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"Wishing Don't Make it So"—Why We Need a Randomized Clinical Trial of High-Intensity Hemodialysis

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Defining the Issue

Simply put, there is a stubborn problem in the modern practice of dialysis for end-stage renal disease (ESRD) in the US—mortality. Despite the availability of advanced technology, a well-trained workforce that includes thousands of physicians, and broad access to therapy because of Medicare and other health insurance coverage, annual mortality rates remain distressingly high: in the range of 20% or more (1). Life expectancies for persons with ESRD are at or below those associated with the most malignant of diseases, including metastatic colorectal and breast carcinoma, advanced heart failure, cirrhosis, and AIDS. Although epidemiologic studies have identified some important correlates of mortality and morbidity (*e.g.*, advanced age, white race, diabetes mellitus, anemia, and markers of malnutrition and inflammation), few interventions have materially influenced outcomes in this population. Major efforts that are underway include the HEMOdialysis study, a 7-yr NIH-funded randomized clinical trial (RCT) comparing two dose ranges of hemodialysis using urea kinetic modeling, in which subjects were randomized to receive an equilibrated Kt/V (eKt/V) of 1.05 *versus* 1.45. A study examining the effects of the HMG-CoA reductase inhibitor, cerivastatin, on mortality and cardiovascular events was recently discontinued due to safety considerations. Another NIH-funded RCT aimed to reduce vascular access thrombosis will begin shortly (the Dialysis Access Consortium).

Although we struggle with why we have observed such a high mortality rate in the US ESRD population, we are reminded that outcomes elsewhere in the world and in some parts of the US are less discouraging. The patients of Charra *et al.* (2) have consistently achieved annual mortality rates below 10% in the Tassin region in the south of France, despite a case mix similar to the United States. The nocturnal hemodialysis schedule (8 h, thrice weekly) at Tassin provides more than twice the number of dialysis hours than most US patients receive. Charra and colleagues have consistently observed improved control of hypertension, volume overload, and uremic symptoms in the Tassin patients, despite more liberal dietary intake, and in the vast majority of patients (>90%), freedom from antihypertensive and other medications that are prescribed routinely for hemodialysis patients in the US.

Although unconventional, Charra *et al.* (2) have not been alone in prescribing "high-intensity" dialysis. Buoncristiani *et al.* (3) are often credited for pioneering the practice of "daily" dialysis (5 to 6 times per wk) and were among the first to publish favorable results. Soon after, Pierratos *et al.* (4) pioneered high-intensity home dialysis in Toronto, Ontario.

In the United States, relatively few clinicians and investigators have challenged the thrice weekly, short time (≤4 h) hemodialysis schedule that has become the solid standard of care. However, within the past five years, centers in Virginia, Washington State, and elsewhere have reported provocative results, and the dialysis community has taken notice (the invited lectures covering high-intensity hemodialysis at the 2000 American Society of Nephrology in Toronto, Ontario, were among the most well-attended of any session in recent memory). The interest and commitment on the part of the National Institutes of Health and the Center for Medicare and Medicaid Services (formerly the Health Care Financing Administration) is impressive Those who have promoted novel, more intensive dialytic approaches have clearly been heard. Now the question remains—how do we proceed?

Terminology—"High-Intensity" Hemodialysis

Before examining existing evidence on the use of high-intensity hemodialysis and addressing the need (or lack thereof) for an RCT, we must determine the appropriate terminology for the methods of dialysis in use today. In this domain, Prof. Z. Twardowski (5) deserves credit for humorously delineating the inconsistencies of the current nomenclature. For instance, the term "daily dialysis" may not accurately reflect either the frequency (*e.g.*, 5 to 6 times per week, not 7), or the timing (*i.e.*, daytime, or hemeral *versus* nocturnal). He suggests the term "quotidian," from the Latin *quotidie*, each day. Although quotidian is an improvement over "daily" or "daily nightly," it does not acknowledge intensive intermittent therapy, such as that practiced in Tassin, a program for which we have more data than virtually any other. The term "high-intensity" hemodialysis is suggested here, without any specific reference to urea kinetic modeling or any target value of urea or other solute clearance. Any hemodialytic method providing significantly more time or frequency (≥4 times per wk), day or night, in-home or in-center, would be included within this construct.

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The Totality of Evidence

The level of enthusiasm for high-intensity dialysis has been fueled by ongoing frustration with high mortality and hospitalization rates for conventional dialysis and less-than-optimal rehabilitation and health-related quality of life. As with most professionals, we have a strong desire to believe in what we do. However, "wishing don't make it so."

The evidence base on which high-intensity hemodialysis stands is weak. Aside from the Tassin experience in several hundred patients over more than a decade, most published reports include 5 to 20 patients, often carefully selected for motivation and other clinical characteristics, including in some cases the facility to undergo dialysis at home with little or no monitoring. Table 1 summarizes the available reports that have been published as peer-reviewed manuscripts (data published only in abstract form were not included). This table was not meant to serve as a comprehensive review of high-intensity dialysis experience; Lacson and Diaz-Buxo (6) have recently provided a thorough review published elsewhere. Rather, Table 1 serves to provide the reader with an outline of study characteristics and quality frequently used by experts who judge the strength of published evidence. It is worth noting that none of

Table 1. Characteristics of selected published studies of high-intensity hemodialysis[a]

Study	Randomized?	Blinded?	Prospective?	Outcomes	Comparison Group	Concurrent or Historical Control?	Conclusion
DePalma *et al.*, 1969 (8)	No	No	Yes	BP Body weight Serum creatinine	Same subjects[b]	Historical	More frequent home-based hemodialysis is feasible
Buoncristiani *et al.*, 1988 (3)	No	No	Yes	BP Dry body weight Hemoglobin Chemistries	Same subjects[b]	Historical	Daily hemodialysis improves hypertension control and corrects metabolic abnormalities
Charra *et al.*, 1992 (2)	No	No	Yes	Survival Hospitalization BP Serum phosphate Dry body weight	None	Not applicable	Nocturnal hemodialysis controls hypertension and volume overload and reduces death and cardiovascular disease
O'Sullivan *et al.*, 1998 (9)	No	No	Yes	BP Dietary intake Chemistries	Same subjects[b]	Historical	Nocturnal hemodialysis improves biochemical and hormonal millieu
Mucsi *et al.*, 1998 (10)	No	No	Yes	Serum phosphate Serum calcium	Same subjects[b]	Historical	Nocturnal hemodialysis improves phosphorus control
Woods *et al.*, 1999 (11)	No	No	No	Survival Fistula patency BP Dry body weight Hematocrit Serum albumin	Same subjects[b]	Historical	Daily hemodialysis improves hypertension control and corrects nutritional and metabolic abnormalities. Vascular access patency rates and corrects nutritional and metabolic
Kooistra and Vos, 1999 (12)	No	No	Yes	BP Volume control HR-QOL (Nottingham Health Profile and SF-36)	Same subjects[b]	Historical	Daily home hemodialysis improved BP, volume control, and general physical and mental health with fewer and less dramatic metabolic changes than other reports
Lockridge *et al.*, 1999 (13)	No	No	Yes	HR-QOL (SF-36) BP Anti-HTN drugs Binders Erythropoietin Hospital days Costs	Same subjects[b]	Historical	Dramatic improvement in many parameters, marked reduction in anti-HTN, binder, and EPO use. No inference tests conducted
Pinciaroli, 1999 (14)	No	No	No	BP Hemoglobin LV dimensions Body weight Serum albumin, transferrin, total protein Hormones Erectile function	Same subjects[b]	Historical	Partial correction of uremic hormonal millieu, and improved nutritional status
Hanly and Pierratos, 2001 (15)	No	No	Yes	Apneic episodes during sleep Apnea-hypopnea index	Same subjects[b]	Historical	Nocturnal hemodialysis corrects sleep apnea

[a] HR-QOL, health related quality of life; HTN, hypertension; LV, left ventricular.
[b] Not a crossover design; order = (1) conventional, then (2) extended duration or frequency; no return to conventional therapy.

the published reports were derived from RCT. Lindsay (7) reported the only prospective (nonrandomized) trial, although the results have not yet been published except in abstract form. The majority of published studies are unidirectional case series with all subjects beginning on conventional hemodialysis and with no crossover back to conventional therapy after experiencing high-intensity hemodialysis.

Despite the paucity of data, some advocates of high-intensity hemodialysis have argued that an RCT comparing conventional *versus* high-intensity therapy should not be performed because high-intensity therapy is so clearly superior to conventional therapy so as to render such a study unethical. Others argue that a registry of patients treated with high-intensity hemodialysis and examined using techniques of observational data analysis will so clearly demonstrate the superiority of the technique and that an RCT would be a waste of research effort and expense. I find these arguments fully unsatisfactory. Although few would doubt the economic importance of erythropoietin dosing or the potential clinical benefits that might be gained with better control of hypertension, anemia, hyperphosphatemia, and endocrinopathies, modest changes in these intermediate outcomes are hardly sufficient to warrant a profound change in practice and an enormous increase in the expense of hemodialysis. Moreover, although high-intensity hemodialysis may improve health-related quality of life in selected individuals, it may have dysutility in others in relation to the increase in direct time and effort involved. To answer the fundamental questions of whether high-intensity hemodialysis improves outcomes, and if so, by how much, we should move forward with an RCT.

Feasibility

Some have suggested that an RCT of conventional *versus* high-intensity dialysis is not feasible and that persons with ESRD would not be willing to be randomized. These arguments have come from both sides—practitioners with experience in high-intensity hemodialysis, who state that conventional hemodialysis would be unacceptable, and more commonly from those who do not believe that ESRD patients would accept such a time-intensive regimen if given the choice between the two. I disagree, twice.

In truth, we do not know whether high-intensity hemodialysis will be more efficacious or whether any benefit might be considered worthwhile in a quality-adjusted analysis, such as the QTWiST (quality-adjusted time without symptoms or toxicity of therapy). However, we will not achieve significant improvements without further, more thorough clinical research. If practitioners who maintain equipoise communicate effectively with their patients, all would realize that trying something new might be of benefit, not only to participants directly, but to others who in the future may share their suffering. Indeed, if nephrologists, nurses, and social workers educated ESRD patients more regularly regarding average life expectancies in ESRD and how certain actions might affect an individual's risk, we might see fewer "difficult" or "noncompliant" patients in the US hemodialysis program.

Breast cancer is a serious condition. Whether radical mastectomy or lumpectomy and radiation therapy was superior was unknown. Yet dedicated oncology researchers with equipoise (being "on the fence") were able to randomize large numbers of women, despite the profound effects on body image associated with the two methods of cancer control. Comparing coronary artery bypass grafting surgery with medical therapy is another well-known example of a clinical decision for which randomization was effectively performed. When considering these experiences, few nephrologists can claim that an RCT of high-intensity *versus* conventional hemodialysis is not feasible. It's all about education and equipoise.

Outcomes and Summary

This editorial is not the venue to describe a particular study design for an RCT, which would require more detail and words than are available here. However, I would propose that an RCT not be limited to one form of high-intensity hemodialysis. In other words, it should not be restricted to in-center daily therapy while excluding home-based therapies and *vice versa*. To be generalizable, high-intensity hemodialysis strategies should be flexible; if there is truly a substantial benefit to much more intensive therapy than is currently being delivered, then the exact timing, duration, and locale should not be critical. The primary outcome of a high-intensity hemodialysis trial should be mortality alone, or mortality combined with a major morbid event whose frequency might be expected to be reduced by a more intensive dialysis regimen (*e.g.*, mortality or nonfatal myocardial infarction or stroke). The link between intermediate outcomes and mortality and morbidity in hemodialysis patients is too weak to justify a major RCT aimed to change them. Although the sample size needed to identify a significant change in a Short Form–36 subscale score (a continuous variable) would likely be much smaller than the sample size required to show a significant increase in survival (if an increase truly existed), we should not be tempted into doing the wrong study.

Now is the time for the nephrology community, guided by the NIH and CMS, to properly test the hypothesis boldly generated by the clinicians, investigators, and ESRD patients who have at once challenged conventional hemodialysis and conventional wisdom. Wishing, simply, don't make it so.

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