interested, and motivated access cannulator are important but difficult-to-quantitate factors, in contrast to the FHN trial that indirectly highlighted the patient ‘burnout’ that may occur from daily travel for in-center dialysis. There is also indirect evidence that increasing the frequency of longer dialysis (e.g., 5–7 episodes of nocturnal home dialysis) may further improve patient outcomes, compared with three times a week nocturnal dialysis. In the study by Nesrallah et al.,\textsuperscript{16} nocturnal treatment with frequencies higher than three times per week had a lower hazard risk of mortality (HR = 0.55), compared with the study by Lacson et al.,\textsuperscript{18} which found an HR of 0.75 in patients undergoing in-center (three times per week) nocturnal dialysis. Nevertheless, the reduced hazard risk of mortality in the ‘longer and more frequent’ approach should be balanced against the increased burden on the patient’s quality of life, particularly if the intensive therapy is provided in-center. Longer dialysis sessions, at a frequency of at least three times a week, may also have physiologic advantages; short, daily dialysis primarily promotes the removal of urea and other small molecules, whereas the longer dialysis session is associated with a higher fractional removal of larger molecules compared with smaller molecules.\textsuperscript{28,29} Finally, longer dialysis sessions (accompanied by an emphasis on reduced dietary salt intake and an individualized or reduced dialysate sodium\textsuperscript{30}) would allow a UFR that should not exceed 10 ml/kg/h, a critical UFR above which there is an associated increase in mortality (Figure 1).\textsuperscript{31}

One potential argument against longer dialysis sessions at a frequency of only three times per week is the study by Foley et al.,\textsuperscript{32} which highlights a higher mortality rate after a long interdialytic time. Although such conclusions were derived from the USRDS data, which include primarily the traditional, brief (3.5 h) dialysis session of three times per week, it may be worthwhile to have a similar analysis in patients dialyzed for longer periods of time but at the same frequency of three times a week. If confirmed, a potential compromise is to consider alternate-day nocturnal dialysis, which may reduce the excess hazard of the longer interdialytic interval.\textsuperscript{32}

**WHAT SHOULD THE MINIMUM DIALYSIS SESSION LENGTH BE?**

Tentori et al.\textsuperscript{2} found that longer TT was strongly associated with lower mortality in Japan, Europe, Australia, and New Zealand but not in North America; however, when they...
adjusted for non-adherence, they found a similar effect of dialysis time on mortality in North America. Although longer dialysis time outside the United States is associated with financial incentives (Japan) or penalties (England) or may be the result of regulatory requirements (Germany), and the conclusion by DOPPS may reflect such ‘dose-targeting bias’, the ‘as-treated’ analysis by DOPPS provides strong support for the longer dialysis time. Longer TT was associated with lower mortality in Japan (HR = 0.75 per 30 min longer TT) and in European countries, Australia, and New Zealand (HR 0.94 per 30 min longer TT). The study by Saran et al. using the DOPPS database and more recently by Flythe et al. using the database of a large dialysis provider have both shown that the UFR has a significant impact on HD mortality rate: UFR > 10 ml/kg/h is associated with increased all-cause and cardiovascular mortality, possibly on the basis of cardiac stunning, subclinical cardiac ischemia, and hemodynamic instability during rapid ultrafiltration.

Subsequently, Flythe et al. reported on the association between TT and survival, and found a substantial mortality increase associated with a dialysis session of < 4 h, even when adjusted for body size (Figure 2). The adverse impact of short dialysis (< 4 h) session on blood pressure control was also highlighted in a study by Tandon et al. The study by Flythe was critically analyzed by Daugardas, who cautioned against interpreting these results as ‘cause and effect’ and that conclusions from such studies may reflect a ‘dose-targeting bias.’

**CONCLUSIONS**

The weight of current evidence, particularly when considering patient acceptance, compliance, and maintenance of vascular access, is in favor of increased dialysis time to at least 4 h per session, and preferably as nocturnal dialysis with each session length of 6-8 h, with a minimum frequency of three times per week (Figure 3). Longer dialysis sessions allow for a lower UFR (preferably ≤ 10 ml/kg/h) and a higher removal of middle-size molecules. Longer dialysis but at a minimum frequency of three times weekly compared with short daily dialysis also reduces the risk of malfunction of the patient’s access, an important outcome that has been discussed recently. Finally, from a societal point of view, given the extraordinarily high per-patient cost of the current ESRD program, the economic viability of more frequent in-center short dialysis strategies is questionable.

It would be ideal if our conclusions could be tested by prospective randomized studies; the likelihood of successfully financing and implementing such studies is unknown; in the meantime, we owe it to our patients to provide them with longer time therapy (> 4 h or nocturnal) at a frequency of at least three times a week that is based on a preponderance of evidence and which is consistent with physiologic principles of dialysis.

**DISCLOSURE**

The authors declared no competing interests.

**REFERENCES**

