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See related articles, "Survival with Three-Times Weekly In-Center Nocturnal Versus Conventional Hemodialysis" and "Intensive Hemodialysis Associates with Improved Survival Compared with Conventional Hemodialysis," on pages 687–695 and 696–705, respectively.

Intensive Hemodialysis: Back to the Beginning?

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Despite the recent advances in science and technology, as well as the vast clinical experience with renal replacement therapies, patients with ESRD on maintenance dialysis suffer from unacceptably high mortality rates.¹ The epidemic of obesity and diabetes mellitus combined with the lack of robust therapies proven to delay progression of CKD render manipulation of the dialytic management strategies an obvious target for improving clinical outcomes in this highly complex patient population.

A number of landmark randomized clinical trials have been published comparing the effects of different dialytic prescriptions. The National Cooperative Dialysis Study and the Hemodialysis study paved the way for the current dialysis practice recommendations and performance measures and also suggested that minor alterations in dialysis techniques are unlikely to make a significant impact on survival.^{2,3} More recently, the Frequent Hemodialysis Network (FHN) trials of daily and nocturnal dialysis were conducted to test the hypothesis that more radical modifications in hemodialysis treatment time and/or frequency would improve patient outcomes.^{4,5} The FHN trials were designed to examine the effects of treatment on a composite of mortality, change in left ventricular mass change, and change in self-reported physical functioning. There was also a range of secondary outcomes that were evaluated in these studies.

The results of these important studies are highly publicized and discussed in various forums. An important aspect of both of these studies is that neither was powered to examine the effects of the treatment interventions on either mortality or hospitalization risks. Given the current economic climate and the priorities of the funding agencies, additional randomized clinical trials examining the effects of increasing hemodialysis frequency and/or treatment time with adequate power to assess hard outcomes are not on the horizon, which makes epidemiologic research even more important for assessing the clinical implications of increasing hemodialysis frequency and/or treatment time.

In this issue of *JASN*, the results of two important observational studies are reported examining the effects of frequency and length of hemodialysis on mortality and other important clinical outcomes. Using the International Quotidian Dialysis registry, Nesrallah *et al.*⁶ conducted a retrospective cohort study to examine whether intensive hemodialysis is associated with better survival than conventional hemodialysis. They matched 420 patients who received intensive home hemodialysis in France, the United States, and Canada between January 2000 and August 2010 with 1388 patients in the Dialysis Outcomes and Practice Patterns Study who received in-center conventional hemodialysis during the same time period by country, ESRD duration, and a propensity score based on the probability of receiving intensive hemodialysis. Their results show that intensive home hemodialysis is associated with markedly improved patient survival (hazard ratio, 0.55) compared with conventional in-center hemodialysis. The strength and direction of the observed association between intensive hemodialysis and improved survival were consistent across all prespecified subgroups and in sensitivity analyses.

In a companion article, Lacson *et al.*⁷ examine survival and clinical changes associated with conversion from conventional hemodialysis to in-center nocturnal hemodialysis in 959 consecutive patients in 77 Fresenius Medical Care (FMC) facilities during 2006 and 2007. The investigators compared mortality risk in a 1:3 propensity score–matched cohort of 746 nocturnal and 2062 control patients on conventional hemodialysis. Their results show that nocturnal hemodialysis associated with a 25% reduction in the risk for death after adjustment for age, body mass index, and dialysis vintage. Furthermore, there were favorable changes in intermediate clinical outcomes in patients on nocturnal therapy. These include improvements in serum albumin, phosphorus and hemoglobin, lower predialysis systolic BP, slower ultrafiltration rate, and lower white blood cell count during the 2-year follow-up.

The studies by Nesrallah *et al.* and Lacson *et al.* have obvious strengths in comparison to previously published reports on the same subjects. Both studies are the largest of their kind, demonstrating generally similar results to previous smaller studies. Both studies have applied rigorous statistical methods to analyze the data. Multiple sensitivity and subgroup analyses are performed, showing high internal consistency. Nesrallah *et al.* used a prospectively designed data source providing the most reliable information available for examination of quotidian dialysis. Lacson *et al.* examined the FMC database for their analysis, which has been carefully constructed and has been subject to peer review in multiple publications.

There are certain limitations of these studies, which are appropriately acknowledged by the authors. In particular, two issues are worth mentioning. First, and foremost, these are observational studies subject to bias and therefore cannot prove causality. Similarly, despite significant efforts to adjust for differences between comparison groups, a degree of residual confounding remains highly likely. For example, the higher transplantation rate observed in the nocturnal group in the study of Lacson *et al.* is an example of unaccounted partiality toward assigning select patients to nocturnal dialysis. The inherent bias to allocate a healthier and more suitable patient to more frequent or nocturnal hemodialysis can only be overcome by randomization.

Notwithstanding the aforementioned strengths and limitations, the results of these two studies have important clinical implications. Undoubtedly, these particular studies represent the largest and best-constructed cohorts to examine the effects of frequent or longer dialysis on survival. Given the low likelihood of an adequately powered randomized clinical trial to examine the effects of these interventions on similar outcomes in the near future, these reports will be the reference standard for clinical decision-making regarding modality choice in ESRD patients.

Given their strengths, these studies may also help shape the policy regarding the payment decision (allocation) for ESRD, at least in the United States. Current ESRD payment structure does not favor frequent treatments, and there are no financial incentives for prolonging treatment time.⁸ The accumulation of more reliable evidence favoring frequent and/or prolonged

hemodialysis may lead to incorporation of certain financial incentives within the payment structure to motivate suitable subjects to at least try these otherwise costly therapies. Provision of financial incentives based on certain clinical outcomes is already incorporated in the bundled payment system. Some of these outcomes such as phosphorus and hemoglobin are already shown to be influenced positively by nocturnal hemodialysis in the study by Lacson *et al.* Finally, these studies provide a detailed description of the patients who have been exposed to, and potentially benefited from, more frequent and nocturnal hemodialysis. Clearly, not every hemodialysis patient is appropriate for these treatments, and these data may allow identification of these individuals for efficient resource allocation.

In summary, convincing data are accumulating to indicate that more radical alterations in hemodialysis regimens are likely to improve patient outcomes. The excellent studies by Nesrallah *et al.* and Lacson *et al.* add further evidence to these observations. While indisputable evidence to show beneficial effect on survival can only be obtained by randomized clinical trials, it is unrealistic to expect such an initiative in the near future. Therefore, acquisition of reliable and comprehensive observational data is of the utmost importance to reliably examine the clinical consequences of more radical modifications in dialysis therapies. The International Quotidian Dialysis registry is an excellent example of such an effort.⁹ These initiatives must be expanded to include more granular data collection and extended to other subgroups for appropriate comparisons.

In the meantime, clinicians should be encouraged to use the invaluable information gathered from these studies to apply to their practice to choose the right patient for the prescribed therapy. Concurrently, given the cost and inconvenience of these treatment choices, appropriate financial incentives should be incorporated within the payment system. Advances in hemodialysis treatment has been stagnant for decades, and it might be time to go back to the beginning—an era where more frequent and longer treatment was frequently provided compared with current practice.¹⁰

DISCLOSURES

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Improvement in Kidney Function: A Real Occurrence

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CKD is thought traditionally to follow an unremittingly progressive decline over time. Because of this, guidelines and public health campaigns have focused on early detection and treatments directed to slow the progression of CKD and delay the onset of ESRD. Progression of kidney disease has been studied in both observational and clinical trial settings.^{1–7} However, there has been considerable variability in progression reported, ranging from rapid progression to nonprogressive stable kidney function to an improvement in kidney function over time.^{2,6–8} Recent studies that attempted to characterize patients who experience an improvement in kidney function were plagued by the variability inherent in serum creatinine measurements used to estimate GFR.

In this issue of *JASN*, Hu *et al.*⁹ report improvement in kidney function among a subset of patients with hypertensive CKD. The authors use data from the AASK (The African-American Study of Kidney Disease and Hypertension) trial,^{3,10} which was designed to evaluate the effect of BP and antihypertensive drug therapy on the rate of decline of renal function in participants with mild-to-moderate chronic renal insufficiency caused by hypertension. The participants were 1094 African Americans 18–70 years of age, with GFRs between 20 and 65 ml/min per 1.73 m² at enrollment. Kidney function was determined by direct measurement of GFR from ¹²⁵I-iothalamate clearances for the trial phase of the study. An equation was derived from this measured GFR data to estimate GFR (eGFR) using serum creatinine. This eGFR was used for the longitudinal assessment of kidney function.

To avoid the acute hemodynamic changes in eGFR related to drug interventions, the authors focused on chronic eGFR slopes among the 949 participants with three or more eGFR measurements (61% male) with a baseline mean age of 55 (SD:11) years. During the 8.8 years of follow-up, the median number of eGFR measurements was 16. Bayesian linear mixed effects models were applied to derive the probability that each patient's true underlying slope was greater than zero and could not be explained by random measurement variation; clear improvers were defined as patients with a probability of at least 0.95 of having positive eGFR slopes. Among the participants, 3.3% ($n=31$) demonstrated clear positive eGFR slopes—that is an improvement in kidney function over time. The mean slope of these patients was +1.06 (SD: 0.12) ml/min per 1.73 m² per year, compared with –2.45 (SD: 0.07) ml/min per 1.73 m² per year among remaining patients. Relative to nonimprovers, improvers were more likely to be younger, have low baseline proteinuria, and lower BP goal assignment at randomization. Younger age and lower levels of proteinuria were associated with improvement in kidney function in the multivariate model.

Methodological and analytical differences across studies make it difficult to directly compare results from prior studies to those reported by Hu *et al.* However, several prior studies have