Dose of Hemodialysis and Survival
Differences by Race and Sex

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Context.—Although blacks receive lower doses of hemodialysis than whites, their survival when receiving dialysis treatment is better than that for whites. Previous studies of the relationship between the dose of dialysis and patient survival have not controlled for differences in patient characteristics.

Objective.—To examine the association of mortality with the dose of hemodialysis for clusters of patients categorized by race and sex.

Design.—Retrospective analysis of laboratory data and mortality outcomes from 1994, using a national database of hemodialysis patients.

Patients.—A total of 18,144 black and white patients receiving hemodialysis 3 times weekly who either lived the entire year receiving hemodialysis or died.

Main Outcome Measures.—The fractional reduction of urea in a single dialysis session as the measured hemodialysis dose (urea reduction ratio [URR]) after controlling for race, sex, age, and diabetes mellitus. Mortality was determined by strata of URRs and albumin and creatinine levels.

Results.—Across all age categories, blacks had lower URRs than whites, and men had lower URRs than women. In an age-adjusted model for evaluating interactions among URRs, race, sex, and diabetes, the association of URR with mortality risk was weak among blacks, particularly black men. After adjustment for age and diabetes, death probability curves were most steep for white women with URR values less than 60%. The death probability curves were least steep for black men. There was no meaningful difference between death probability and albumin or creatinine concentration among the race by sex clusters.

Conclusion.—Using URR, the usual measure of hemodialysis dose, the assumption that the association between dialysis dose and survival is uniform across demographic groups appears incorrect. Comparisons of the quality of dialysis patient care should not rely on URR alone to predict patient survival.

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BECAUSE the uremic toxin(s) has not been identified, the quantity of urea removed during hemodialysis is a clinically accepted surrogate to define the patient’s risk profile. Numerous studies have demonstrated an association between the dose of hemodialysis and mortality among patients with end-stage renal disease (ESRD), when all demographic groups of patients are evaluated together. The 2 commonly accepted measures of hemodialysis dose are based on the fractional reduction of blood urea nitrogen concentration during a single hemodialysis treatment. The most frequently used measure of hemodialysis dose is the urea reduction ratio (URR), calculated by dividing the decrease in blood urea nitrogen (predialysis minus postdialysis blood urea nitrogen) by the predialysis concentration, expressed as a percentage. Another measure of hemodialysis dose is based on the pharmacokinetic theory that the fractional decrease in urea during a dialysis treatment is a mathematical function of the artificial kidney’s clearance of urea (Kt/V) times the length of the treatment (t), divided by the urea distribution volume (V), approximated by the total body water (TBW). This ratio, Kt/V, can be calculated from the URR and they are conceptually and mathematically similar. Patient mortality is higher when the amount of urea removed (hemodialysis “dose”) is low, and vice versa. Retrospective studies of mortality outcome for patients with ESRD suggest that the odds of death progressively increase when URR falls lower than 60% to 65%. Such findings, and an evidence-based professional consensus, have led 3 national processes had 3 parts. First, the logistic

METHODS

Data were taken from the routine analytical files of Fresenius Medical Care–North America (Lexington, Mass) for 1994, Patients not classified as black or white were excluded, leaving 18,144 patients who received hemodialysis treatments 3 times weekly, and either lived the entire year receiving dialysis or died. Values for the URR and serum albumin and creatinine concentrations measured during the last 3 months of 1993 were averaged for each patient. All measurements were performed by a single laboratory (LifeChem Clinical Laboratories, Rockleigh, NJ). Total body water and body surface area were calculated using accepted formulas. Two complementary strategies were used. Both focused on the association of mortality with URR, albumin, and creatinine within clusters of patients categorized by race and sex. The independent target measures of URR, albumin, and creatinine were treated as continuous variables. The process had 3 parts. First, the logistic

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form of the relationship between odds of death and each measure was evaluated as previously reported.21,22,24 Odds ratios (ORs) for death, adjusted for age, sex, race, and diabetes mellitus, were compared with a reference stratum for each to visually evaluate the form of the mortality relationships among all patients. Separate models, in which each target was treated as either a first (eg, URR, a linear form) or second (eg, URR and URR², a quadratic form of URR) order polynomial adjusted for age, race, sex, and diabetic status, were also evaluated. Second, each of the 3 primary targets was evaluated using a logistic regression model that included race, sex, age, and diabetes as well as interaction terms between the target and the race, sex, and diabetes clusters. Third, separate URR, albumin, and creatinine logistic models were evaluated for each race by sex cluster adjusting for age and diabetes. First-order models were used for albumin and creatinine; the second order model was used for URR.

Four ordered strata, each for URR, albumin, and creatinine, were constructed based on clinically relevant and statistically practical values for each variable. Mortality gradients between the strata of URR, albumin, and creatinine were evaluated by χ² analysis. The χ² was partitioned into linear and residual components, allowing evaluation of whether there existed a linear trend difference among the strata and/or if there existed differences not explained by a linear trend.22,28

**RESULTS**

The patients' median age was 63.2 years (black men, 60.0 years; black women, 64.1 years; white men, 62.6 years; white women, 66.7 years). Thirty-nine percent of the patients were diagnosed as having diabetes (black men, 29.4%; black women, 46.6%; white men, 36.7%; white women, 43.3%). Blacks had lower mortality rates than whites. Table 1 shows summary statistics for race by sex clusters. The differences in weight (F = 537; P < .001), TBW (F = 4140; P < .001), and body surface area (F = 1196; P < .001) among clusters were significant. All these values were higher in blacks than whites and in men than women. Similarly, URR values differed significantly among clusters (F = 588; P < .001), highest among black women and lowest among black men. The URR was inversely associated with body weight (r = -0.33; P < .001), TBW (r = -0.38; P < .001), body surface area (r = -0.36; P < .001), creatinine (r = -0.22; P < .001), and albumin (r = -0.016; P < .04). Albumin and creatinine concentrations were higher in men and blacks. The association of creatinine and albumin with TBW was direct (rcreatine = 0.35, P < .001; rablumin = 0.16, P < .001).

**Logistic Modeling**

Logistic modeling using continuous rather than stratified variables revealed significant first-order effects for URR, serum albumin, and creatinine concentrations. However, significant second-order effects were observed for URR only. Since including the second-order URR² term better described what was observed clinically, and was statistically significant, the remaining logistic evaluations of URR included a second-order term.

Table 2 summarizes the age-adjusted model, evaluating interactions between URR and the race, sex, and diabetes clusters. There was a strong interaction between race and URR (race × URR; race × URR²), suggesting that the significant association of mortality risk with URR was manifest mainly among whites. In contrast, the interactions among URR and sex and diabetes were not significant (sex × URR; sex × URR²; diabetes × URR; diabetes × URR²). The association between URR and mortality was not significant (P = .10) after adjustment for the cluster variables and interactions, suggesting that the association of URR with mortality risk was weak among blacks, particularly men.

Table 3 shows a similar model evaluating possible interactions with the serum albumin concentration. The inverse association of albumin with death risk was highly meaningful (OR, 0.19). There were significant interactions of albumin with sex and diabetes (sex × albumin; diabetes × albumin), each serving to increase the OR for death associated with it (ORsex × albumin, 0.23; ORdiabetes × albumin, 0.25). The race interaction nearly achieved statistical significance (ORrace × albumin, 0.23). However, interactions with albumin were small, and the effect of albumin was highly meaningful among all clusters. A similar analysis of creatinine concentration was performed (data not shown). Creatinine was also inversely associated with odds of death (OR, 0.89; 95% confidence interval, 0.92-0.88 per 1 mg/dL increase); there were no significant interactions with race, sex, or diabetes.

Figure 1 shows death probability curves associated with URR, albumin,
Table 3.—Logistic Regression Model of Association of Serum Albumin Concentration With Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>( \chi^2 )</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.9169</td>
<td>0.4005</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Age</td>
<td>0.0284</td>
<td>0.0015</td>
<td>372.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race†</td>
<td>−0.5491</td>
<td>0.4071</td>
<td>1.8</td>
<td>.18</td>
</tr>
<tr>
<td>Sex‡</td>
<td>−1.3125</td>
<td>0.4098</td>
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<td>.002</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus§</td>
<td>−0.8440</td>
<td>0.4137</td>
<td>4.2</td>
<td>.04</td>
</tr>
<tr>
<td>Serum albumin concentration</td>
<td>−1.6782</td>
<td>0.1034</td>
<td>273.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex × serum albumin concentration</td>
<td>0.2033</td>
<td>0.1094</td>
<td>3.4</td>
<td>.06</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus × serum albumin concentration</td>
<td>0.2895</td>
<td>0.1113</td>
<td>6.7</td>
<td>.009</td>
</tr>
</tbody>
</table>

*Exponentiating the coefficient gives an estimate of the death odds ratio for the albumin in that group. For groups that are not reference groups, combining the interaction coefficients with the albumin coefficient gives coefficients for particular groups. Ellipses indicate data not applicable because intercept cannot have \( \chi^2 \) or \( P \) values.
†Black is the reference group.
‡Men are the reference group.
§Individuals not having type 2 diabetes mellitus are the reference group.

**Figure 1.—**Composite illustrating the death probability functions by race and sex for urea reduction ratio, serum albumin concentration, and serum creatinine concentration.

And creatinine that resulted from separate logistic models evaluated for each race by sex cluster, after adjustment for age and diabetes. A steep increase in the risk of death occurred among white women as URR values fell below 60%. To a lesser extent, an increased death risk was also seen at similar URR values among white men. The association of URR with mortal risk was least steep among black men and women. The increase in risk at low albumin concentrations was steeper among men than women. The form of the relationship between mortality and creatinine did not differ between the race by sex clusters.

**Stratification**

Table 4 evaluates the strata of URR, albumin, and creatinine among all patients. The gradients along the strata for albumin and creatinine were monotonic and inverse. The death rate for each stratum of higher concentrations of albumin or creatinine was lower than for adjacent strata of lower concentrations. This was not observed for URR. Statistical tests revealed highly significant linear trends for each measure. Residual differences among the strata were smaller or did not exist.

**Figure 2 illustrates** the relationship of URR to death rate for each race by sex cluster. Neither the linear (\( \chi^2 = 0.99 \)) nor residual (\( \chi^2 = 0.54 \)) differences between the strata were significant for black men. The linear value (\( \chi^2 = 3.81; P = .05 \)) but not the residual value (\( \chi^2 = 3.12; P = .21 \)), was significant for black women. The relationship between URR and death rate was monotonic and highly significant among white women. Among white men it was nonmonotonic; both linear and residual \( \chi^2 \) statistics were significant. If only the lower 3 strata (URR ≤ 55% through 60%–65% for white men) were considered, the linear difference among strata was significant (\( \chi^2 = 18.42; P < .001 \)), while the residual component was not (\( \chi^2 = 0.03; P = .85 \)). Thus, the significant residual \( \chi^2 \) statistic was caused by the slightly greater death rate observed in the highest URR strata.

**Figure 3 shows** death rates associated with albumin concentration among the race by sex clusters. The relationships were monotonic in all clusters. The linear \( \chi^2 \) value was highly significant for all 4 clusters (\( P < .001 \)) and residual \( \chi^2 \) value was only highly significant for black and white men. For creatinine concentration, the relationship to death rate was also monotonic, inverse, and similar among the clusters (data not shown). The linear \( \chi^2 \) value was highly significant for all 4 clusters (\( P < .001 \)) but residual \( \chi^2 \) value was not (\( P > .05 \)). Further partitioning of the race by sex clusters by diabetes revealed similar trends for all 3 primary target variables (data not shown).

**COMMENT**

A hypothesis offered for the enhanced survival enjoyed by blacks receiving dialysis is that blacks and whites have differential sensitivity to the hemodialysis dose. The goal of the current analysis was to evaluate the assumed null hypothesis of no difference among the races and sexes with respect to their mortality response to URR. Many mathematical models can be used to describe relationships among even a limited number of variables. All such models must be regarded as taken from a number of possible models, and it is difficult to say with certainty which representation best reflects reality. Therefore, we supplemented logistic modeling with evaluation of simple contingency tables of the race by sex clusters stratified by URR, albumin, or creatinine. The decline in survival at lower URR was higher among whites than blacks, especially among white women. Such differences among the race by sex clusters were much less for the other predictors (serum albumin and creatinine concentrations) of survival in patients with ESRD. Therefore, the data suggest that the hypothesis of no difference is incorrect.

An arguable criticism of the current analysis is that URR is an imprecise measure of the total urea clearance during a single hemodialysis session. The URR does not account for convective clearance of solute achieved by fluid removal during hemodialysis. Black patients may have larger weight gains than white patients, so affect more solute clearance than is appreciated by URR. However, there is no evidence that blacks routinely have greater weight gains, especially across all age groups. An additional issue is that URR does not account for the contribution of residual renal function. Arguably, blacks with ESRD may have greater residual renal function, so they require less clearance from hemodialysis. There is no evidence to confirm or dispute this hypothesis.

Differential racial sensitivity to hemodialysis dose may contribute to the survival advantage of blacks with ESRD. If blacks are less sensitive to lower doses...
of hemodialysis, black patients with URR values lower than 65% will not exhibit an exaggerated mortality in comparison with whites. A fundamental biological question is the explanation for this difference. The data presented herein suggest that one component is that the prevalent measure of the dose of hemodialysis is flawed. Blacks were observed to have greater weight, TBW, body surface area, serum albumin levels, and creatinine concentrations than whites. Therefore, lower URRs among blacks and men were a consequence of their larger urea distribution volume. Since TBW was directly associated with albumin and creatinine concentrations, urea distribution volume may be viewed as a nutritional surrogate. Such nutritional surrogates are powerful and independent mortality outcome predictors for dialysis patients.\textsuperscript{14,11,21-25} We propose that the nutritional-derived effect of urea distribution volume on death risk may supersede its mortality impact by way of the hemodialysis dose.\textsuperscript{22} As viewed by segregating them into their components, a low URR or mathematical function of the artificial kidney’s clearance of urea times the length of the treatment, divided by the urea distribution volume (Kt/V) may have 2 etiologies that result in different mortality effects. A low URR may be due to a low mathematical function of the artificial kidney’s clearance of urea times the length of the treatment (eg, too little solute removal), which would enhance the patient’s death risk. Alternatively, a low URR may be due to a large urea distribution volume (eg, improved muscle mass and nutrition), and the latter would confer a lower death risk. We propose these complex clinical, laboratory, and statistical linkages may contribute to the observed differential death risk in small white women and large black men, respectively. This statistical and clinical chain of logic suggests that different doses of hemodialysis are not required for blacks and whites. Instead, the conventional measure of dialysis dose needs to be refined.

Urea reduction ratio is illustrative of the difficulty encountered establishing national clinical performance measures and clinical performance goals. The iterative and evolutionary nature of the science behind clinical practice recommendations mandates that they be dynamic. The 1997 Balanced Budget Amendment mandates the development of methods to measure and report on the quality of renal dialysis services provided under Medicare.\textsuperscript{24} Because of this mandate, URR was offered.\textsuperscript{25} A fundamental assumption, supporting the use of URR as a national clinical performance measure, is that its statistical relationship to patient mortality is the same for all patient subgroups.\textsuperscript{3} Using this chain of logic, manipulating URR is a simple way to predictably affect dialysis patient mortality.\textsuperscript{12,11} However, based on the representative patient database presented herein, manipulating URR alone may not be sufficient to improve mortality. A differential mortality response to changes in dialysis dose may account for the lesser improvement in survival probability for blacks in comparison with whites from 1984 to 1994, a period during which the amount of dialysis increased for all racial groups.\textsuperscript{13,36}

### Table 4.—Stratification of Urea Reduction Ratio, Serum Albumin Concentration, and Serum Creatinine Concentration Survival Statistics for All Patients

<table>
<thead>
<tr>
<th>Urea Reduction Ratio</th>
<th>Serum Albumin Concentration</th>
<th>Serum Creatinine Concentration</th>
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</thead>
<tbody>
<tr>
<td>Strata, %</td>
<td>No. of Patients</td>
<td>% Died</td>
</tr>
<tr>
<td>≤55</td>
<td>2769</td>
<td>20.98</td>
</tr>
<tr>
<td>55-60</td>
<td>3328</td>
<td>18.51</td>
</tr>
<tr>
<td>60-65</td>
<td>4625</td>
<td>17.51</td>
</tr>
<tr>
<td>&gt;65</td>
<td>7422</td>
<td>17.73</td>
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</table>

Statistic

<table>
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<tr>
<th>Parameter</th>
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<tr>
<td>(x^2)</td>
<td>.001</td>
<td>(x^2)</td>
<td>.001</td>
<td>(x^2)</td>
<td>.001</td>
</tr>
<tr>
<td>Linear</td>
<td>.001</td>
<td>Linear</td>
<td>.001</td>
<td>Linear</td>
<td>.001</td>
</tr>
<tr>
<td>Residual</td>
<td>.08</td>
<td>Residual</td>
<td>.001</td>
<td>Residual</td>
<td>.001</td>
</tr>
</tbody>
</table>

*To convert creatinine from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 88.4.

Figure 2.—Death rates for each race by sex cluster stratified by urea reduction ratio. The \(\chi^2\) statistic is partitioned into linear and residual components.
The observation of different patient outcomes by race and sex confounds the application of URR as a core indicator or clinical performance measure for hemodialysis. Patient mortality may not be within immediate physician control by effecting this process measure. Furthermore, quality comparisons of dialysis care that use URR as a clinical performance measure should be circumspect of the previous assumption that lower URR values routinely mean that patients’ outcomes will be compromised. External comparisons of URR profiles of different nephrologists and dialysis units should likewise be undertaken with consideration of these constraints. However, lower hemodialysis doses should not be prescribed based on race or sex differences. Validation of these findings from prospective trials and using other databases with more precise measures of dialysis dose, such as the National Institutes of Health’s HEMOdialysis Study, are needed. Finally, because higher URR frequently requires increasing the duration of hemodialysis, and this is a major quality-of-life issue for many patients, correct advice about the consequences of a low URR must be based on accurate information about death risk in the context of the patient’s demographic profile.

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