

Hemodialysis Research Update: **A Summary of Current Projects and What Lies Ahead**

Martin Kuhlmann, Peter Kotanko, Nathan W. Levin

Frequent Hemodialysis Network (FHN) Trial

Previous observational studies had suggested that the high mortality and morbidity of ESRD patients on hemodialysis (HD) might be improved by increasing the delivered dose of dialysis. This hypothesis was recently tested in the HEMO study (1). Patients on conventional, three-times-weekly HD were randomized in a 2x2 factorial design to receive an eKt/V_{urea} of 1.45 versus 1.15, or high-flux versus low-flux dialyzers. There were no significant differences between the two dose groups with respect to mortality, hospitalizations, or other secondary endpoints. However, females benefited from the intensified dialysis treatment and an advantage of high-flux dialyzers compared to low-flux dialyzers for cardiovascular outcomes on secondary analysis was shown.

The negative findings of the HEMO study have been explained in several ways: since solute removal occurs predominantly early during HD, minimal increases in time on conventional HD may have little effect; the long interdialytic interval results in large peaks and valleys in blood solute concentrations; a relatively short increase in time on conventional HD does not result in substantial increases in removal of toxic middle molecules and phosphate; increasing HD session time does not prevent extracellular fluid accumulation during the long interdialytic period. From a perspective of weekly dialysis dose

expressed as an equivalent of continuous renal urea clearance (standard Kt/V), the difference between the two groups was only small. Standard Kt/V increased by 20-30% from 2.2 to 2.8 per week. Much higher weekly dialysis doses can be achieved by increasing the frequency of dialysis.

The multi-center, randomized, controlled Frequent Hemodialysis Network (FHN) trial aims to compare nocturnal home dialysis (6x/week; 125 patients) with conventional in-center dialysis (125 patients), and short, daily in-center dialysis (6x/week; 125 patients) with conventional thrice weekly hemodialysis (125 patients). The trial will be performed with high-flux dialyzers.

The FHN trial commenced in December 2003 is expected to be completed by November 2008 (FHN, <https://clinapps.bio.ri.ccf.org/fhn/webdocs/fhn.html>). Patient enrollment started in January 2006. Each patient will be treated and followed for 12 months; patient follow-up will end on June 30, 2008. Trial results will be available by the end of 2008. Nathan W. Levin (Renal Research Institute; New York) and Glenn Chertow (University of California San Francisco) are the principal investigators of the daily study; Robert Lindsay (University of Western Ontario, London, Ontario) is co-principal investigator; Michael V. Rocco (Wake Forest University) is the principal investigator of the nocturnal study.

For the daily study, subjects will be recruited from dialysis units affiliated with clinical centers in the United States and Canada. Daily HD will be delivered for 1.5 to 2.75 hours, six days per week. The dialysis prescriptions will target an eKt/V of 0.9 at each of the six weekly dialysis sessions.

For the nocturnal home hemodialysis arm, patients will be recruited from clinical centers in the United States and Canada. Patients assigned to the six-times-per-week nocturnal dialysis will follow any dialysis pre-

Martin Kuhlmann, MD is director of the Department of Nephrology at Vivantes-Klinikum im Friedrichshain in Berlin, Germany.

Peter Kotanko, MD is research laboratory director at the Renal research Institute in New York, NY and is deputy head of the department of internal medicine at the Krankenhaus der Barmherzigen Bruder in Graz, Austria.

Nathan W. Levin, MD is medical and research director at the Renal Research Institute in New York, NY and clinical professor of medicine at Albert Einstein College of Medicine.

Table 1. Primary and main secondary outcomes: All changes are measured over 12 months (daily study) and 14 months (nocturnal study) of follow-up.

<p style="text-align: center;">Domain:</p> <ul style="list-style-type: none"> • Cardiovascular structure and function • Health-related quality of life and physical function 	<p style="text-align: center;">Co-Primary Outcome:</p> <ul style="list-style-type: none"> • Composite of mortality and change in left-ventricular mass index by cine-MRI • Composite of mortality and change in SF-36 RAND physical health composite score
<p style="text-align: center;">Domain:</p> <ul style="list-style-type: none"> • Cardiovascular structure and function • Health-related quality of life/physical function • Depression/burden of illness • Cognitive function • Nutrition and inflammation • Mineral metabolism • Survival and hospitalisations • Hypertension • Anemia 	<p style="text-align: center;">Main Secondary Outcome Measure:</p> <ul style="list-style-type: none"> • Change in left ventricular mass index by cine-MRI • Change in SF-36 RAND physical health composite score • Change in Beck depression inventory score • Change in trail making test B score • Change in serum albumin concentration • Change in pre-dialysis serum phosphorus concentration • Rate of non-access hospitalization or death

scription provided their prescribed standard-Kt/V is at least 4.0 and treatment time is at least six hours, six times per week. In the conventional HD group, subjects will remain on their usual dialysis prescriptions subject to a minimum prescribed eKt/V of 1.1. The projected median weekly treatment time is 14.2 hours in the daily HD arm and 10.5 hours in the conventional HD arm.

The primary and main secondary outcomes are listed in Table 1 (<https://clinapps.bio.ri.ccf.org/fhn/web-docs/fhn.html>).

From the FHN study, a definitive answer on the significance of daily hemodialysis can be expected; this trial will have important implications for dialysis therapy in the next decade.

International Mortality Differences

Mortality rates within dialysis populations remain excessive worldwide with significant national, racial, and ethnic differences in dialysis patient mortality rates. These differences were initially considered to be the result of differences in practice patterns or of differences in dietary behavior, but even after several years of study these differences are largely unexplained. In a cross-sectional, multinational study, all-cause and atherosclerotic cardiovascular disease mortality rates were compared between general populations and dialysis populations

using most recent data from the WHO mortality database (67 countries; 1.57 billion population) and from national renal registries (26 countries; 623,900 population). Atherosclerotic cardiovascular disease mortality rates in dialysis populations and in the general populations were significantly correlated with Eastern European countries clustering in the upper and Southeast and East Asian countries in the lower rate ranges (Yoshino M, et al.; abstract presented at the meeting of the American Society of Nephrology, 2004).

It is concluded that a substantial portion of the variability in mortality rates observed across dialysis populations worldwide is attributable to the variability in background atherosclerotic cardiovascular disease mortality rates in the respective general populations. Genetic and environmental factors may underlie these differences.

What's on the Horizon?

Dry Weight Monitor

Hydration status is related to clinical outcome in long-term dialysis patients, with chronic overhydration being associated with arterial hypertension, left ventricular hypertrophy and dilatation, and congestive heart failure (2). Optimal management of hydration status involves restriction of interdialytic fluid and sodium intake, and strict definition of dry weight. Dry weight is defined as

the post-dialysis weight at which the patient is as close as possible to a normal hydration state, which can be defined by total body extracellular fluid volume (ECV) in the normal range of a healthy population. Clinically determination of dry weight is difficult due to the fact that some liters of fluid may accumulate in the body before edema becomes evident. In clinical practice dry weight is currently determined as the lowest weight a patient can tolerate without developing intra- or interdialytic symptoms. The problem with this method is the risk for the occurrence of intradialytic hypotensive episodes, which have been shown to be independently associated with an increased mortality risk. Intradialytic hypotensive episodes may occur despite the presence of marked overhydration, especially in the presence of cardiac failure and autonomic dysfunction. Objective methods for determination of dry weight are needed.

Since bioelectrical impedance technology (BI) allows for direct estimation of whole body ECV, several approaches to dry weight determination utilizing BI technology have been developed. Several groups have proposed to predict an absolute dry weight from one pre-dialysis measurement of whole body ECV. Absolute dry weight is then derived from comparing the measured pre-HD ECV with the normal ECV range of a matched healthy population (3, 4). This comparison with a healthy population, however, poses a problem since the variation of normal ECV varies by more than 2 kg. Further refinements of these methods, especially in regard of a narrower normal ECV range, are the subject of ongoing research.

A newly developed method of continuous intradialytic calf-bioimpedance spectroscopy (BIS) is based on the innovative idea that changes in calf-ECV directly reflect changes in whole body ECV during HD (5). It is assumed that during HD the calf will be the last region of the body from which excess ECV will be completely removed, because, due to gravity effects, the relative volume of excess ECV is higher in the calf than in the arm or trunk. Thus, calf-ECV may be used as a window to monitor intradialytic changes in whole body ECV. Using multifrequency BI technology, the changes in extracellular resistance over a short distance of 10 cm across the lateral side of one calf are continuously recorded during HD. These changes, which directly reflect changes in calf ECV, are displayed in real-time in the form of a BI-curve. During removal of excess ECV from the calf, the slope of the BI-curve declines. It is

considered that the occurrence of a stable flattening of the BI-curve despite ongoing ultrafiltration indicates that all excess ECV has been removed from the calf. Thus, the new calf-BI method allows identification of the time point during HD at which all excess ECV has been removed and the patient is assumed to be at dry weight. At this time point ultrafiltration should then be stopped and the patient's weight at this time is assumed the individual dry weight. Continuation of UF beyond this point will be associated with a potentially rapid decline of blood volume and an increasing risk for the occurrence of intradialytic complications. Preliminary results of an ongoing study show that the dry weight determined by the calf-BI method is on average 700 g higher than the weight where symptoms of underhydration occur. In some instances, flattening of the BI-curve may be observed independent from dry weight, for example when UF is stopped or ECV removal from the calf is hindered due to venous thrombosis or lymphatic edema. This new method still needs external validation, but appears to be a promising tool for determination of dry weight in hemodialysis patients. Recent data obtained in patients on short daily hemodialysis treatment indicate that achievement of an accurate dry weight may even reduce the inflammatory burden of dialysis patients, an important contributor to cardiovascular mortality in this patient population.

Artificial Wearable Kidney

Recently a human nephron filter (HNF) utilizing nanotechnology has been proposed (6) that would eventually make feasible a continuously functioning, wearable or implantable artificial kidney. The device consists of two membranes operating in series within one device cartridge, creating an ultrafiltrate of plasma containing a full spectrum of desirable and undesirable solutes. The first membrane (G membrane) mimics the function of the glomerulus, using convective transport to generate a plasma ultrafiltrate; this commercial G membrane discriminates between solutes based on molecular size containing all solutes approaching the molecular weight of albumin. The second membrane (T membrane) mimics the function of the renal tubules, rejecting the majority of solutes but selectively reclaiming designated solutes to maintain body homeostasis. The T membrane is supported on a substrate and contains the molecularly engineered pores that make this technology unique. Each pore is a designed discriminator, and the membrane is

made up of a two-dimensional array of pores. Total surface area needed is just over 0.01 square meters. The membrane consists of approximately 1.6×10^{16} pores, 1 to 5 nm apart. Pores can be constructed in various sizes and shapes. A pore library will permit custom membranes to be produced, depending on patient needs. No dialysis solution is used in this device. The HNF has been computer-modeled: operating the HNF 12 hr per day, seven days per week provides the equivalent of 30 mL/min glomerular filtration rate. Animal studies have been announced to within two years.

What are the Challenges?

Care of HD Patients With Low Blood Pressure, CHF, and Autonomic Neuropathy

The number of dialysis patients with heart disease is steadily increasing. In patients with congestive heart failure, the development of low blood pressure is associated with poor outcome. Low blood pressure is a particular risk in patients on hemodialysis, and its presence is associated with poor survival. In order to deal with that group of patients, proper diagnosis is required. Many patients with systolic blood pressure below 120 mmHg pre-dialysis may have heart failure, including diastolic dysfunction. Autonomic neuropathy with an inability to respond adequately to hemodynamic challenges such as fluid removal during dialysis and may play an additional role. More frequent and prolonged dialysis sessions may be the preferred therapeutic option on these patients (7).

Vascular Access Monitoring

Vascular access failure is one of the largest causes of morbidity for chronic hemodialysis patients: 16 to 25% of hospital admissions among United States end-stage renal disease (ESRD) patients are related to vascular access complications (8). The most frequent cause of AV access-graft failure is thrombosis that occurs as a result of stenosis at or near the venous anastomosis. Over 50% of existing vascular access-grafts in the U.S. are 6 mm PTFE tubes and their thrombosis rate is much higher than that of native arteriovenous fistulas.

Several studies have shown that early detection and repair of stenosis can prevent access thrombosis (9). The cost of duplex ultrasound for access monitoring is prohibitive. Blood flow, measured by indicator-dilution methods, seems to be a reliable indicator of impending

access failure, but recent randomized controlled studies intended to examine this were equivocal (10, 11).

A prospective randomized study in 220 patients funded by the NIH aims to determine if a new Doppler ultrasound instrument to monitor access blood flow can reduce graft failure and associated costs. In a pilot study using the new Doppler ultrasound instrument for weekly monitoring, conducted by the Renal Research Institute, New York, and funded by the NIH, the method predicted impending graft failure with 80% sensitivity and a false-alarm rate of less than 0.5/year. It measures access blood flow in less than three minutes, and uses almost no consumables. ■

References

1. **Eknoyan G, Beck GJ, Cheung AK, et al.** Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002;347(25):2010-9.
2. **Parfrey PS, Harnett JD, Griffiths SM, Gault MH, Barre PE.** Congestive heart failure in dialysis patients. *Arch Intern Med* 1988;148(7):1519-25.
3. **Chamney PW, Kramer M, Rode C, Kleinekofort W, Wizemann V.** A new technique for establishing dry weight in hemodialysis patients via whole body bioimpedance. *Kidney Int* 2002;61(6):2250-8.
4. **Piccoli A, Rossi B, Pillon L, Bucciante G.** A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. *Kidney Int* 1994;46(2):534-9.
5. **Zhu F, Kuhlmann MK, Sarkar S, et al.** Adjustment of dry weight in hemodialysis patients using intradialytic continuous multifrequency bioimpedance of the calf. *Int J Artif Organs* 2004;27(2):104-9.
6. **Nissenson AR, Ronco C, Pergamit G, Edelstein M, Watts R.** The human nephron filter: toward a continuously functioning, implantable artificial nephron system. *Blood Purif* 2005;23(4):269-74.
7. **Ayus JC, Mizani MR, Achinger SG, Thadhani R, Go AS, Lee S.** Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol* 2005;16(9):2778-88.
8. **Silver MR, Cain JA.** Managing the lifeline: preemptive access management for better outcomes for hemodialysis patients and programs. *Medical Review Board of The Renal Network, Inc. Adv Ren Replace Ther* 2000;7(4 Suppl 1):S45-55.
9. **McCarley P, Wingard RL, Shyr Y, Pettus W, Hakim RM, Ikizler TA.** Vascular access blood flow monitoring reduces access morbidity and costs. *Kidney Int* 2001;60(3):1164-72.
10. **Ram SJ, Work J, Caldito GC, Eason JM, Pervez A, Paulson WD.** A randomized controlled trial of blood flow and stenosis surveillance of hemodialysis grafts. *Kidney Int* 2003;64(1):272-80.
11. **Moist LM, Churchill DN, House AA, et al.** Regular monitoring of access flow compared with monitoring of venous pressure fails to improve graft survival. *J Am Soc Nephrol* 2003;14(10):2645-53.

The Dawn of a New Era in Weighing Systems!



Innovative Stow-A-Weigh® Fold-Up Scales by Scale-Tronix.

Now there are stand-on, wheelchair and stretcher scales that do a big job while taking up a small space. They mount snug to the wall and protrude a mere 4" when not in use!

The large weighing platforms fold down easily, no bending is required. These battery powered, digital scales automatically turn on and zero as the platform is opening. Shut-off is also automatic. The weighing surface is only 1 1/2" high for easy patient access. Capacity is 660 lb/300 kg. And new Stow-A-Weighs have all the advanced features of other Scale-Tronix weighing systems.

Also available in other sizes.



5202
Stand-On
Scale



6202D
Stretcher
Scale



6202
Wheelchair
Scale

For More Information or a Demonstration, Call 800-873-2001

200 East Post Rd., White Plains, NY 10601 Tel: 914-948-8117 Fax: 914-948-0581 Web: www.scale-tronix.com