Determinants of Left Ventricular Mass in Patients on Hemodialysis

Frequent Hemodialysis Network (FHN) Trials

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Background—An increase in left ventricular mass (LVM) is associated with mortality and cardiovascular morbidity in patients with end-stage renal disease.

Methods and Results—The Frequent Hemodialysis Network (FHN) Daily Trial randomized 245 patients to 12 months of 6 times per week daily in-center hemodialysis or conventional hemodialysis; the FHN Nocturnal Trial randomized 87 patients to 12 months of 6 times per week nocturnal hemodialysis or conventional hemodialysis. The main cardiac secondary outcome was change in LVM. In each trial, we examined whether several predefined baseline demographic or clinical factors as well as change in volume removal, blood pressure, or solute clearance influenced the effect of frequent hemodialysis on LVM. In the Daily Trial, frequent hemodialysis resulted in a significant reduction in LVM (13.1 g; 95% CI, 5.0–21.3 g; \(P = 0.002\)), LVM index (6.9 g/m\(^2\); 95% CI, 2.4–11.3 g/m\(^2\); \(P = 0.003\)), and percent change in geometric mean of LVM (7.0%; 95% CI, 1.0%–12.6%; \(P = 0.02\)). Similar trends were noted in the Nocturnal Trial but did not reach statistical significance. In the Daily Trial, a more pronounced effect of frequent hemodialysis on LVM was evident among patients with left ventricular hypertrophy at baseline. Changes in LVM were associated with changes in blood pressure (conventional hemodialysis: \(R = 0.28\), \(P = 0.01\), daily hemodialysis: \(R = 0.54\), \(P < 0.001\)) and were not significantly associated with changes in other parameters.

Conclusions—Frequent in-center hemodialysis reduces LVM. The benefit of frequent hemodialysis on LVM may be mediated by salutary effects on blood pressure.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00264758.

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Key Words: blood pressure, daily hemodialysis, frequent hemodialysis, left ventricular mass, nocturnal hemodialysis

Cardiac mortality is the leading cause of death in patients with end-stage renal disease (ESRD).\(^1\) An increase in left ventricular mass (LVM) is associated with mortality and cardiovascular morbidity.\(^2\) Experts have suggested that multiple biological pathways contribute to the pathogenesis of left ventricular hypertrophy (LVH) in this population.\(^3\) Some of the putative risk factors leading to LVH in ESRD include expanded extracellular fluid volume, hypertension, and accumulation of uremic toxins.\(^5\)

Clinical Perspective on p 261

The Frequent Hemodialysis Network (FHN) Trials aimed to examine the effects of frequent (6× per week) hemodialysis (in the form of in-center daily hemodialysis or nocturnal home hemodialysis) versus conventional 3 times per week hemodialysis on multiple intermediate outcome measures.\(^6\) The objectives and protocol summaries of both trials have been previously published.\(^6\) Limited by sample size, the FHN Trials were not designed to assess the effects of frequent hemodialysis on death or major health events. Given the link between LVH and mortality in patients on dialysis,\(^7\) death or change in LVM was designated as 1 of 2 coprimary composite outcomes for the FHN Trials. The Daily Trial showed a significant benefit in this composite outcome;\(^8\) the direction and magnitude of the effects in the Nocturnal Trial were

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similar but did not reach statistical significance.\textsuperscript{6} Nine pre-specified domains were also identified as main secondary outcomes with change in LVM being designated as the main secondary outcome for the cardiac domain. Among the major goals of the FHN Trials, addressed in the present report, was to fully characterize the change in LVM and to explore which if any factors influence the therapeutic response to frequent hemodialysis. In this report, we explore associations among changes in LVM and changes in each of 3 potential mechanistic pathways: volume removal, blood pressure, and serum phosphorus.

Methods

FHN Trials

The FHN Daily and Nocturnal Trials were multicenter, randomized, prospective trials of in-center daily hemodialysis and home nocturnal hemodialysis, respectively, sponsored by the National Institutes of Health, National Institutes Diabetes, Digestive and Kidney Diseases, and the Center for Medicare and Medical Services. The designs and inclusion and exclusion criteria of both Daily and Nocturnal Trials were described previously.\textsuperscript{6,10} Of note, the residual renal function exclusion criterion was higher in the FHN Nocturnal Trial than in the FHN Daily Trial (>10 mL/min/1.73 m\textsuperscript{2} as calculated as the average of the urea and creatinine clearances and >3 mL/min/1.73 m\textsuperscript{2} of urea clearance, respectively). Patients were enrolled between March 2006 and May 2009 and the trials concluded in May 2010. Both trials were approved by the local Institutional Review Board at each participating site. An independent Data Safety Monitoring Board provided oversight of both trials.

Dialysis Intervention

Patients in the conventional arm of both trials remained on their usual 3-times-per-week hemodialysis prescription subject to a prescribed equilibrated Kt/Vurea >1.1, a standardized Kt/Varea of >2.0, and a treatment time ≥2.5 hours/session (the majority of patients in the Nocturnal Trial randomized to conventional hemodialysis received therapy at home rather than in-center). Patients randomized to the frequent arm of the Daily Trial were targeted to an equilibrated Kt/Vn, in which Vn the frequent arm of the Daily Trial were targeted to an equilibrated Kt/Vurea prescription subject to a pre-scribed equilibrated Kt/Vurea >1.1, a standardized Kt/Varea of >2.0, and a treatment time ≥2.5 hours/session (the majority of patients in the Nocturnal Trial randomized to conventional hemodialysis received therapy at home rather than in-center). Patients randomized to the frequent arm of the Daily Trial were targeted to an equilibrated Kt/Vn, in which Vn = 3.271 × V\textsuperscript{2/3}, of 0.9 provided that the length of the session was between 1.5 and 2.75 hours. Patients randomized to the frequent arm of the Nocturnal Trial followed hemodialysis prescriptions subject to a weekly standard Kt/Varea of ≥4.0 and a treatment time of ≥6 hours.

Cardiac MRI

We measured LVM by cardiac MRI (CMRI) in all randomized patients at baseline and at 12 months where feasible. All CMRI images were analyzed centrally in a blinded manner. CMRI was performed on 1.5-T MRI systems (minimum gradient performance: peak strength ≥12 mTm, slew rate ≥40 mTm/s with dedicated surface coils. Sites were required to use standardized protocols using breath-held, retrospective electrocardiography-gated steady-state free precession imaging in contiguous short-axis views (20–25 phases, 8-mm slice thickness, 2-mm gap) that were carefully prescribed using orthogonal long-axis imaging. Imaging parameters were adjusted on each specific CMRI scanner to provide 20 to 25 cardiac phases with an in-plane spatial resolution superior of ≤2 mm and a temporal resolution <50 ms. Using validated software (Argus; Siemens Medical Solutions, Erlangen, Germany), we measured myocardial volume on end-diastolic frames by manual tracing of endocardial and epicardial contours and using a standard Simpson method. We excluded papillary muscles from the calculation of myocardial volume. Subsequently, this volume was multiplied by the specific density of the myocardium (1.05 g/cm\textsuperscript{3}) to obtain LVM.\textsuperscript{11} We used the formula of DuBois and Dubois to index LVM to body surface area.\textsuperscript{12} We calculated anthropometric volume using the Watson equation.\textsuperscript{13} LVM was defined as LVM index (LVM/body surface area)>84.1 g/m\textsuperscript{2} (male) or >66.8 g/m\textsuperscript{2} (female)\textsuperscript{14} according to Alfakih et al.

Outcome Measures

Change in LVM

The treatment effect of frequent hemodialysis on myocardial mass was assessed by examining the differences in LVM, LVM index, and percent change of the geometric mean of LVM at baseline and 12 months. To avoid confounding with changes in weight, we defined the LVM index as the ratio of the LVM to baseline body surface area. A reduction of ≥60 g in LVM was defined arbitrarily as a “pronounced response.”

Subgroup Analyses

We a priori categorized 8 subgroups to explore whether baseline demographic or clinical variables modified the effect of frequent hemodialysis on the change in LVM. These baseline subgroups were: age (<50, ≥50 years), gender, anthropometric total body water volume (<40 L, ≥40 L), vintage of ESRD (<4 years, >4 years), daily urine volume (<100 mL or ≥100 mL [Daily Trial] and <500 mL or ≥500 mL [Nocturnal Trial]), race (black versus white), baseline LVM (using median value, presence or absence of LVM), and diabetes status (yes/no).

Correlational Analyses

Surrogate measures of each of the 3 mechanistic pathways were defined a priori. Predialysis systolic and diastolic blood pressure, weekly per-session volume removal rate and interdialytic weight change, and predialysis serum phosphorus concentration were selected as markers of each pathway.

Data Analysis

Descriptive statistics for continuous variables were summarized using mean±SD. Categorical variables were summarized using proportions. Descriptive summaries of changes in treatment-related variables are provided for the constant cohort with nonmissing values at baseline and 12 months after randomization.

The effects of randomized treatment assignment on LVM and LVM index were estimated by applying a mixed-effects model to baseline and 12-month values using an unstructured covariance matrix with covariate adjustment including a time interaction for the baseline outcome measures plus prespecified covariates age, diabetes, clinical center for the Daily Trial, and age, diabetes, and baseline glomerular filtration rate in the Nocturnal Trial. Because outcomes were assessed at a single follow-up time, this model produced results essentially identical to a linear regression of the change in the outcome on the treatment assignment and the same covariates. For other outcomes, treatment effects were estimated with adjustment for the baseline level of the outcome (both Trials) and clinical center (Daily Trial only). For outcomes measured monthly (eg, predialysis blood pressure and measures of net volume removal), we applied mixed-effects models with the same baseline covariates using a combined compound-symmetry first-order autoregressive covariance matrix to account for correlations in measurements over time.\textsuperscript{15} For these outcomes we report treatment effects on mean change from baseline to the average over Months 10 to 12.

For each of the 8 prespecified factors, we used separate linear regression analyses to relate the change in LVM to treatment assignment, the prespecified baseline covariates, and to corresponding interaction terms. When evaluating baseline LVM as a subgroup factor, we used separate variance terms for patients with baseline LVM <132 versus ≥132 g to account for a greater variability in change in LVM among patients with higher baseline LVM. The primary assessment of treatment interactions with quantitative subgroup factors was based on a test for linear interaction, which treated the subgroup factor as a continuous variable; estimated treatment effects are also provided for the subgroups defined by the previously indicated cutoffs for descriptive purposes. In the Daily Trial, we present probability values for the interactions without adjustment for multiple comparisons. Due to its limited sample size, we considered
subgroup analyses in the Nocturnal Trial in an exploratory fashion without significance testing.

The potential modifying role of baseline LVM on the effect of frequent hemodialysis was further explored by extending the described linear regression model to include natural cubic splines (with 3 equally spaced interior knot points) in baseline LVM and in the interaction of treatment with baseline LVM. We provide both pointwise 95% confidence limits and Sheffe-type simultaneous 95% confidence bands to summarize the precision of this analysis.

Sensitivity analyses were performed by repeating each analysis evaluating the subgroup factors with log transformed LVM as the outcome to assess if results were appreciably changed when evaluating the percentage rather than the nominal change in LVM.

The described analyses of LVM exclude deaths, potentially leading to a selection bias. Hence, applying a similar strategy to that used for the trial’s coprimary intent-to-treat analyses, we performed further sensitivity analyses applying the nonparametric log-rank test to composite rank-based end points defined by the change in LVM for patients providing 12-month measurements and time of death for patients who died before these assessments. Hazard ratios and 95% CIs were estimated using Cox regression. In the Daily Trial, we also applied separate Cox regression analyses to relate the LVM/mortality composite rank scores to treatment interaction terms with the 8 subgroup factors in models also including main effects to treatment and the baseline factor plus the prespecified covariates.

We depicted the association of changes in LVM with changes in other factors for individual patients using scatterplots with separate nonparametric local regression curves for each treatment group and also provided Pearson correlations between the changes for each group. We also performed a multiple regression analysis to relate change in LVM jointly to the changes in average sessional interdialytic weight change, predialysis systolic blood pressure, and serum phosphorus at the same time as controlling for the baseline levels of each of these factors as well as for baseline LVM, treatment group, age, and diabetes.

All analyses were performed using SAS Version 9.2. Two-tailed probability values <0.05 were considered statistically significant unless otherwise indicated.

Results

The FHN Trials randomized 245 patients to 12 months of frequent versus conventional in-center hemodialysis and 87 patients to 12 months of home nocturnal hemodialysis versus conventional hemodialysis. Selected baseline demographics, clinical characteristics, cardiovascular risk profile, medication use, and biochemical status are summarized in Table 1. Fourteen patients died (5 frequent in-center and 9 conventional) in the Nocturnal Trial. Their baseline median LVM was 154.3 g (range, 97.3–269.6 g). The patients who survived during the follow-up had a baseline median LVM of 129.9 g (range, 34.7–360.8 g). Three patients died (2 frequent nocturnal and 1 conventional) in the Nocturnal Trial. Their baseline median LVM was 181.3 g (range, 107.7–227.4 g). The patients who survived during the follow-up had a baseline median LVM of 132.7 g (range, 47.0–257.3 g; Figure 1).

Overall Effect on LVM

In the Daily Trial, frequent hemodialysis resulted in a significant relative reduction in LVM (13.1 g; 95% CI, 5.0–21.3 g; P=0.002) with adjustment for baseline LVM, age, diabetes, and center (Table 2). In the Nocturnal Trial, frequent hemodialysis also resulted in a reduction in LVM, although the change relative to conventional hemodialysis did not reach statistical significance. Indeed, the change in LVM induced by frequent nocturnal hemodialysis was not statistically different than the change induced by frequent in-center hemodialysis. The effect of frequent hemodialysis on LVM was consistent whether LVM was considered by itself or normalized to body surface area or expressed as a percent change in geometric mean of LVM (Table 2).

In the Daily Trial, 9 subjects experienced a reduction in LVM of ≥60 g; all 9 were in the group randomized to frequent hemodialysis. All were <50 years of age and had baseline LVM >140 g. One of the 9 had diabetes. Eight had negligible residual urine volume. Baseline characteristics and changes in LVM, interdialytic weight change, blood pressure, and serum phosphorus for subjects who had a pronounced response versus the remainder of the population receiving frequent in-center hemodialysis are shown in Table 3.

Subgroup Analyses

Table 4 shows the 8 prespecified factors and the degree to which these factors appeared to influence the effect of frequent hemodialysis on change in LVM. Of note, 34% (Daily Trial) and 28% (Nocturnal Trial) of subjects had LVH at baseline. In the Daily Trial, the treatment effect was more pronounced (interaction probability value <0.001) among patients with elevated LVM at baseline. As shown in Figure 2, the change in LVM, either as an absolute number or as percent change, was related in a continuous fashion to the baseline value of left ventricular mass. This interaction was also seen when change in LVM was log-transformed to evaluate percentage change (P=0.014) and for the rank-based mortality/LVM composite outcome (P=0.005).

Related Outcomes

Mean changes in measures of volume removal, interdialytic weight change, blood pressure, and solute clearance are shown by treatment group in Table 5. Uniformly, frequent hemodialysis led to reductions in interdialytic weight change, volume removal rate, pre- and postdialysis blood pressure, and serum phosphorus concentrations. There were no between-groups differences in parathyroid hormone (baseline to 12 months; from 282 [44–846] to 258 [46–832] pg/mL [3×/week]; 322 [94–824] to 370 [120–972] pg/mL [6×/week], P=0.09 [Daily Trial] and from 335 [112–631] to 283 [38–1364] pg/mL [3×/week]; 296 [76–650] to 233 [13–672] pg/mL [6×/week] P=0.07 [Nocturnal Trial]). The mean hemoglobin was maintained in a relatively narrow range in frequent and conventional groups in both trials. Among Daily Trial patients reporting medications use at both baseline and 12 months, the mean number of antihypertensives was 2.8 at baseline and 2.6 at 12 months in the conventional hemodialysis group and was 2.7 at baseline and 1.8 at 12 months in the daily hemodialysis group (P<0.001, stratified Wilcoxon rank sum test). The corresponding means in the Nocturnal Trial were 1.7 and 2.0 at baseline and 12 months in the conventional hemodialysis group and were 2.7 and 1.4 at baseline and 12 months in the nocturnal hemodialysis group (P<0.001). Similarly, among Daily Trial patients, the proportion using angiotensin-converting enzyme or angiotensin receptor blocker therapy was 0.61 at baseline and 0.60 at 12 months in the conventional hemodialysis group and was 0.63
at baseline and 0.40 at 12 months in the daily hemodialysis group. The corresponding proportions in the Nocturnal Trial were 0.46 and 0.49 at baseline and 12 months in the conventional hemodialysis group and were 0.49 and 0.35 at baseline and 12 months in the nocturnal hemodialysis group.

Correlational Analyses
In multiple regression analysis, we found no significant independent association of change in LVM with changes in serum phosphorus, parathyroid hormone, hemoglobin, or in sessional interdialytic weight change. There was an associa-

Table 1. Characteristics During Baseline for FHN Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daily Trial 3 Times/Wk (N=120; Conventional)</th>
<th>6 Times/Wk (N=125; Daily)</th>
<th>Nocturnal Trial 3 Times/Wk (N=42; Conventional)</th>
<th>6 Times/Wk (N=45; Nocturnal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.0±14.1</td>
<td>48.9±13.6</td>
<td>54.0±12.9</td>
<td>51.7±14.4</td>
</tr>
<tr>
<td>Male</td>
<td>73 (60.8%)</td>
<td>78 (62.4%)</td>
<td>28 (66.7%)</td>
<td>29 (64.4%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>53 (44.2%)</td>
<td>49 (39.2%)</td>
<td>11 (26.2%)</td>
<td>12 (26.7%)</td>
</tr>
<tr>
<td>White</td>
<td>46 (38.3%)</td>
<td>43 (34.4%)</td>
<td>21 (50.0%)</td>
<td>27 (60.0%)</td>
</tr>
<tr>
<td>Native American, Aboriginal, Alaskan, First Nation</td>
<td>4 (3.3%)</td>
<td>4 (3.2%)</td>
<td>2 (4.8%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (4.2%)</td>
<td>11 (8.8%)</td>
<td>7 (16.7%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>3 (2.5%)</td>
<td>1 (0.8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other/mixed/unknown</td>
<td>9 (7.5%)</td>
<td>17 (13.6%)</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hispanic/Latino ethnicity</td>
<td>31 (26%)</td>
<td>38 (30%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Weekly standard Kt/V</td>
<td>2.53±0.39</td>
<td>2.50±0.31</td>
<td>2.34±0.34</td>
<td>2.35±0.28</td>
</tr>
<tr>
<td>Residual urine volume, L/24 h</td>
<td>0 (0–3.47)</td>
<td>0 (0–2.94)</td>
<td>0.54 (0–9.11)</td>
<td>0.40 (0–8.63)</td>
</tr>
<tr>
<td>Residual renal clearance, mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>72 (60.0%)</td>
<td>90 (72%)</td>
<td>11 (26.2%)</td>
<td>13 (28.9%)</td>
</tr>
<tr>
<td>0–1</td>
<td>19 (15.8%)</td>
<td>18 (14.4%)</td>
<td>9 (21.4%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>1–3</td>
<td>27 (22.5%)</td>
<td>15 (12.0%)</td>
<td>14 (33.3%)</td>
<td>14 (31.1%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2 (1.7%)</td>
<td>2 (1.6%)</td>
<td>8 (19.0%)</td>
<td>11 (24.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (92.5%)</td>
<td>117 (93.6%)</td>
<td>39 (92.9%)</td>
<td>41 (91.1%)</td>
</tr>
<tr>
<td>Coronary artery disease (myocardial infarction)</td>
<td>16 (13.3%)</td>
<td>11 (8.8%)</td>
<td>4 (9.5%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24 (20.0%)</td>
<td>25 (20.0%)</td>
<td>7 (16.7%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (7.5%)</td>
<td>5 (4.0%)</td>
<td>0 (0.0%)</td>
<td>6 (13.3%)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>10 (8.33%)</td>
<td>15 (12.0%)</td>
<td>7 (16.7%)</td>
<td>8 (17.8%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (7.5%)</td>
<td>9 (7.2%)</td>
<td>1 (2.4%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50 (41.7%)</td>
<td>50 (40.0%)</td>
<td>18 (42.9%)</td>
<td>19 (42.2%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5 (4.2%)</td>
<td>6 (4.8%)</td>
<td>2 (4.8%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dialysis access*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistula</td>
<td>72 (59.2%)</td>
<td>83 (65.8%)</td>
<td>18 (41.9%)</td>
<td>24 (51.1%)</td>
</tr>
<tr>
<td>Graft</td>
<td>23 (18.9%)</td>
<td>22 (17.5%)</td>
<td>4 (9.3%)</td>
<td>3 (6.4%)</td>
</tr>
<tr>
<td>Catheter</td>
<td>27 (22.1%)</td>
<td>21 (16.7%)</td>
<td>21 (48.8%)</td>
<td>20 (42.6%)</td>
</tr>
<tr>
<td>Vasoactive medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>38 (31.7%)</td>
<td>42 (33.6%)</td>
<td>12 (28.6%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>45 (37.5%)</td>
<td>51 (40.8%)</td>
<td>8 (19.1%)</td>
<td>17 (37.8%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>49 (40.8%)</td>
<td>41 (32.8%)</td>
<td>16 (38.1%)</td>
<td>20 (44.4%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>22 (18.3%)</td>
<td>23 (18.4%)</td>
<td>6 (14.3%)</td>
<td>12 (26.6%)</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>13 (10.8%)</td>
<td>23 (18.4%)</td>
<td>0 (0%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.0±1.2</td>
<td>11.9±1.3</td>
<td>11.9±1.1</td>
<td>11.6±1.1</td>
</tr>
<tr>
<td>ESA use</td>
<td>111 (92.5%)</td>
<td>117 (93.6%)</td>
<td>37 (88.1%)</td>
<td>38 (84.4%)</td>
</tr>
<tr>
<td>Vitamin D use, yes</td>
<td>74 (79.6%)</td>
<td>79 (76.0%)</td>
<td>10 (25.6%)</td>
<td>15 (40.5%)</td>
</tr>
<tr>
<td>Phosphate binder use, yes</td>
<td>111 (92.5%)</td>
<td>118 (94.4%)</td>
<td>38 (80.5%)</td>
<td>43 (95.6%)</td>
</tr>
</tbody>
</table>

Results are shown as mean±SD, median and 10th and 90th percentiles range, or frequency (%), as appropriate.
FHN indicates Frequent Hemodialysis Network; ESA, erythropoiesis-stimulating agents.
*Patients may have >1 hemodialysis access at baseline.
tion between the change in systolic blood pressure and the change in LVM. In the Daily Trial, each 10-mm Hg reduction in predialysis systolic blood pressure was associated with a 6.6 ± 1.8-g larger reduction in LVM in the conventional hemodialysis group and with a 10.1 ± 1.5-g larger reduction in LVM in the frequent in-center hemodialysis group. Similar results were observed in the Nocturnal Trial (Figure 3A–C).

Discussion

Left ventricular hypertrophy is a potent prognostic marker in patients with ESRD.2 Recent studies have demonstrated that regression of LVH is feasible with intensive hemodialysis.17 The present study adds to the emerging literature by determining the magnitude of LVM reduction by frequent hemodialysis, identifying patient characteristics associated with pronounced treatment response of LVM to frequent hemodialysis, and exploring links between changes in putative parameters of volume removal, blood pressure, and solute clearance that may help to elucidate mechanism(s) of change in LVM.

The present study suggests that 12 months of frequent hemodialysis might be expected to reduce LVM by approximately 7% to 10% on average. Our results are similar to those found in non-ESRD trials, in which more pronounced LVM regression was measured in groups in which baseline LVH was used as an inclusion criterion.18,19 This relative extent of LVM reduction is of similar magnitude to changes observed in other randomized controlled studies of dialysis.17 In this regard, it is of importance to distinguish between relative and absolute change in LVM because these may have important implications for prognosis. In a recent meta-analysis of antihypertensive trials using echocardiography (all of which excluded patients with ESRD), the overall amount of relative LVM regression in 168 trials amounted to 10.9% ± 0.4%.18 Interestingly, in the studies included as part of the meta-analysis, the baseline LVM was higher with mean LVM of 248 ± 4.4 g amounting to an average regression of 27 g. In our analyses that explored effect modification by baseline factors, the most important factor appeared to be baseline LVM with the absolute changes in LVM being most dramatic in those patients with extreme baseline LVM (Table 3). In support of this, recent studies with pharmacological intervention in which LVH was minimal at baseline (by MRI), very small absolute changes in LVM were seen despite similar relative changes.18,20 Thus, it is reasonable to postulate that the absolute extent of LVM regression with dialysis may be driven by the extent of LVH at baseline.

In our study, the percentages of subjects with baseline LVH, using the criteria of >84 g/m² for men and >66.8 g/m² for women suggested by Alfakih et al,14 were only 34% and 28% for the Daily and Nocturnal Trials, respectively. This LVH prevalence is lower than that reported by older studies in which LVM was assessed using echocardiography.2,4 In our trial, we measured LVM by steady-state free precession pulses CMRI. Earlier methods relying on turbogradient echo CMRI have been largely replaced by newer methods using steady-state free precession pulses. Thus, the prevalence rate of LVH that we found in our study has to be put into context of how LVM was measured. Still, our results suggest that maximum benefits of LVM reduction will be found in those patients who have the highest baseline values of LVM.

More than 40% of patients randomized to both Daily and Nocturnal Trials had diabetes mellitus. Although not definitive in the face of multiple subgroup analyses, it was interesting to observe a trend for a lesser benefit of frequent hemodialysis in terms of LVM reduction for patients with diabetes. A number of different hypotheses might be generated to explain a lack of benefit associated with diabetes; a complete analysis will require further examination of potential confounding factors in patients with and without diabetes in these trials, including blood pressure, residual kidney function, and baseline LVM. Residual kidney function (as reflected by either solute clearance or urine volume) is a logical effect modifier in any trial of intensified dialysis, because the residual nephron collective exerts a powerful influence on survival, LVM, serum phosphorus, hospitalization, and other markers of health.21 The beneficial effect of residual urine volume on the pathogenesis of LVH has been
Table 2. Change in LVM in Daily and Nocturnal Trials

<table>
<thead>
<tr>
<th></th>
<th>Daily Trial</th>
<th></th>
<th>Nocturnal Trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change, Adjusted <em>t</em> for Baseline Value, <em>t</em> Age, Diabetes, Center*</td>
<td>Unadjusted Mean Δ</td>
<td>HR for Rank Based Analysis Including Death</td>
<td>Mean Change, Adjusted <em>t</em> for Baseline Value, <em>t</em> Age, Diabetes, GFR*</td>
</tr>
<tr>
<td>LVM, g</td>
<td>−13.1 (−21.3 to −5.0) [0.002]</td>
<td>−13.9 (−23.1 to −4.8) [0.003]</td>
<td>0.61† (0.46–0.82) [&lt; 0.001]</td>
<td>−10.9† (−23.7 to 1.8) [0.09]</td>
</tr>
<tr>
<td>LVM/baseline BSA, g/m²</td>
<td>−6.9 (−11.3 to −2.4) [0.003]</td>
<td>−7.1 (−12.0 to −2.2) [0.005]</td>
<td>0.65 (0.49–0.87) [0.003]</td>
<td>−5.2 (−11.4 to 1.0) [0.10]</td>
</tr>
<tr>
<td>Percent change in geometric mean of LVM</td>
<td>−7.0 (−12.6 to −1.0) [0.02]</td>
<td>−7.5 (−13.2 to −1.5) [0.02]</td>
<td>0.64 (0.48–0.85) [0.002]</td>
<td>−9.1 (−17.0 to −0.5) [0.04]</td>
</tr>
</tbody>
</table>

LVM indicates left ventricular mass; HR, hazard ratio; GFR, glomerular filtration rate; BSA, body surface area.

*Estimated treatment effects are provided with adjustment for the specified baseline covariates and interaction terms allowing different coefficients at the baseline and follow-up visits. Results were similar under corresponding models without interaction terms for the baseline factors other than LVM: the estimated treatment effect on LVM (g) was −13.8 g (95% CI, −21.9 to −5.8 g), P<0.001 in the Daily Trial [12], and was −8.0 g (95% CI, −20.7 to 4.8 g), P=0.22 in the Nocturnal Trial.

†Corresponds to primary intent-to-treat analysis without covariate adjustment.

Table 3. Baseline and Changes in LV Mass, Blood Pressure, Interdialytic Weight Change, and Serum Phosphorus among Patients Who Had a Pronounced Response

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, Y</th>
<th>Dialysis Vintage, Y</th>
<th>Baseline LV Mass, g</th>
<th>ΔLV Mass, g</th>
<th>Baseline Predialysis Systolic Blood Pressure, mm Hg</th>
<th>ΔPredialysis Systolic Blood Pressure, mm Hg</th>
<th>ΔNo. of Antihypertensive Medications</th>
<th>Baseline Serum Phosphorus, mg/dL</th>
<th>ΔSerum Phosphorus, mg/dL</th>
<th>Baseline Interdialytic Weight Change, L</th>
<th>ΔInterdialytic Weight Change, L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42.40</td>
<td>5.16</td>
<td>360.80</td>
<td>−174.5</td>
<td>159.46</td>
<td>−30.68</td>
<td>−2.00</td>
<td>5.65</td>
<td>1.05</td>
<td>4.28</td>
<td>−1.71</td>
</tr>
<tr>
<td>2</td>
<td>26.35</td>
<td>0.99</td>
<td>222.10</td>
<td>−115.1</td>
<td>161.67</td>
<td>−20.81</td>
<td>1.00</td>
<td>6.65</td>
<td>−0.05</td>
<td>2.51</td>
<td>−0.69</td>
</tr>
<tr>
<td>3</td>
<td>41.55</td>
<td>7.24</td>
<td>228.20</td>
<td>−112.6</td>
<td>163.83</td>
<td>−37.00</td>
<td>−2.00</td>
<td>6.55</td>
<td>−0.42</td>
<td>3.63</td>
<td>−1.31</td>
</tr>
<tr>
<td>4</td>
<td>45.79</td>
<td>3.15</td>
<td>222.20</td>
<td>−91.40</td>
<td>191.33</td>
<td>−63.88</td>
<td>0.00</td>
<td>6.35</td>
<td>−0.58</td>
<td>2.48</td>
<td>−0.93</td>
</tr>
<tr>
<td>5</td>
<td>37.55</td>
<td>10.69</td>
<td>239.90</td>
<td>−87.30</td>
<td>141.67</td>
<td>2.11</td>
<td>3.00</td>
<td>6.10</td>
<td>−2.67</td>
<td>3.85</td>
<td>−1.27</td>
</tr>
<tr>
<td>6</td>
<td>41.98</td>
<td>0.14</td>
<td>203.20</td>
<td>−75.50</td>
<td>162.17</td>
<td>1.00</td>
<td>−6.00</td>
<td>6.60</td>
<td>−2.77</td>
<td>3.53</td>
<td>−0.76</td>
</tr>
<tr>
<td>7</td>
<td>35.57</td>
<td>3.96</td>
<td>265.15</td>
<td>−68.10</td>
<td>157.00</td>
<td>−10.56</td>
<td>−7.00</td>
<td>4.15</td>
<td>−2.52</td>
<td>1.45</td>
<td>−0.80</td>
</tr>
<tr>
<td>8</td>
<td>35.58</td>
<td>9.31</td>
<td>263.00</td>
<td>−65.85</td>
<td>160.83</td>
<td>−34.56</td>
<td>−2.00</td>
<td>7.75</td>
<td>0.82</td>
<td>2.72</td>
<td>−0.82</td>
</tr>
<tr>
<td>9</td>
<td>49.50</td>
<td>11.95</td>
<td>142.00</td>
<td>−63.00</td>
<td>162.33</td>
<td>−23.50</td>
<td>−4.00</td>
<td>4.75</td>
<td>1.08</td>
<td>2.27</td>
<td>−1.07</td>
</tr>
<tr>
<td>Mean of remainder of all patients receiving daily hemodialysis</td>
<td>49.55</td>
<td>6.23</td>
<td>132.33</td>
<td>−8.61</td>
<td>145.90</td>
<td>−8.71</td>
<td>−0.79</td>
<td>5.84</td>
<td>−0.62</td>
<td>3.23</td>
<td>−1.11</td>
</tr>
<tr>
<td>SD of all patients receiving daily hemodialysis</td>
<td>13.00</td>
<td>6.88</td>
<td>50.32</td>
<td>24.26</td>
<td>18.94</td>
<td>17.45</td>
<td>1.65</td>
<td>1.73</td>
<td>1.68</td>
<td>0.99</td>
<td>0.83</td>
</tr>
</tbody>
</table>

LV indicates left ventricle.
studied in patients on peritoneal dialysis.22,23 The contribution of urine volume to LVM in patients on hemodialysis has not been studied systematically. Our data suggested a more pronounced effect of frequent dialysis on LVM when residual urine output was low, although the interaction did not reach statistical significance. However, it should be noted that the majority of patients who experienced a marked reduction in LVM had negligible baseline residual urine volume. It is possible that with higher urine output, the differential benefits of more frequent dialysis are attenuated.

Fluid overload has been found to be present in patients on dialysis with hypertension24,25 and is thought to contribute toward larger left ventricular dimensions, stroke volume, and end-diastolic pressure, ultimately leading to LVH.26 Indeed, observational studies suggest that strict control of hypervolemia and salt intake may result in reduction in LVM in patients with ESRD treated by 3-times-a-week hemodialysis.27 More frequent hemodialysis, whether given daily in-center or in long-session nocturnal mode, reduced the mean interdialytic weight change, resulting in less cyclic expansion and contraction of extracellular volume. One might theorize that reduction in extremes of mechanical stretch and neurohumoral variables involved in hypertrophic and extracellular matrix expansion may have a favorable impact on LVH.

Table 4. Subgroup Trends in Estimated Treatment Effects for LVM

<table>
<thead>
<tr>
<th>Subgroup Factor</th>
<th>Subgroup</th>
<th>Estimated Effect (CI)</th>
<th>Interaction P Value for Mixed Model</th>
<th>Interaction P Value for Rank-Based Test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤50 y</td>
<td>-20.1 (-31.6 to -8.6)</td>
<td>0.16</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>&gt;50 y</td>
<td>-5.8 (-17.5 to 5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>-12.8 (-23.1 to -2.5)</td>
<td>0.90</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>-13.9 (-27.5 to -0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Nondiabetic</td>
<td>-20.2 (-30.7 to -9.8)</td>
<td>0.038</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>-2.9 (-15.5 to 9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>-18.8 (-34.2 to -3.3)</td>
<td>0.69</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>-14.8 (-27.4 to -2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthropometric volume</td>
<td>≤40 L</td>
<td>-9.5 (-20.3 to 1.2)</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>&gt;40 L</td>
<td>-17.9 (-30.7 to -5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vintage of ESRD</td>
<td>&lt;4 y</td>
<td>-10.0 (-20.8 to 0.8)</td>
<td>0.38</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>&gt;4 y</td>
<td>-15.9 (-28.8 to -3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline urine volume</td>
<td>≤100 mL</td>
<td>-17.4 (-27.2 to -7.5)</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>&gt;100 mL</td>
<td>-3.6 (-18.3 to 11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LVM</td>
<td>&lt;132 g</td>
<td>-3.6 (-12.4 to 5.2)</td>
<td>&lt;.0001</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>≥132 g</td>
<td>-22.7 (-36.7 to -8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LVMI</td>
<td>Normal</td>
<td>-4.7 (-13.1 to 3.7)</td>
<td>0.001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>-36.5 (-56.3 to -16.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LVM indicates left ventricular mass; ESRD, end-stage renal disease; LVMI, left ventricular mass index.

*P values for interaction terms between the baseline subgroup factors and treatment group in Cox regression analysis.

†Due to its limited sample size, we considered subgroup analyses in the Nocturnal Trial in an exploratory fashion without inference testing.

Figure 2. The effect of baseline left ventricular mass on the change in left ventricular mass in the Daily Trial.
regression, although excess volume in patients on dialysis has a
cyclical and a constant component. Despite the attractiveness of this
theory, differences in interdialytic weight change were not associated with
changes in LVM when analyzed within each trial separately.

Apart from the hemodynamic changes associated with constant
as well as cyclical volume overload, the net volume removal rate during
each dialysis session can be another source of cardiac stress. The volume
removal rate is a function not only of the amount of weight gained during
the preceding interdialytic interval, but also of the session length.
Ultrafiltration rate has been linked with the severity of myocardial
stunning during dialysis and also has been associated with mortality when
expressed as a function of body size. Because the weekly dialysis time was
only marginally increased in the Daily Trial, there was not significant
reduction of ultrafiltration rate, and for this reason, ultrafiltration rate reduction
cannot be used to explain the observed reduction in left ventricular mass.
However, more frequent dialysis has been associated with less evidence
of myocardial stunning and also has been associated with mortality when
expressed as a function of body size. Because the weekly dialysis time was
only marginally increased in the Daily Trial, there was not significant
reduction of ultrafiltration rate, and for this reason, ultrafiltration rate reduction
cannot be used to explain the observed reduction in left ventricular mass.
However, more frequent dialysis has been associated with less evidence
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reduction of ultrafiltration rate, and for this reason, ultrafiltration rate reduction
cannot be used to explain the observed reduction in left ventricular mass.
However, more frequent dialysis has been associated with less evidence
of myocardial stunning and also has been associated with mortality when
expressed as a function of body size.

Higher systolic blood pressure and wider pulse pressure
have been shown to be independent risk factors for the
development of LVH and cardiovascular mortality in
ESRD. Several observational studies and controlled trials
(randomized and otherwise) have suggested that frequent
hemodialysis can lower blood pressure and facilitate control
of hypertension (allowing a reduction in antihypertensive
therapy). To date, most hypertension treatment trials
aimed to promote regression of LVH have a concomitant fall
in systolic and diastolic blood pressures by 10% using various
pharmacological approaches.

The FHN Trials confirmed that frequent hemodialysis
reduced blood pressure with fewer antihypertensive medi-
cations. Importantly, despite a reduction in medications, which
block the renin–angiotensin system, there was a substantial
fall in LVM in patients who were assigned to and received
frequent hemodialysis. Additionally, there was a strong asso-
ciation between changes in blood pressure and changes in
LVM. Taken together, our results reflect the importance
between hypertension management and regression of LVH in
this population, which merits further investigation.

Multiple observational studies in hemodialysis have sug-
gested that hyperphosphatemia is associated with mortality
and cardiovascular morbidity. Several studies of frequent
hemodialysis have explored these links. For example, Ayus et
al compared changes in LVM in 26 patients selected to
undergo daily hemodialysis (6 sessions per week, 3 hours per
session) and 51 control patients who remained on conven-
tional hemodialysis. At the 12-month follow-up, patients on
daily hemodialysis experienced a 30% decrease in LVM
index (154±33 g/m² to 108±25 g/m²; P<0.0001) despite
minimal changes in blood pressure. Patients on conventional
and frequent hemodialysis had similar blood pressure at
baseline and at the end of the trial. Ayus et al contended that
among the potential mechanisms to explain the reduction in
LVM was improved control of hyperphosphatemia. Recently,
other mediators of mineral metabolism such as fibroblast
growth factor 23 were shown to correlate inversely with
LVM in patients with chronic kidney disease and was
demonstrated to be an independent predictor of death in the
hemodialysis population. The FHN Trials confirmed that
frequent hemodialysis lowered serum phosphorus. Among
the 9 patients with a pronounced reduction in LVM, 3 who
did not experience marked reductions in blood pressure did
experience marked reductions in serum phosphorus. The lack
of a significant association between changes in phosphorus
and LVM does not eliminate the possibility that other
biological active mediators of mineral metabolism may con-
tribute to the regression of LVH.

Strengths of the current study include the trial design: a
multicenter randomized clinical trial with broad diversity of
subjects in terms of age, sex, race/ethnicity, vintage and
primary causes of kidney disease as well as blinded central-
ized assessment of LVM. Moreover, adherence was excellent
in the Daily Trial and very good in the Nocturnal Trial. In our

Table 5. Adjusted Mean Changes in Net Volume Removal, Blood Pressure, and Predialysis Phosphorus Over 12 Months*
analyses of LVM, we accounted for baseline measurements and several other key covariates. There were some important limitations as well. There is no specific definition of LVH in the hemodialysis population. Normal values for left ventricular mass may vary from laboratory to laboratory with CMRI and thus the range of findings from this study may not be directly extrapolated to other CMRI laboratories. A minority of randomized patients had baseline LVH and the clinical

Figure 3. A, Closed circles indicate patients with reductions in LV mass >60 g between baseline and 12 months. Although LV mass may be viewed as the response variable in this relationship, we have plotted LV mass on the horizontal axis in A–C to better display the role of these outliers with large LV mass reductions. Correlations between changes in net volume removal and changes in LVM in the Daily Trial (3 times/week hemodialysis: \( R=0.15, P=0.16 \); 6 times/week hemodialysis: \( R=0.06, P=0.54 \)) and Nocturnal Trial (3 times/week hemodialysis: \( R=-0.20, P=0.24 \); 6 times/week hemodialysis: \( R=-0.11, P=0.54 \)). B, Correlations between changes in predialysis systolic blood pressures and changes in LVM in the Daily Trial (3 times/week hemodialysis: \( R=0.28, P=0.01 \); 6 times/week hemodialysis: \( R=0.54, P<0.001 \)) and Nocturnal Trial (3 times/week hemodialysis: \( R=0.14, P=0.41 \); 6 times/week hemodialysis: \( R=0.51, P=0.001 \)). C, Correlations between changes in predialysis serum phosphorus and changes in LVM in the Daily Trial (3 times/week hemodialysis: \( R=0.11, P=0.30 \); 6 times/week hemodialysis: \( R=0.1, P=0.35 \)) and Nocturnal Trial (3 times/week hemodialysis: \( R=0.12, P=0.46 \); 6 times/week hemodialysis: \( R=0.23, P=0.18 \)). LV indicates left ventricle; LVM, left ventricular mass.
significance of reducing left ventricular mass in individuals without LVH is uncertain. Measures of net volume removal and blood pressure were obtained with monthly kinetic modeling sessions. More frequent tracking of these metrics might have yielded more precision in the analysis. Moreover, we did not collect data on dietary sodium intake, fluid intake, or ambulatory (continuous) blood pressure, which might have helped to refine our analyses. We are also limited in study design, power, and generalizability to extrapolate the noted change in LVM with clinical outcomes. Additional investigations are required to understand the mechanism(s) by which frequent hemodialysis decreases or increases the likelihood of important cardiovascular end points.

In summary, the FHN Trials demonstrated that frequent hemodialysis results in a reduction in LVM and suggested several factors, including higher baseline LVM, that were associated with more pronounced effects. Although the trials were not designed to determine the mechanism of benefit, salutary effects on hypertension may play an important role. The extent to which frequent hemodialysis may be offered as a therapeutic option for patients with ESRD and LVH or other forms of structural heart disease remains to be determined. For now, more frequent hemodialysis could be expected to reduce LVH in patients with ESRD, which may further prevent important cardiovascular complications.

Acknowledgments
A list of members of the FHN Trial Group for each study has been published.8,10

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

An increase in left ventricular mass is associated with mortality in patients with end-stage renal disease. The Frequent Hemodialysis Network (FHN) Daily Trial randomized 245 patients to 12 months of 6-times-per-week daily in-center hemodialysis or conventional hemodialysis; the FHN Nocturnal Trial randomized 87 patients to 12 months of 6-times-per-week nocturnal hemodialysis or conventional hemodialysis. The FHN Trials demonstrated that frequent hemodialysis results in reductions in left ventricular mass and blood pressure, and suggested several factors, including higher baseline left ventricular mass, that were associated with more pronounced effects. In addition, the changes in left ventricular mass were associated with the changes in blood pressure. Although not designed to determine survival benefit, more frequent hemodialysis could be expected to reduce left ventricular hypertrophy in patients with end-stage renal disease, which may further prevent important cardiovascular complications.
Determinants of Left Ventricular Mass in Patients on Hemodialysis: Frequent Hemodialysis Network (FHN) Trials
Christopher T. Chan, Tom Greene, Glenn M. Chertow, Alan S. Kliger, John B. Stokes, Gerald J. Beck, John T. Daugirdas, Peter Kotanko, Brett Larive, Nathan W. Levin, Ravindra L. Mehta, Michael Rocco, Javier Sanz, Brigitte M. Schiller, Phillip C. Yang, Sanjay Rajagopalan and the Frequent Hemodialysis Network (FHN) Trial Group

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