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See related article, "Generation of Urinary Albumin Fragments Does Not Require Proximal Tubular Uptake," on pages 591–596.

The Eternal (Nocturnal) Quest for Better Dialysis Outcomes

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Twenty years ago, Bernard Charra and colleagues from Tassin, France, published a seminal paper on the survival rate of patients undergoing thrice weekly 8-hour in-center hemodialysis (HD) treatments.[1] This publication, which still represents the gold standard for outcome in thrice weekly dialysis regimens, induced a global search for improved dialysis regimens leading to better outcomes. Twenty years, millions of dollars, and a multitude of clinical studies later, the quest for improved dialysis outcomes is still ongoing.

The first decade since 1992 was mainly Kt/V-oriented, with clinical studies trying to define an optimum dialysis dose with respect to the diffusive elimination of small water-soluble uremic compounds. Eventually, the HEMO study, a randomized controlled trial comparing sessional target Kt/Vs of 1.20 and 1.45, put an end to this discussion by demonstrating in thrice weekly conventional HD that increasing sessional target Kt/V beyond 1.2 did not improve survival further.[2] Recognition of these obvious limitations of a urea-centered dialysis world led to renewed interest in the removal of other potentially relevant azotemic toxins such as β-2-microglobulin, phosphate, and middle molecules.

At the beginning of the second decade after Tassin, the research focus shifted toward convection, dialysis length, and treatment frequency. Several randomized controlled studies comparing hemodiafiltration (HDF) with conventional low or high-flux HD were initiated, which have either recently been completed or are still ongoing. Data from two of those studies, the Dutch Convective Transport Study and a Turkish study, have been presented in oral or abstract form in 2011, indicating that increasing convection by thrice weekly 3- to 5-hour on-line HDF had no significant effect on the outcome of dialysis patients.

At the same time, there was an accumulation of encouraging data from small controlled or larger observational studies on the positive effects of more intense dialysis regimens on patient satisfaction and outcome. To answer the crucial question, whether the outcome of dialysis patients is significantly improved by maximally increasing dialysis dose and frequency, the two-armed Frequent Hemodialysis Network (FHN) Study was initiated. The first arm of the study examined the effect of short daily in-center HD compared with conventional thrice weekly HD over a 12-month period and had a positive result with the two primary endpoints, mortality or increase in left ventricular mass, and mortality or decrease in physical health composite score, being significantly lower in the more frequent HD group.[3] The second arm was designed to examine the effect of daily nocturnal, 6- to 8-hour home HD compared with conventional thrice weekly home HD. Although in the nocturnal FHN arm, the delivered dialysis dose was profoundly higher than in the short FHN arm, there was no effect on the same predefined primary outcome parameters.[4] The nocturnal FHN arm suffered from a slow and difficult recruiting process, which allowed only 87 patients to be randomized and thus may be considered severely underpowered.[5] Because the FHN nocturnal study was not able to give the desired final answer on dialysis dosing, the book on nocturnal HD is not closed.

Twenty years after the Charra publication, it appears that there is a revival of thrice weekly in-center nocturnal HD, not only in Europe, but also in the United States, where, for example,

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in-center nocturnal HD is offered by >120 Fresenius Medical Care North America dialysis units to more than 1400 patients.[6] This large in-center nocturnal HD population builds a solid basis for observational outcome studies, such as the one by Lacson *et al.* published in this issue of *JASN*.[7]

They report on 2-year survival of 746 patients who converted to in-center nocturnal HD for the first time during 2006 and 2007 compared with a propensity score-matched control cohort of 2062 dialysis patients undergoing conventional thrice weekly 3- to 5-hour HD. Their data show an impressive 25% reduction of mortality risk in the in-center nocturnal HD group together with an improvement of several relevant clinical features and biomarkers, such as BP control, phosphate levels, and body weight. As with any observational study, these data demonstrate an association between extended dialysis length and outcome rather than a causal relationship.

For interpretation, it is important to understand some caveats of this study. The in-center nocturnal HD group was a selected patient population of younger, mainly male African Americans with a body mass index >30 kg/m^2, which were in many cases referred for in-center nocturnal HD for reasons of high ultrafiltration requirements, making it difficult to reach target postdialysis weights within the constraints of conventional dialysis. The relatively low baseline mortality risk associated with these in-center nocturnal HD patient characteristics is reflected in the only 15% 1-year mortality rate observed in the propensity score-matched control cohort, which is better than overall prevalent dialysis mortality rates of approximately 21% reported in the United States for 2008. It can be concluded that preferentially younger, heavier, and healthier low-risk dialysis patients are represented in the in-center nocturnal HD group.

The propensity score was based on age, sex, race, dialysis vintage, diabetes, body mass index, and vascular access. The fact that there was no information available on comorbid conditions leaves room for substantial residual confounding. Importantly, besides serum albumin levels, there was little information on the general health status of the patient population. There are some indications that the general health status may have been substantially better in the in-center nocturnal HD group. The strongest indicator is the large difference in the dropout rate for kidney transplantation, which was 12% in the nocturnal HD cohort compared with only 6% in the control group. This may be caused by a higher fraction of nocturnal HD patients registered on a waitlist for kidney transplantation rather than by better survival of these patients, as suggested by the authors. In another study on frequent HD published in this issue of *JASN* by Nesrallah *et al.*,[8] where propensity scores included the status of waitlist registration, transplantation rates between conventionally and more intensively treated cohorts of dialysis patients were similar. Transplant eligibility is a good indicator of general health status of dialysis patients and should be included in propensity scores in all future studies on dialysis outcomes.

In almost 50% of in-center nocturnal HD patients, a central venous catheter (CVC) was used for vascular access. Taking into consideration the relatively young age and healthy condition of the patient cohort, this number is alarming and a cause for concern. At first view, the use of CVCs for in-center nocturnal HD may allow for better sleep quality during treatment and thus appears attractive for patients and also for dialysis staff. However, CVCs impose an unnecessary infection risk to patients and increase long-term mortality, whereas dialysis with a fistula is recognized to be associated with better outcome.[9] The report by Lacson *et al.* does not include data on hospitalization or infection rates, and it is not clear as to what respect the low 2-year technique survival rate of only 25% may be caused by catheter problems. Data from other countries clearly demonstrate the feasibility of using native fistulas in >90% of in-center nocturnal HD patients.[10] Especially in nocturnal HD programs, the "Fistula First" approach should be of highest priority.[11]

At the beginning of the third decade after Tassin, we are still unable to reach the low mortality rates described by Charra and colleagues in the majority of their dialysis patients. We have come a long way to realize that dialysis dose, length, and frequency are important aspects of a general strategy to reach the goal of improved outcomes and that these factors need to be complemented by many other measures, such as adequate nutritional support, achievement of mineral and salt homeostasis, BP control, and, last but not least, prevention of complications, such as catheter infections. We cannot go this alone. Good arguments can also be made for finding a way to improve the health literacy of our patients.[12]

DISCLOSURES

None.

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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.