More Frequent Hemodialysis: Back to the Future?

Michael V. Rocco

An increase in the length of the standard in-center hemodialysis treatment by 30 to 45 minutes per session was not associated with an improvement in mortality in long-term hemodialysis patients enrolled in the HEMO study. Testing the possibility that delivering still higher doses of hemodialysis may have a beneficial effect on patient outcomes will require the use of more frequent hemodialysis or a much longer duration for each dialysis session. “Short-daily hemodialysis,” actually 6 times per week hemodialysis for 1.5 to 3 hours per session, can provide some increase in small molecule clearance as measured by urea kinetics. “Long nocturnal daily hemodialysis,” actually 6 times per week hemodialysis for 6 to 8 hours per session, provides a significant increase in both small-molecular-weight and large-molecular-weight clearance and often alleviates the need to take phosphate binders. The National Institutes of Health is sponsoring 2 clinical trials via the Frequent Hemodialysis Network to determine the impact of these 2 modalities on intermediate outcomes, compared with standard 3-times-per-week hemodialysis.

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Index Words: Daily hemodialysis; nocturnal hemodialysis; home hemodialysis; hypertension; anemia; hyperphosphatemia; quality of life; access complications

The impact of a higher dose of dialysis on patient mortality and morbidity has been studied in several randomized clinical trials, including the National Cooperative Dialysis Trial and the HEMO study. The latter trial, conducted from 1995 to 2002 and the largest conducted to date in long-term hemodialysis patients, was designed to determine if a higher dose of dialysis, as provided by a 3-times-per-week schedule, or the use of high-flux dialyzers decreased mortality and morbidity in long-term hemodialysis patients. Those patients randomized to the high-dose arm (mean equilibrated Kt/V [eKt/V] of 1.53 ± 0.09, mean single pool Kt/V [sp Kt/V] of 1.71 ± 0.11) had a mortality that was no different than patients randomized to the standard-dose arm (mean eKt/V 1.16 ± 0.08, mean sp Kt/V of 1.32 ± 0.09; relative risk [RR] = 0.96, 95% confidence interval [95% CI] = 0.84 to 1.10; P = 0.53) (Fig 1).1,2 Similarly, those patients randomized in the high-flux arm (beta-2 microglobulin [β2M] clearance of greater than 20 mL/min) had a mortality that was no different than patients randomized to the low-flux arm (β2M clearance less than 10 mL/min; RR = 0.92, 95% CI = 0.81 to 1.05; P = .23). Post hoc analysis revealed that in the high-flux group, significant reductions were seen in the risk of death from cardiac causes and in the combined outcome of first hospitalization for cardiac causes or death from cardiac causes.

Several explanations are possible for the negative results of the primary and secondary outcomes of the HEMO study. First, the increase in the weekly clearance of small molecules, such as urea, in the high-dose arm of the trial was relatively small. The standard or weekly Kt/V urea for the 2 groups was approximately 2.4 and 2.0 respectively, indicating a weekly Kt/V urea value that was about 20% higher in the high-dose group. Similarly, the clearance of middle molecules is much more dependent on the total time on dialysis. Patients in the high-dose group were on dialysis, on average for approximately 90 minutes more per week (15%) than patients in the standard arm. When the HEMO study results are viewed in this light, the failure of these modest changes in small-molecule and middle-molecule clearance to result in im-

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proved patient outcomes is not quite as surprising. With current technology, to significantly increase the weekly clearance of small and middle molecules with 3-times-per-week hemodialysis will be difficult. Thus, to determine if still higher doses of dialysis may result in improved patient outcomes, patients will need to receive hemodialysis more than 3 times per week or for a much greater duration than 3 to 5 hours per session.

The negative results of the HEMO study have intensified research efforts in the area of more-frequent hemodialysis. Regimens for more-frequent hemodialysis include “short-daily” hemodialysis and “long slow nocturnal-daily” hemodialysis. Short-daily hemodialysis is typically performed 6 to 7 days per week, and each session usually lasts from 1.5 to 3.0 hours. These sessions are usually performed by use of dialyzers of large surface area (about 2 m²) with high blood-flow (400 to 500 mL/min) and dialysate-flow (500 to 800 mL/min) rates. The dialysis sessions can be performed either in-center or at home, although the cost of performing this therapy in-center may be prohibitive. Nocturnal home hemodialysis is performed 3 to 6 nights per week, with each dialysis session usually lasting between 5 and 8 hours. Dialyzers of a smaller surface area are often used, with low blood (200 to 300 mL/min) and dialysate (100 to 200 mL/min) flow rates. Some centers will use single-needle instead of double-needle dialysis for these sessions to help minimize the number of sticks for the dialysis access. No data suggests that either single-needle hemodialysis or the use of a buttonhole technique for fistula access reduces the rate of vascular access complications.

Both short-daily and nocturnal hemodialysis have their origins in the early days of long-term hemodialysis therapy. Daily in-center hemodialysis was first conducted in the late 1960s and early 1970s in both the United States and Europe. Bonomini et al noted in 1972 that in 6 patients who had uremic-type symptoms, despite increased time on dialysis from 22 to 30 hours per week, a change to short-daily dialysis (3 to 4 hours for 5 days per week) led to a resolution of signs and symptoms such as severe anemia, polyneuropathy, insomnia, pruritus, restless leg syndrome, anorexia, amenorrhea, and impotence. Similar improvements in these areas and others, such as blood pressure control and left ventricular hypertrophy, have been noted by many other investigators since that time in both Europe and North America. During the past 5 years, this modality has seen a resurgence and is offered in a number of centers in the United States, Canada, and Europe (Fig 2).

Nocturnal home hemodialysis was devel-
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operated in the 1960s, typically for 3-times-per-week therapy, although in at least 1 report, a patient received nocturnal hemodialysis 5 times per week in 1968. Home hemodialysis was actually quite common in the 1960s, with about 40% of all long-term dialysis patients using this modality in both the United States and Great Britain. Home hemodialysis was largely abandoned in the ensuing decades because of funding for in-center hemodialysis units and the development of continuous ambulatory peritoneal dialysis.

A variation on the theme of overnight dialysis was developed by Dr. Charra and his group from Tassin, France. This group dialyzed patients in-center overnight for 8 hours 3 times per week. Their groundbreaking article in 1992 described a survival rate of 87% at 5 years, 75% at 10 years, 55% at 15 years, and 43% at 20 years of hemodialysis; much higher than that from any other chronic hemodialysis registry. Uldall et al and Kooistra in Toronto, Canada adapted this long, overnight, in-center hemodialysis therapy by combining 3 old concepts—more frequent hemodialysis, longer duration of hemodialysis, and home hemodialysis—into the modern version of nocturnal home hemodialysis, in which patients perform hemodialysis at home for 5 to 8 hours per night for 5 to 6 nights per week. Since that time, nocturnal hemodialysis has spread outside of Canada to centers in the United States (Fig 3), Europe, Australia, and New Zealand.

Both forms of more-frequent dialysis provide a higher quantity of solute removal and a more physiologic modality of solute removal than does conventional thrice-weekly hemodialysis. Short-daily hemodialysis takes advantage of the increased removal of small solutes in the first 120 minutes of hemodialysis compared with the subsequent 120 minutes on hemodialysis. This rapid initial removal of urea caused by both a higher diffusion rate driven by the large initial concentration difference between blood and dialyzer and the multicompartment structure of the human body. Therefore, whereas stopping a hemodialysis session after the first 2 hours will reduce the removal capability for low-molecular-weight solutes, such as urea, by 30% to 40% per session, the doubling of the number of hemodialysis sessions per week will increase the weekly removal of urea by 20% to 40%. Increased clearance of other non–protein-bound solutes such as creatinine and uric acid, as well as increased clearance of some protein-bound solutes, including indole-
3-acetic acid, indoxyl sulfate, and p-cresol, also occurs. However, an increase in the clearance of \(\beta_2\)M does not appear to occur with short-daily hemodialysis. In nocturnal dialysis, a significantly increased clearance of larger molecules, as well as charged molecules, also occurs. For example, the plasma concentration of \(\beta_2\)M declines by about 50% in patients on nocturnal hemodialysis 6 nights per week. The estimated clearance for phosphorus is equivalent to or exceeds the phosphorus intake in most patients. The removal of larger molecules such as \(\beta_2\)M is mostly dependent on time, and the much longer duration of nocturnal dialysis (30 or more hours per week) compared with either conventional hemodialysis (9 to 15 h/wk) or short-daily hemodialysis (9 to 18 h/wk) accounts for the higher clearance of these larger molecules.

Despite the growth of both daily and nocturnal hemodialysis programs, a paucity of data is available on outcomes with these modalities. A review of reports of daily in-center hemodialysis programs, published in 2006, was able to identify only 25 manuscripts that met the following criteria: (1) 5 or more adult patients, (2) follow-up of at least 3 months, (3) prescription of 1.5 to 3 hours 5 to 7 days per week, and (4) published after 1989.

A total of 14 cohorts with 268 unique patients were described in these publications, with only 1 cohort enrolled in a randomized trial. A review of these studies in toto, showed a clear benefit of daily in-center hemodialysis to improve the control of hypertension, by either reducing the number of antihypertensive medications required or improving systolic and diastolic blood pressures. Less clear was the benefit of this modality on anemia, with 7 of 11 studies showing an improvement in the treatment of anemia, either by a reduction in erythropoietin dose or by an increase in hemoglobin levels. The findings for both serum albumin levels and quality of life were mixed, with 5 of 10 studies demonstrating an improvement in these areas. Improvement in phosphate control, as determined by either serum phosphate levels or a decrease in the utilization of phosphate binders, was seen in only 2 of 8 studies. Finally, no change occurred in the rate of vascular-access dysfunction in 5 of the 7 reported studies.

However, none of these studies can be considered definitive for the following reasons. First, the largest cohort was only 42 patients.
Second, the duration of follow-up was modest, with a range from 3 to 24 months, and a mean of 12 months. Third, information on the dialysis prescription was available for only 6 of the 14 studies. The duration of therapy per session may be an important parameter in at least some of these secondary outcomes. For example, a longer session duration may improve phosphate control.25

A smaller number of studies have been published in nocturnal hemodialysis, and a recent review was able to identify only 10 manuscripts and 4 abstracts that met the following criteria: (1) prescription of at least 5 nights per week and 6 hours per session, (2) reported on at least 1 of 4 outcomes of interest, (3) follow-up of at least 4 weeks, and (4) included a comparator group (case-control or pre/post within-patient comparison).26 A total of 4 cohorts with 4 to 63 patients per cohort were described, with no randomized trials. Since the time of the review, a randomized trial of 3-times-per-week versus nocturnal 6-times-per-week hemodialysis conducted in Alberta Canada has been concluded in about 50 patients.27 At the current time, no results have been published for this trial.

Follow-up for the studies reviewed by Walsh and coworkers27 ranged from 6 weeks...
to 3.4 years. A clear benefit of daily in-center hemodialysis is improvement in the control of hypertension, as evidenced both by the reduction in the number of antihypertensive medications required and by the improvement in the systolic and diastolic blood pressures. This modality also had a beneficial effect on anemia, with 3 of 3 studies showing an improvement in the treatment of anemia, either by a reduction in erythropoietin dose or an increase in hemoglobin levels. Improvement in phosphate control, as determined by either serum phosphate levels or a decrease in the utilization of phosphate binders, was seen in only 1 of 2 studies. Here again, the importance of the dialysis prescription is important in interpreting the findings. In the study that showed a benefit in phosphate control, all patients were receiving double-needle hemodialysis, whereas in the negative study, most patients were receiving single-needle hemodialysis. An additional study not included in the review has also demonstrated that patients receiving double-needle nocturnal hemodialysis 5 to 7 times per week have an improvement in both serum phosphate levels and the number of binders needed for phosphate control. In the study with negative results, however, patients were receiving single-needle hemodialysis. Quality of life was measured by different methods in these cohorts, so providing a summary statistic in this area was not possible; however, in each of the studies, an improvement was seen in quality of life. In observational studies, improvements have also been described for patients with sleep apnea. The decrease in β2M levels may be significant because, as has been shown by use of HEMO study data and a time-dependent Cox regression models, mean cumulative predialysis serum β2M levels were associated with all-cause mortality (relative risk = 1.11 per 10-mg/L increase in β2M level; 95% CI, 1.05 to 1.19; P = .001), after adjustment for residual kidney urea clearance and number of prestudy years on dialysis.

No data on access complications were provided in these reviewed manuscripts. Since the time of the review, however, Lockridge et al and Perl et al have published experiences with the use of central venous catheters (CVC) for dialysis access in home nocturnal hemodialysis patients. In the Toronto group, the incidence and prevalence of CVC use was 35% and 25%, respectively. Of 81 CVCs being used in 33 patients (17,150 CVC days); 40 CVCs were exclusively used for conventional 3-times-weekly hemodialysis, and 25 CVCs were exclusively used for nocturnal home hemodialysis. When these 2 hemodialysis modalities were compared, no significant differences were seen in total rates of infection, thrombolytic administration, or access-related hospitalization. Catheter survival was superior in nocturnal hemodialysis compared with conventional hemodialysis (P = .03). Adverse terminal catheter events were higher during conventional hemodialysis compared with nocturnal hemodialysis (5.84 versus 2.92 events per 1000 CVC days; P = .03).

In the Lynchburg cohort, 34 nocturnal home hemodialysis patients were using tunneled internal-jugular catheters (930 patient-months of follow-up), 10 were using arteriovenous fistulas (190 patient-months), and 1 was using an arteriovenous graft (20 patient-months). Mean catheter life was 8.5 months, with a range from 0.2 to 66.7 months. Exit site and infection rates for catheters were 0.35 and 0.52 episodes per 1000 patient days. The AV fistula and graft exit-site and sepsis infection rates were 0.16 and 0 episodes per 1000 patient days, respectively. Catheter complications included 1 episode of disconnect because of patient’s failure to use the locking device, 1 episode of central stenosis, and 1 episode of intracranial hemorrhage, caused by prolonged INR, with resolution of symptoms.

Finally, additional data on short-daily and nocturnal dialysis patients are being collected via an international registry. As of February 15, 2006, 146 patients from the United States and Canada were entered into the registry, and ethics approval was submitted for programs in Australia, New Zealand, France, Sweden, the United Kingdom, Germany, and Italy. Despite the research performed thus far in these daily hemodialysis modalities, more data are needed before more frequent dialysis regimens are routinely recommended for long-term hemodialysis patients. The workgroup for the 2006 KDOQI update in hemodi-
analysis recognized the lack of definitive evidence in this area and, thus, did not provide any guidelines, only clinical practice recommendations (or opinions). In the opinion of the workgroup, more frequent hemodialysis should be considered in those patients with hyperphosphatemia (nocturnal hemodialysis), those with chronic fluid overload, or those who are either malnourished or losing weight. Frequent hemodialysis may be helpful for improving: quality of life, improving quality of sleep, reducing sleep apnea (nocturnal hemodialysis), and improving the sensitivity to erythropoietin stimulating agents.4

The NIH sponsored Frequent Hemodialysis Network (FHN) is designed, in part, to address these gaps in the literature. Two trials in 6 times per week, or “daily,” dialysis are being performed through the FHN consortium. In the daily study, 250 patients will be randomized to receive either in-center hemodialysis 6 times per week or conventional in-center hemodialysis 3 times per week. Patients in the daily arm of the trial will be on dialysis for 1.5 to 2.75 hours, with the individual prescription designed to achieve a median eKt/V of 0.92 per session (range: 0.74 to 1.02). In the nocturnal study, 250 patients will be randomized to receive either 6 times per week nocturnal or overnight hemodialysis or conventional 3-times-per-week home hemodialysis.33 Patients in the nocturnal arm of the trial will receive dialysis for a minimum of 6 hours 6 times per week. The typical dialysis prescription and estimated clearances for patients in the FHN nocturnal study are shown in Table 1. Similar data for the FHN Daily Study are shown in Table 2. In sum, the daily in-center arm of the trial provides a modest but significant increase in the weekly clearance of small molecules, whereas the nocturnal arm of the trial will provide for markedly high clearances of both small and middle molecules. Both of the daily arms will allow for a shorter interdialytic interval and a lower interdialytic weight gain than does conventional 3-times-per-week therapies.

The small sample size for these 2 trials does not allow for sufficient power to detect clinically significant differences in either mortality or hospitalization rates. Thus, a number of intermediate outcomes have been chosen for

### Table 2. Typical Dialysis Prescriptions and Estimated Clearances in the FHN Daily Trial Compared with Standard 3-Times-per-Week Hemodialysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional Hemodialysis (CHD)</th>
<th>Daily Hemodialysis (DHD)</th>
<th>% Difference in Medians (DHD vs CHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions per week</td>
<td>3</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Target prescription eKt/V</td>
<td>eKt/V = 1.10</td>
<td>eKt/(Vn) = 0.90</td>
<td>—</td>
</tr>
<tr>
<td>Hours per session</td>
<td>≥ 2.5 (median = 3.50)</td>
<td>1.50 to 2.75 (median = 2.36)</td>
<td>−33%</td>
</tr>
<tr>
<td>Maximum interdialysis interval (median hours)</td>
<td>68.5</td>
<td>45.6</td>
<td>−33%</td>
</tr>
<tr>
<td>Average interdialysis interval (median hours)</td>
<td>52.5</td>
<td>25.6</td>
<td>−51%</td>
</tr>
<tr>
<td>Hours per week (median, 5th to 95th percentile)</td>
<td>10.5 (9.0-13.1)</td>
<td>14.2 (11.5-16.5)</td>
<td>+35%</td>
</tr>
<tr>
<td>eKt/V urea per treatment (median, 5th to 95th percentile)</td>
<td>1.39 (1.12-1.75)</td>
<td>0.92 (0.74-1.05)</td>
<td>−34%</td>
</tr>
<tr>
<td>Weekly stdKt/V urea (median, 5th to 95th percentile)</td>
<td>2.46 (2.16-2.80)</td>
<td>3.82 (3.32-4.17)</td>
<td>+55%</td>
</tr>
<tr>
<td>Weekly eKR β₂-microglobulin (ml/min per 35 L total urea volume)(median, 5th to 95th percentile)</td>
<td>12.8 (10.7-15.2)</td>
<td>17.6 (14.6-9.8)</td>
<td>+38%</td>
</tr>
<tr>
<td>Standard phosphorus removal (g/wk) (median, 5th to 95th percentile)</td>
<td>2.09 (1.78-2.62)</td>
<td>2.91 (2.37-3.48)</td>
<td>+39%</td>
</tr>
</tbody>
</table>

Abbreviations: eKR, continuous equivalent renal clearance; eKt/V, equilibrated Kt/V; stdKt/V, standard weekly Kt/V.
primary and secondary endpoints for both trials and are the same for both trials. The 2 coprimary outcomes are a composite of mortality, with the change over 12 months in left ventricular mass as measured by cardiac magnetic resonance imaging, and a composite of mortality, with the change over 12 months in the SF-36 RAND physical health composite. Nine secondary outcome domains will also be evaluated, with both primary (noted in parentheses) and secondary outcomes for each of these domains. These secondary outcomes are cardiovascular structure and function (change in left ventricular mass), health-related quality of life/physical function (change in the physical health composite), depression/burden of illness (change in Beck Depression Inventory), nutrition and inflammation (change in serum albumin level), cognitive function (change in the Trail Making Test B), mineral metabolism (change in average predialysis serum phosphorus), and survival and hospitalization (rate of nonaccess hospitalization or death). In addition, hypertensive status and anemia have been designated as main outcome domains but without single first priority outcomes. Vital status, hospitalizations, and access procedures will be monitored throughout the 12-month follow-up period.

These trials are expected to be completed in late 2009 or early 2010. The results from these trials should help to determine if providing patients with a higher level of solute clearance from dialytic therapies will reduce the unacceptably high mortality and hospitalization rates in dialysis-dependent, stage 5 CKD patients.

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