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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 Kt/V_{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)[7] and the Hemodialysis Study Group (HEMO)[8] 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_{urea}) and concluded that lower TAC_{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 ($P = 0.06$).[7] 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.'[9] In a reanalysis of the NCDS, the TAC_{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_{urea} is $\geqslant 1.0$ (single pool).[10] 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%[1] 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_{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.[8] 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) 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.[8] 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.[11] Although these *post-hoc* results were interpreted as strongly biased (dose-targeting bias),[12] they also pointed out the possibility that total weekly dialysis time, independent of Kt/V_{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_{urea} of $\geqslant 1.0$. 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.[13] 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.[13,14]

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.[15] Therefore, although the