Background—Patients with chronic kidney disease (stage 5) who undergo hemodialysis treatment have similarities to heart failure patients in that both populations retain fluid frequently and have excessively high mortality. Volume overload in heart failure is associated with worse outcomes. We hypothesized that in hemodialysis patients, greater interdialytic fluid gain is associated with poor all-cause and cardiovascular survival.

Methods and Results—We examined 2-year (July 2001 to June 2003) mortality in 34 107 hemodialysis patients across the United States who had an average weight gain of at least 0.5 kg above their end-dialysis dry weight by the time the subsequent hemodialysis treatment started. The 3-month averaged interdialytic weight gain was divided into 8 categories of 0.5-kg increments (up to ≥4.0 kg). Eighty-six percent of patients gained >1.5 kg between 2 dialysis sessions. In unadjusted analyses, higher weight gain was associated with better nutritional status (higher protein intake, serum albumin, and body mass index) and tended to be linked to greater survival. However, after multivariate adjustment for demographics (case mix) and surrogates of malnutrition-inflammation complex, higher weight-gain increments were associated with increased risk of all-cause and cardiovascular death. The hazard ratios (95% confidence intervals) of cardiovascular death for weight gain <1.0 kg and ≥4.0 kg (compared with 1.5 to 2.0 kg as the reference) were 0.67 (0.58 to 0.76) and 1.25 (1.12 to 1.39), respectively.

Conclusions—In hemodialysis patients, greater fluid retention between 2 subsequent hemodialysis treatment sessions is associated with higher risk of all-cause and cardiovascular death. The mechanisms by which fluid retention influences cardiovascular survival in hemodialysis may be similar to those in patients with heart failure and warrant further research. (Circulation. 2009;119:671-679.)

Key Words: renal dialysis | heart failure | ultrafiltration | cardiovascular death | obesity

Fluid retention is a major clinical problem in individuals with advanced chronic kidney disease (CKD), also known as stage 5 CKD or end-stage renal disease, and is associated with morbid conditions such as lower-extremity edema, anasarca, ascites, pulmonary vascular congestion or edema, hypertension, and worsening heart failure.1–3 Not infrequently, dialysis treatment needs to be initiated to prevent or treat complications related to fluid retention, especially when diuretic therapy fails. Hence, removal of fluid during the dialysis treatment, also known as ultrafiltration, is the cornerstone of volume management in advanced-stage CKD. Ultrafiltration is also used occasionally in heart failure patients resistant to medical treatment.4 A main challenge related to ultrafiltration interventions is assessment of the required magnitude and frequency of fluid removal; however, it is not clear whether fluid removal can improve clinical outcomes in CKD or heart failure patients.

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In addition to a tendency to retain fluid, patients undergoing long-term dialysis have other similarities to heart failure patients; for instance, they both have excessively high mortality (currently 20% to 25% per year in the United States), most of which is attributable to cardiovascular causes.5 Furthermore, both dialysis and heart failure patients experience chronic wasting syndrome,6–8 and both exhibit survival
paradoxes such as the obesity or cholesterol paradox.\textsuperscript{9–11} Hence, studying the risk factors of poor survival in the dialysis patient population may help advance strategies to mitigate high mortality in both dialysis and heart failure patients. Because fluid retention is a major morbid condition in both populations, we hypothesized that in long-term dialysis patients, greater interdialytic (between 2 consecutive dialysis treatment sessions) fluid gain is associated with poor all-cause and cardiovascular survival. In the present study, we examined a 2-year cohort of \textgreater 34,000 long-term hemodialysis outpatients across the nation, because currently, \textgreater 90\% of individuals who need dialysis therapy undergo thrice-weekly hemodialysis treatment in outpatient dialysis clinics in the United States and many other countries. We also hypothesized that the association between greater fluid retention and poor survival persists in diverse subgroups of hemodialysis patients. In particular, because the interdialytic weight gain is a function of oral fluid intake, which includes routine food ingestion, we hypothesized that the mortality predictability of higher fluid gain would remain independent of other outcome predictors, such as nutritional status.

Methods

Patients

The present study examined data from all individuals with CKD stage 5 who underwent long-term hemodialysis treatment from July 1, 2001, to June 30, 2003, in 1 of the 580 outpatient dialysis clinics of a large dialysis organization in the United States (DaVita, Inc, El Segundo, Calif). The study was approved by the institutional review committees of both the Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research.

Clinical and Demographic Measures and Comorbid States

The creation of the 2-year cohort has been described previously.\textsuperscript{12–15} To minimize measurement variability, all repeated measures for each patient during any given calendar quarter (ie, over a 13-week interval) were averaged, and the summary estimate was used in all models. Averaged values were obtained for up to 8 calendar quarters (quarters 1 through 8) for each laboratory and clinical measure for each patient over the 2-year cohort period. Dialysis treatment vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort. The first (baseline) studied quarter for each patient was the calendar quarter in which the patient’s dialysis treatment vintage was \textgreater 90 days during at least half of that given quarter.

In addition to the presence or absence of diabetes mellitus, histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to Medical Evidence Form 2728 of the United States Renal Data System\textsuperscript{16} and categorized into 11 comorbid conditions: (1) ischemic heart disease, (2) congestive heart failure, (3) post–cardiac arrest, (4) post-myocardial infarction, (5) pericarditis, (6) cardiac dysrhythmia, (7) peripheral vascular disease (8) chronic obstructive pulmonary disease, (9) HIV/AIDS status, (10) ambulatory status, and (11) cancer. Computerized causes of death were obtained, and cardiovascular death was defined as death due to myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident, and other cardiac causes.

Interdialytic Fluid Gain Measurement

Because hemodialysis patients usually undergo thrice-weekly (Monday–Wednesday–Friday or Tuesday–Thursday–Saturday) dialysis treatment for 3 to 5 hours, they usually gain weight during the time between the 2 consecutive dialysis treatments, which is almost entirely due to fluid retention. Hence, the amount of fluid that is ultrafiltered during the subsequent hemodialysis treatment (ie, the difference between the prehemodialysis [wet] and posthemodialysis [dry] weight) is equivalent to the magnitude of weight gain immediately before the treatment, as shown in Figure 1. To mitigate the interpersonal variability over short periods, we calculated the 13-week averaged prehemodialysis and posthemodialysis weights for each patient during each of the 8 calendar quarters of the 2-year cohort (ie, for up to 39 dialysis treatments per calendar quarter). The averaged amount of fluid gain or ultrafiltration for each patient was the difference between prehemodialysis and posthemodialysis weight (Figure 1). Hence, a surviving patient could have up to 8 quarterly ultrafiltration or fluid retention values over the 2 years of follow-up. In the present report, we chose to use kilograms instead of liters as the unit of fluid gain measurement. The body mass index was calculated with the posthemodialysis (dry) weight divided by height squared.

Laboratory Measures

Blood samples were drawn by uniform techniques in all of the DaVita dialysis clinics and transported to the DaVita Laboratory in Deland, Fla, typically within 24 hours. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, creatinine, albumin,
Epidemiological and Statistical Methods

We used logistic regression models to calculate the multivariate adjusted odds ratio (OR) of interdialytic weight gain ≥1.5 kg (compared with <1.5 kg). We chose the 1.5-kg cutoff level because targeting an interdialytic fluid gain below 1.5 to 2.0 kg is suggested as the optimal target. In survival analyses, patients with fluid retention between 1.5 and 2.0 kg were the reference group as the immediately adjacent category to this cutoff level. Survival analyses were performed with time-dependent (quarterly varying) Cox models that included all repeated measures that were averaged over each 13-week calendar quarter. In particular, we examined the association between quarterly averaged ultrafiltration volume and all-cause and cardiovascular mortality during each calendar quarter. For each analysis, 3 levels of multivariate adjustment were examined:

1. A minimally adjusted (here referred to as “unadjusted”) model that included mortality data, ultrafiltration volume categories, baseline height and weight, and the entry calendar quarter (quarters 1 through 8);
2. Case-mix-adjusted models that included all of the above plus age, sex, race, ethnicity (African Americans and other self-categorized blacks, Non-Hispanic whites, Asians, Hispanics and others), diabetes mellitus and 11 preexisting comorbid states, history of tobacco smoking, categories of dialysis vintage (<6 months, 6 months to 2 years, 2 to 5 years, and ≥5 years), primary insurance (Medicare, Medicaid, private, and others), marital status (married, single, divorced, widowed, and other or unknown), the standardized mortality ratio of the dialysis clinic during the entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a dialysis catheter, and residual renal function during the entry quarter (ie, urinary urea clearance); and
3. Malnutrition-inflammation-cachexia syndrome–adjusted models that included all of the covariates in the case-mix model, body mass index, and 12 laboratory variables as surrogates of the nutritional state or inflammation with known association with clinical outcomes in hemodialysis patients: nPNA as an indicator of daily protein intake; serum albumin; serum total iron-binding capacity; serum ferritin; serum creatinine; serum phosphorus; serum calcium; intact parathyroid hormone; serum bicarbonate; peripheral white cell count; lymphocyte percentage; and hemoglobin.

Missing covariate data (<2% for most laboratory and demographic variables and <18% for any of the 10 comorbid conditions) were imputed by the mean or median of the existing values, whichever was more appropriate. All descriptive and multivariate statistics were calculated with SAS version 9.1 (SAS Institute, Inc, Cary, NC) and Stata version 9.0 (Stata Corp, College Station, Tex).

Dr Kalantar-Zadeh contributed to the design and funding of the study, collation and analysis of data, and writing of the manuscript and its revisions. Drs Regidor, Kovesdy, and Bunnapradist contributed to the analysis of the data and reviewed and approved the final manuscript. Dr Van Wyck contributed to the provision of data and final review and approval of the manuscript. Drs Horwich and Fonerow contributed to the study design and manuscript preparation and reviewed and approved the final manuscript.

Results

A total of 69 819 hemodialysis patients underwent long-term hemodialysis treatment over 500 DaVita dialysis clinics across the nation during the 2-year (July 2001 to June 2003) study interval. After the exclusion of patients who did not remain in DaVita beyond 3 months of hemodialysis (ie, 5600 patients from the first 7 calendar quarters and 5870 patients from the last quarter), 58 058 hemodialysis patients remained,
of whom 42,996 hemodialysis patients had all the required prehemodialysis and posthemodialysis weight data documented electronically during every hemodialysis treatment. After weight values of up to 39 thrice-weekly hemodialysis treatments were averaged per each calendar and the averaged fluid retention data per quarter were obtained, patients with a mean interdialytic weight gain $\geq 0.5$ kg in any of the 8 cohort quarters (n = 8,889) were excluded, because they likely had either significant residual renal function or other unusual or acute conditions (such as diarrhea, vomiting, starvation, or blood loss) that could confound the analyses. Hence, the study cohort comprised 34,107 hemodialysis patients, including 21,828 patients (64%) from the first calendar quarter data set (summer 2001) and 12,279 from the subsequent 7 calendar quarters (quarters 2 through 8).

Table 1 compares 4,900 hemodialysis patients whose interdialytic fluid gain was between 0.5 and 1.5 kg with 29,207 hemodialysis patients who gained >1.5 kg of fluid. The greater fluid retainers were younger, included more men and diabetic patients, and had higher body mass index and dietary protein intake (estimated by nPNA), higher serum levels of albumin, creatinine, and phosphorus, and higher total iron-binding capacity concentrations. To examine the correlates of interdialytic fluid gain $>1.5$ kg, we calculated ORs using logistic regression models as shown in Table 2. Older age and female sex were associated with lower likelihood of fluid retention. Diabetic status and longer dialysis vintage over 5 years were associated with 94% and 67% higher risk of greater fluid retention, respectively. Higher dietary protein intake (nPNA), higher serum creatinine, phosphorus,
covariates, a higher interdialytic weight gain (especially after we controlled for demographics and other case-mix factors) was intuitively lower across greater fluid retention volumes, but the reference group, death hazard ratios appeared counterintuitive across higher increments of fluid gain. To study the independent mortality trends across fluid retention categories, we calculated death hazard ratios using time-dependent survival models at 3 levels of multivariate adjustment, as shown in Figure 2. With 1.5 to 2.0 kg of interdialytic fluid gain, a weight gain >4.0 kg over 2 consecutive dialysis sessions was associated with a 28% risk of death, whereas with minimal fluid retention between 0.5 and 1.0 kg, a 26% higher chance of survival was found. A very similar trend was found with cardiovascular mortality, as shown in Figure 3, with 25% increased and 23% decreased cardiovascular death risk for the above-mentioned fluid-gain groups, respectively.

To examine whether greater fluid retention is associated with poor survival across different groups of hemodialysis patients, the mortality predictability of interdialytic weight gain ≥1.5 kg was studied within diverse patient subgroups as shown in Figure 4, and the death risk of high interdialytic weight gain was found to be consistently increased across most of these groups. The death risk due to greater fluid retention was significant among black or nondiabetic hemodialysis patients, those with higher serum albumin levels, and those who had undergone dialysis treatment for <2 years.

### Table 3. Categories of Interdialytic Weight Gain (Fluid Retention) and Mortality and Other Relevant Characteristics in 34 107 HD Patients

<table>
<thead>
<tr>
<th>Fluid Retention Categories, kg</th>
<th>n (%)*</th>
<th>All-Cause Death, n (%)†</th>
<th>Albumin, mg/dL, Mean (SD)</th>
<th>Weight, kg, Mean (SD)</th>
<th>BMI, kg/m², Mean (SD)</th>
<th>Protein Intake, g/kg⁻¹·d⁻¹, Mean (SD)</th>
<th>Patient Age, y, Mean (SD)</th>
<th>Women, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–1.0</td>
<td>1561 (5)</td>
<td>457 (29)</td>
<td>3.65 (0.53)</td>
<td>65.4 (16.7)</td>
<td>23.9 (5.32)</td>
<td>0.88 (0.24)</td>
<td>63.5 (16.3)</td>
<td>57</td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>3025 (9)</td>
<td>785 (26)</td>
<td>3.68 (0.48)</td>
<td>66.7 (16.7)</td>
<td>24.4 (5.3)</td>
<td>0.90 (0.23)</td>
<td>63.8 (15.7)</td>
<td>58</td>
</tr>
<tr>
<td>1.5–2.0 (Reference)</td>
<td>4630 (14)</td>
<td>1103 (24)</td>
<td>3.73 (0.43)</td>
<td>67.9 (16.4)</td>
<td>24.9 (5.4)</td>
<td>0.95 (0.25)</td>
<td>63.1 (15.7)</td>
<td>56</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>5636 (17)</td>
<td>1231 (22)</td>
<td>3.75 (0.41)</td>
<td>70.7 (17.3)</td>
<td>25.5 (5.7)</td>
<td>0.99 (0.24)</td>
<td>61.6 (15.5)</td>
<td>51</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>5700 (17)</td>
<td>1181 (21)</td>
<td>3.76 (0.39)</td>
<td>73.6 (17.8)</td>
<td>26.3 (5.8)</td>
<td>1.02 (0.25)</td>
<td>60.6 (15.1)</td>
<td>47</td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>4679 (14)</td>
<td>936 (20)</td>
<td>3.78 (0.38)</td>
<td>76.8 (18.4)</td>
<td>27.0 (6.1)</td>
<td>1.03 (0.24)</td>
<td>58.5 (15.0)</td>
<td>42</td>
</tr>
<tr>
<td>3.5–4.0</td>
<td>3522 (10)</td>
<td>710 (20)</td>
<td>3.77 (0.39)</td>
<td>80.8 (19.6)</td>
<td>27.9 (6.6)</td>
<td>1.05 (0.25)</td>
<td>57.0 (14.3)</td>
<td>37</td>
</tr>
<tr>
<td>≥4.0</td>
<td>5354 (16)</td>
<td>1025 (20)</td>
<td>3.78 (0.38)</td>
<td>89.6 (24.4)</td>
<td>29.9 (7.6)</td>
<td>1.07 (0.25)</td>
<td>53.5 (13.6)</td>
<td>28</td>
</tr>
</tbody>
</table>

*Values in parentheses represent the proportion of hemodialysis patients in each weight-change category.†Values in parentheses indicate the crude death rate in the indicated group during the 3 years of observation.

BMI indicates body mass index.

To examine the incremental effect of interdialytic weight gain on survival, we created 8 a priori–defined increments of fluid retention that included seven 0.5-kg increments between 0.5 and 4.0 kg and the group with ≥4.0 kg of interdialytic fluid retention. Patient weight and body mass index were higher across increments of fluid retention categories, as were serum albumin and estimated protein intake via nPNA. Crude (unadjusted) mortality appeared lower across higher increments of fluid gain.

To study the independent mortality trends across fluid retention categories, we calculated death hazard ratios using time-dependent survival models at 3 levels of multivariate adjustment, as shown in Figure 2. With 1.5 to 2.0 kg used as the reference group, death hazard ratios appeared counterintuitively lower across greater fluid retention volumes, but after we controlled for demographics and other case-mix covariates, a higher interdialytic weight gain (especially >3.0 kg) was associated with increased risk of death. Additional adjustment for measures of nutritional status did not change the risk of death considerably. In fully adjusted models, compared with 1.5 to 2.0 kg of interdialytic fluid gain, a weight gain >4.0 kg over 2 consecutive dialysis sessions was associated with a 28% risk of death, whereas with minimal fluid retention between 0.5 and 1.0 kg, a 26% higher chance of survival was found. A very similar trend was found with cardiovascular mortality, as shown in Figure 3, with 25% increased and 23% decreased cardiovascular death risk for the above-mentioned fluid-gain groups, respectively.

To examine whether greater fluid retention is associated with poor survival across different groups of hemodialysis patients, the mortality predictability of interdialytic weight gain ≥1.5 kg was studied within diverse patient subgroups as shown in Figure 4, and the death risk of high interdialytic weight gain was found to be consistently increased across most of these groups. The death risk due to greater fluid retention was significant among black or nondiabetic hemodialysis patients, those with higher serum albumin levels, and those who had undergone dialysis treatment for <2 years.

![Figure 2](image-url). Hazard ratios (and 95% confidence interval error bars) for all-cause death for the entire range of interdialytic fluid gain categories in 34 107 hemodialysis patients over 2 years (July 2001 to June 2003). Hazard ratios were calculated via time-dependent Cox regression with 3 levels of multivariate adjustment (i.e., minimally adjusted [herewith referred to as “unadjusted,” including adjustment for baseline height and weight and calendar quarter, adjusted for case mix [including additional adjustment for age, sex, race/ethnicity, diabetes mellitus and other comorbid states, dialysis vintage, tobacco smoking, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function], and malnutrition-inflammation-cachexia syndrome [MICS] surrogates (including 10 laboratory markers; see text). Note that patient population frequency in each group is demonstrated via background gray bars. Weight change 1.5–1.99 is the reference group.
Patients with no history of cardiovascular disease also exhibited stronger death predictability of fluid gain (data not shown).

Discussion

We found that among 34,107 long-term hemodialysis patients from a large dialysis organization in the 21st century, 86% gained >1.5 kg of body fluid between 2 consecutive dialysis treatment sessions. Younger patients, male and diabetic patients, and those with higher protein intake and better nutritional status were greater fluid retainers. After we controlled for these confounders, higher interdialytic weight gain was incrementally associated with increased risk of death over 2 years of observation. The incremental death predictability of fluid retention was robust for both all-cause and cardiovascular mortality. The mortality association of interdialytic weight gain >1.5 kg appeared somewhat consistent across different subgroups of hemodialysis patients. Patients with the lowest interdialytic fluid retention (<1.0 kg) had a robust survival advantage and the lowest cardiovascular death risk irrespective of confounders. These data suggest that in individuals with advanced CKD who require maintenance dialysis treatment, higher amounts of fluid gain are associated with poor survival and increased cardiovascular death.

Fluid retention is the main clinical feature in several pathological conditions, including a number of renal and cardiovascular disorders. Fluid overload is usually the main manifestation of decompensated heart and kidney failure, so that not infrequently, these 2 conditions cannot be distinguished from each other solely on the basis of clinical signs or symptoms.18 In advanced heart failure, compensatory mechanisms may lead to maladaptive consequences.19 Increased sympathetic nervous system, renin-angiotensin-aldosterone system, and antidiuretic hormone release can lead to a vicious circle in that augmentation of preload, contractility, and afterload via these mechanisms may worsen fluid overload.20–22 Even though diuretics remain the main medical therapy in both heart failure and CKD, administration of...
albumin or neurohormonal antagonists such as vasopressin receptors antagonists, aldosterone antagonists, or nesiritide may help restore plasma volume and osmolality.23 In refractory fluid-retention cases, however, fluid removal via dialysis treatment (ie, the so-called ultrafiltration) offers a fast and effective alternative to medical therapy.24

Thrice-weekly hemodialysis treatment is currently offered to some 400 000 Americans with CKD stage 5 to remove uremic toxins and to restore electrolyte balance. Concurrent fluid removal via ultrafiltration, however, is also performed during virtually each hemodialysis treatment. This intermittent ultrafiltration leads to nonphysiological fluctuations in body fluid, as shown in Figure 1. More frequent (eg, daily) hemodialysis or peritoneal dialysis treatments that appear more consistent with the physiological fluid alterations are currently administered in fewer than 10% of all adult dialysis patients in the United States. Hence, it is common for patients to gain weight due to fluid retention between 2 consecutive hemodialysis sessions, usually 2 to 3 days apart. Adherence to fluid restrictions represents one of the most difficult aspects of the hemodialysis treatment regimen.25,26 We found that 86% of the 34 107 dialysis patients in the present study retained at least 1.5 L of fluid during 2 consecutive dialysis sessions. In addition to younger age, male sex, longer dialysis vintage, diabetic status, and larger body size, having a better nutritional status that included a higher dietary protein intake was also associated with higher likelihood of excessive fluid retention. Most of the foregoing associations are biologically and clinically plausible, given the assumption that greater appetite and food intake is also associated with higher amount of fluid intake, with resultant fluid overload. Nevertheless, nutritional status per se is a strong and robust predictor of greater survival in both dialysis and heart failure patients. Hence, the association between increased interdialytic weight gain and mortality may be confounded and overshadowed by the nutritional link with survival. Consistent with the latter expectation, the present analyses showed that crude mortality appeared paradoxically lower in individuals with higher fluid retention (Table 3). However, after multivariate adjustment, an opposite association was disclosed (online-only Data Supplement Table and Figures 2 and 3). Among the case-mix variables, age was the most influential confounder in reversing the associations, followed by sex and race. Younger patients, who are usually healthier and who have greater appetite, have greater food and fluid intake, which leads to the spurious association in unadjusted models. Hence, all things being equal, restriction of fluid gain appears to be associated with greater survival.

In the present study, we found that greater interdialytic weight gain was also associated with an incrementally higher risk of cardiovascular mortality. Similarly, in heart failure patients, volume overload, as indexed by pulmonary capillary wedge pressure, is associated with worse outcomes.27 Among dialysis patients, almost half of the cases of mortality, which currently exceeds 20% per year, are attributed to cardiovascular diseases.28 Traditional cardiovascular risk factors such as hypercholesterolemia, hypertension, or obesity are not associated with this excessive cardiovascular death risk in dialysis patients, an unresolved survival paradox that is also observed in chronic heart failure.5,9,29–32 Instead, malnutrition, inflammation, and wasting are strong correlates of cardiovascular mortality in dialysis patients.33 Although a diagnosis of heart failure per se is associated with higher risk of death in dialysis patients,34 the association we found between higher fluid retention and mortality independent of comorbid conditions is reported for the first time, to the best of our knowledge. Intermittent fluid retention may imitate intermittent episodes of acute decompensated heart failure, leading to fluctuations in compensatory mechanisms, including catecholamine release to increase sympathetic activity,35 as well as changes in the renin-angiotensin-aldosterone system and antidiuretic hormone,19 which alone or together may increase the risk of cardiovascular events and death.18

Another interesting finding was that blacks, who make up almost one third of all dialysis patients in the United States, showed the strongest association between fluid retention and mortality in the present study (Figures 3 and 4). Whereas in the US general population, blacks have a lower life expectancy than whites, they have far greater survival chances once on dialysis, a phenomenon also known as “African American paradox.”10 The fluid-retention–survival association was also stronger in nondiabetic dialysis patients and those who had been undergoing dialysis for <2 years or those with better nutritional status (reflected by serum albumin >3.8 g/L). Nevertheless, we found no group of dialysis patients in whom fluid retention conferred survival advantages.

The present study should be qualified for its observational-epidemiological nature, its retrospective nature, and the lack of more elaborate and precise measures of fluid retention, such as bioelectrical impedance analyses or radioactively-tagged molecules.36,37 Furthermore, the target “dry weight,” which is usually determined by the nephrologist on the basis of his/her clinical judgment, may not necessarily reflect the optimal edema-free status of the patient. However, in thrice-weekly hemodialyzed patients, it is highly unlikely that weight gain between 2 consecutive hemodialysis sessions would be due to reasons other than interdialytic fluid gain. Another limitation was the lack of data on measurement of dietary fluid intake, especially because interdialytic weight gain correlated with surrogates of nutritional status. However, we examined and controlled for biochemical measures of nutritional status, including nPNA (normalized protein catabolic rate) and serum albumin, transferrin, creatinine, and phosphorus. Furthermore, even though we did not have explicit markers of inflammation (themselves strong mortality predictors in dialysis and heart failure patients27,38), we controlled for white blood cell count and administered erythropoietin dose, which have significant associations with inflammation in hemodialysis patients.39,40 Another limitation of the present analysis is that it was based on a 2-year period of the cohort, rather than a longitudinal follow-up of many years. Nonetheless, hemodialysis is a state with high mortality, because on average, more than one third of dialysis patients in the United States die within 2 years of commencing hemodialysis treatment.28 Hence, any insight into the short-term survival of dialysis patients is of major clinical relevance.

The strengths of the present study include the following: (1) its contemporary nature, because all patient data were
obtained from the 21st century (2001–2003); (2) uniform laboratory measurements, with all laboratory data obtained from a single facility; (3) large sample size; (4) 3-month averaged laboratory, predialysis, and postdialysis weight data from virtually every single dialysis session, as well as the use of the means of several measurements to minimize measure- ment variability; (5) a large proportion of incident hemodi- alysis patients, who are less amenable to survivor bias; and (6) the use of time-dependent survival models and sensitivity analyses.

Conclusions
In long-term hemodialysis patients, higher interdialytic weight gain is associated with poor survival and increased cardiovascular death. Patients with the lowest interdialytic fluid retention have the greatest survival. The mortality predictability of higher interdialytic weight gain is observed across most subgroups of hemodialysis patients. Given the striking similarities between individuals with chronic heart failure and those with advanced CKD undergoing long-term dialysis treatment, the mechanisms by which fluid retention influences survival in dialysis patients may be similar to those that occur in heart failure patients. Hence, examination of the pathophysiological mechanisms that link fluid retention to increased cardiovascular death and of effective strategies that can mitigate fluid retention may lead to improved outcome in dialysis patients, and this warrants further research.

Sources of Funding
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Disclosures
None.

References
Management of fluid status is a significant clinical challenge in both individuals with heart failure and those with chronic kidney disease who undergo hemodialysis treatment. Volume overload may be associated with poor clinical outcomes, but it is not clear whether greater amounts of fluid retention are associated with increased mortality. In this 2-year cohort of 34,107 long-term hemodialysis patients across the United States, patients with an average weight gain of at least 0.5 kg between 2 consecutive (thrice-weekly) hemodialysis treatments were studied. We found that 86% of patients gained 1.5 kg or more between 2 hemodialysis sessions, probably due to fluid retention. After controlling for demographics and measures of nutritional status, higher weight gains were incrementally associated with higher all-cause and cardiovascular mortality. These associations remained consistent across different subgroups of hemodialysis patients. Although the mechanisms by which fluid retention influences cardiovascular survival in hemodialysis patients remain unknown, these associations may better justify ongoing efforts to restrict fluid retention in these patients. Given the striking similarities between hemodialysis and heart failure patients and the recently heightened enthusiasm about ultrafiltration treatment in heart failure patients, these findings may have clinical implications for current management of patients with edematous states.
Fluid Retention Is Associated With Cardiovascular Mortality in Patients Undergoing Long-Term Hemodialysis

Kamyar Kalantar-Zadeh, Deborah L. Regidor, Csaba P. Kovesdy, David Van Wyck, Suphamai Bunnpradist, Tamara B. Horwich and Gregg C. Fonarow

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### ON-LINE APPENDIX (optional):

**Table.** Hazard ratios of death for the magnitude of the interdialytic fluid gain, based on time dependent Cox regression models. **Upper panel:** All-cause mortality; **Lower panel:** Cardiovascular (CV) mortality

<table>
<thead>
<tr>
<th>All-cause death</th>
<th>Unadjusted</th>
<th>Case-mix adjusted</th>
<th>Case-mix &amp; MICS adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid gain range (kg)</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>0.5 - 0.99</td>
<td>0.66 (0.60-0.71)</td>
<td>&lt;0.001</td>
<td>0.81 (0.75-0.88)</td>
</tr>
<tr>
<td>1.0 - 1.49</td>
<td>1.00 (0.93-1.07)</td>
<td>0.9</td>
<td>1.00 (0.93-1.08)</td>
</tr>
<tr>
<td>1.5 - 1.99 (reference)</td>
<td>1.00 n/a</td>
<td>1.06 (0.99-1.13)</td>
<td>0.10</td>
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<tr>
<td>2.0 - 2.49</td>
<td>1.01 (0.95-1.09)</td>
<td>0.7</td>
<td>1.05 (0.98-1.12)</td>
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<tr>
<td>2.5 - 2.99</td>
<td>0.89 (0.83-0.96)</td>
<td>0.001</td>
<td>1.16 (1.08-1.25)</td>
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<tr>
<td>3.0 - 3.49</td>
<td>0.92 (0.85-0.99)</td>
<td>0.02</td>
<td>1.14 (1.05-1.23)</td>
</tr>
<tr>
<td>3.5 - 3.99</td>
<td>0.82 (0.76-0.89)</td>
<td>&lt;0.001</td>
<td>1.30 (1.21-1.40)</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>0.82 (0.77-0.88)</td>
<td>&lt;0.001</td>
<td>1.30 (1.21-1.40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular death</th>
<th>Unadjusted</th>
<th>Case-mix adjusted</th>
<th>Case-mix &amp; MICS adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid gain range (kg)</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
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<tr>
<td>0.5 - 0.99</td>
<td>0.57 (0.50-0.65)</td>
<td>&lt;0.001</td>
<td>0.70 (0.62-0.80)</td>
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<td>1.0 - 1.49</td>
<td>0.98 (0.87-1.09)</td>
<td>0.7</td>
<td>0.98 (0.88-1.10)</td>
</tr>
<tr>
<td>1.5 - 1.99 (reference)</td>
<td>1.00 n/a</td>
<td>1.03 (0.92-1.14)</td>
<td>0.6</td>
</tr>
<tr>
<td>2.0 - 2.49</td>
<td>0.98 (0.89-1.09)</td>
<td>0.7</td>
<td>1.07 (0.97-1.19)</td>
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<tr>
<td>2.5 - 2.99</td>
<td>0.93 (0.84-1.03)</td>
<td>0.15</td>
<td>1.17 (1.04-1.30)</td>
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<tr>
<td>3.0 - 3.49</td>
<td>0.93 (0.84-1.04)</td>
<td>0.21</td>
<td>1.19 (1.06-1.34)</td>
</tr>
<tr>
<td>3.5 - 3.99</td>
<td>0.88 (0.78-0.98)</td>
<td>0.03</td>
<td>1.30 (1.17-1.45)</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>0.84 (0.76-0.93)</td>
<td>&lt;0.001</td>
<td>1.30 (1.17-1.45)</td>
</tr>
</tbody>
</table>

MICS: Malnutrition-inflammation complex syndrome, n/a: not applicable.

Hazard ratios are calculated via time-dependent Cox regression with 3 levels of multivariate adjustment, i.e., minimally adjusted (herewith referred to as “unadjusted” including adjustment for baseline height and weight and calendar quarter), adjusted for “case-mix” (including additional adjustment for age, gender, race/ethnicity, diabetes mellitus and other comorbid states, dialysis vintage, tobacco smoking, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function); and “malnutrition-inflammation-cachexia syndrome” (MICS) surrogates (including 10 laboratory markers, see text).