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The dose of hemodialysis and patient mortality

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The dose of hemodialysis and patient mortality. The relationship between the delivered dose of hemodialysis and patient mortality remains somewhat controversial. Several observational studies have shown improved patient survival with higher levels of delivered dialysis dose. However, several other unmeasured variables, changes in patient mix or medical management may have impacted on this reported difference in mortality. The current study of a U.S. national sample of 2,311 patients from 347 dialysis units estimates the relationship of delivered hemodialysis dose to mortality, with a statistical adjustment for an extensive list of comorbidity/risk factors. Additionally this study investigated the existence of a dose beyond which more dialysis does not appear to lower mortality. We estimated patient survival using proportional hazards regression techniques, adjusting for 21 patient comorbidity/risk factors with stratification for nine Census regions. The patient sample was 2,311 Medicare hemodialysis patients treated with bicarbonate dialysate as of 12/31/90 who had end-stage renal disease for at least one year. Patient follow-up ranged between 1.5 and 2.4 years. The measurement of delivered therapy was based on two alternative measures of intradialytic urea reduction, the urea reduction ratio (URR) and Kt/V (with adjustment for urea generation and ultrafiltration). Hemodialysis patient mortality showed a strong and robust inverse correlation with delivered hemodialysis dose whether measured by Kt/V or by URR. Mortality risk was lower by 7% ($P = 0.001$) with each 0.1 higher level of delivered Kt/V. (Expressed in terms of URR, mortality was lower by 11% with each 5 percentage point higher URR; $P = 0.001$). Above a URR of 70% or a Kt/V of 1.3 these data did not provide statistical evidence of further reductions in mortality. In conclusion, the delivered dose of hemodialysis therapy is an important predictor of patient mortality. In a population of dialysis patients with a very high mortality rate, it appears that increasing the level of delivered therapy offers a practical and efficient means of lowering the mortality rate. The level of hemodialysis dose measured by URR or Kt/V beyond which the mortality rate does not continue to decrease, though not well defined with this study, appears to be above current levels of typical treatment of hemodialysis patients in the U.S.

The landmark of experimental dialysis studies, the National Cooperative Dialysis Study (NCDS), was reported in 1983 [1]. This study was and remains the premier scientific effort to quantify the amount and components of dialysis therapy provided to a patient and their correlations with patient outcomes. Both the NCDS and subsequent analyses [2] focused on the serum urea concentration. One formulation of the dose of dialysis for urea is the Kt/V where K is the total (dialyzer plus residual renal function) urea clearance (ml/min), t is the duration of the dialysis treatment (minutes) and V is the patient's urea volume of distribution or total body water volume (ml). Based on the NCDS study data, Gotch and Sargent suggested a minimum target Kt/V of 1.0 (3 times per week) as adequate therapy. When residual renal function is negligible, total K equals dialyzer K. A related measurement of dose of dialysis, the urea reduction ratio (URR), has been utilized by Owen et al [3]. The URR is 1 minus the ratio of the post-dialysis over the pre-dialysis blood urea nitrogen (BUN) expressed in percent. Several investigators have shown a correspondence between Kt/V and URR while some have shown a mathematical relationship between the two measurements [4–7].

The relevance and predictive value of either of these blood urea measurements as indicators of the dose of dialysis therapy is in a general state of refinement with recent developments pointing towards a more widespread acceptance of such quantification in the U.S. [8–10]. The interest in a valid measurement of the adequacy of delivered dialysis is intensified by the high mortality rate for dialysis patients, reports that dialysis patient mortality in the U.S. is higher than in other societies [11, 12], reports of substantial variation in mortality rates by dialysis unit [13], as well as evidence that the level of prescribed dialysis treatment is below "recommended clinical standards" for a substantial fraction of the U.S. dialysis population [14]. What constitutes an optimal prescription for uremic toxin clearance in the chronic hemodialysis patient is still controversial.

There have been very few multicenter studies of the adequacy of dialysis therapy and subsequent mortality in the U.S. or other countries. Owen et al [3], reporting on the experience in over 400 dialysis units of National Medical Care Inc., have shown that mortality is lower at higher doses of dialysis, measured as URR. However, this study did not adjust for comorbid conditions of patients. This and other recent reports suggest a correlation of lower mortality with higher dose of hemodialysis therapy [15–19]. The National Institutes of Health funded a multicenter multiyear prospective randomized trial of the impact of dialysis dose and dialyzer flux on morbidity and mortality which is currently in progress.

The current study reports on the dose of delivered hemodialysis and the correlation of mortality from a national random sample of over 2,300 Medicare ESRD patients. This historical prospective study is also unique in the level of detail of measured patient comorbid conditions determined at the start of the study.

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Methods

Data source

The data used in these analyses originate from the Special Study of Case Mix Adequacy of the United States Renal Data System [20], with supplemental information from the USRDS database.

The goals of this special study included determining the relationship of dose of dialysis, and dialyzer characteristics on patient outcomes. A random sample of 7,096 patients, who were alive on December 31, 1990, was drawn from 523 center hemodialysis units, with an average of 14 patients per dialysis unit. A systematic sample of dialysis units was drawn, based on dialysis unit size and geography from the universe of all Medicare approved dialysis units, which accounts for over 90% of all chronic dialysis units. Patients were subsequently randomly selected (proportional to unit size) from each of the selected units based on the last two digits of their Social Security Number. The Coordinating Center of the USRDS did the selection of dialysis units, and personnel of the 18 ESRD Networks did the random case finding and the abstraction of patient medical records using a USRDS data collection form [20]. Data were abstracted during 1992 and early 1993, and included health insurance information, selected patient comorbid and risk factors, dialysis treatment parameters, psychosocial information, kidney transplant information and laboratory data. The end of study completion date was the date on which each abstraction form was completed for each patient.

The USRDS database (May 31, 1994 HCFA update) was used to provide additional patient data including race, primary cause of ESRD, date of first dialysis treatment, date of death, and date of any transplant. Of the over 7,000 patients sampled in the USRDS Case Mix Adequacy Study, 6,749 patients (95.1%) were identified in the USRDS database. Patients not found in the USRDS database ($N = 348$) were excluded from the analysis.

To yield a prevalent sample in which residual renal function was likely minimal or absent, we excluded patients who started dialysis within 12 months before study start (27%) from this analysis [21]. An additional 2% of patients were deleted, because they recovered renal function, were less than fifteen years old, or because the start of ESRD date could not be identified. Another 2% of patients were deleted because their hemodialysis prescription was not for three treatments per week. The largest exclusion of 32% was made for patients missing data for estimating dialysis dose (primarily a post-BUN reading). The 3% of patients treated with acetate dialysate were also excluded. The final 1% were excluded because the Kt/V dose was estimated to be less than 0.4 or greater than 2.0, or because more than half of comorbid conditions were missing or days alive could not be calculated. The resulting study sample consisted of 2,311 prevalent patients from 347 different dialysis units.

Analytical methods

For variables indicating the presence of comorbid conditions, missing values were coded as not present with a separate binary for missing comorbid condition(s).

The primary study variable, delivered dose of dialysis, was measured alternatively by two indicators, both of which are based on the reduction of urea during the dialysis treatment. The urea reduction ratio (URR, arbitrarily listed first) is defined as follows:

$$\text{URR} = [1 - (\text{post-BUN/pre-BUN})] * 100\%$$

where BUN is the blood urea nitrogen concentration (BUN) and post-BUN refers to the end of dialysis treatment and pre-BUN to the start of the same dialysis treatment.

The alternative measure of dialysis dose Kt/V is the "corrected" delivered Kt/V [22], defined as follows:

$$\text{Delivered Kt/V} = [-\ln((\text{post-BUN/pre-BUN}) - 0.008 * \text{dialysis hours})] + (4\text{-}3.5 * \text{post-BUN/pre-BUN}) * (\text{weight loss/post-weight})$$

where pre- and post-BUN = before and after dialysis BUN, weight loss = change in weight occurring during the dialysis session. The mean value of several Kt/V readings (54% were 3 or more, 46% were 2 or 1 readings) over a six months period (study start ± 3 months for each patient) was used in these calculations. "Corrected" refers to the adjustment for urea generation and weight loss during the dialysis treatment [22]. The time of the post-dialysis urea sample was not clearly specified but assumed to be immediately following termination of dialysis. Therefore, these Kt/V values likely represent the so-called "single pool" kinetics and do not account for rebound of BUN.

In an analysis of the effect of "skipped" outpatient dialysis treatments on mortality, the delivered Kt/V value was multiplied by the fraction of treatments that were not missed during the month. (Abstractors were instructed not to count missed outpatient treatments due to hospitalization as "skipped" treatments.)

Analyses were adjusted for the covariates listed in Table 1, except those noted with an asterisk. Demographics, functional status, dialysis parameters and laboratory data reflect characteristics at study start date. The comorbid/risk factors were those present within 10 years prior to diagnosis of ESRD. Comorbid conditions selected for inclusion were based on the explained variance of mortality in a prior Special Study of Case Mix Severity [23] and on clinical judgment.

The primary dependent variable was the time to death measured in days. Proportional hazards regression techniques [24] were used to estimate the relationship of dose of dialysis with all-cause mortality, given patient characteristics and risk factors. Patients were censored (removed from the analysis alive) at time of transplantation, 60 days after a switch to peritoneal dialysis, and at the study completion date (data abstraction date).

The dose of dialysis was evaluated in two separate main analyses, one being a continuous specification of dose and the other in a categorical specification of dose. These two main analyses were performed for the two alternative indicators of delivered dose, URR and Kt/V for a total of four main analyses. For ease of reporting, the sensitivity analyses are reported using the Kt/V specification. Individual components of dialysis including time, ultrafiltration and treatments per week were evaluated in a multivariate analysis with URR. The role of a reduction in Kt/V by skipped dialysis treatments was studied from the information of missed treatments during the first months of study.

Sensitivity analyses were performed to determine if the extreme values represented errors in the data. The model evaluated the relationship between mortality and corrected Kt/V as a continuous variable over different ranges of Kt/V(0.6 to 1.6 and 0.4 to 1.6).

All analyses were adjusted by covariate for time since first dialysis. We also tested for interactions of time on dialysis with other demographic characteristics in the main models. An analysis

Table 1. Descriptive statistics

Patient characteristics	Sample[a] Analysis[b] N = 2,311	Sample[a] Excluded N = 1,713
Patient demographics		
Age at SSD *mean in years*	57.8	58.0
Years on dialysis	4.6	4.5
White %	58.0	60.5
Black %	38.6	32.6
Other race %	4.4	6.9
Male %	50.0	47.0
Female %	50.0	53.0
Hispanic %	11.3	13.6
Anthropometric characteristics *mean*		
Weight *kg*	69.3	67.1
Height *cm*	167.8	166.7
Body mass index kg/m^2[e]	24.6	24.0
Primary cause of ESRD[c]		
Diabetes	25.0	27.0
Hypertension	28.7	25.6
Glomerulonephritis	15.5	16.1
Other, includes missing	30.6	30.3
Comorbid conditions *% yes at start of study*		
Obese	19.7	16.9
Unable to ambulate independently	7.5	9.0
Active smoker	17.2	15.7
Congestive heart failure	44.0	41.8
Coronary heart disease	48.3	45.6
Left ventricular hypertrophy	43.7	37.4
Cardiomegaly by X-ray examination	49.7	44.5
Neoplasm	8.9	10.1
Peripheral vascular disease	22.8	23.1
Laboratory values *mean at start of study*		
Serum albumin *g/dl*	3.80	3.71
Cholesterol *mg/dl*	178.4	177.3
BUN *pre-dialysis, mg/dl*[e]	76.4	77.3
BUN *post-dialysis, mg/dl*[e]	30.6	n/a
Bilirubin *mg/dl*	0.51	0.50
Patients' residence by Census Region %[d]		
New England	6.7	0.9
Mid-Atlantic	16.2	9.9
South-Atlantic	23.6	14.0
East Central North	11.9	15.4
East Central South	10.4	5.9
West Central North	7.7	8.8
West Central South	11.0	11.0
Mountain	3.5	7.8
Pacific	8.6	26.2
Dialysis characteristic %		
Twice weekly dialysis[e]	n.a.	7.2
High flux (KUF > 20)[e]	19.5	18.3
Temporary vascular access	2.3	3.1
Hospital facility[e]	4.2	6.5
Outcome measures		
Died %	30.0	32.1
Transplanted following start of study %	7.3	7.6
Days to death or censoring *mean*	509	499.6
Sample size *total*	2,311	1,720
Prevalent > 1 year	2,311	1,720
Incident in 1990	0	0

[a] Analysis & Excluded Sample are bicarbonate dialysate only and prevalent > 1 year

[b] Analysis Sample excludes patients without a post-dialysis BUN value, patients with 2 or 4 sessions per week, and patients missing information on at least half comorbid conditions

[c] From the USRDS database

[d] See Reference 26

[e] Variable not used as a covariate in the main analysis

of the geographic distribution of dialyzer membranes and delivered dose of dialysis, suggested that regional differences exist. All proportional hazards analyses were therefore stratified (SAS 6.07) [25] by the nine Census Regions [26].

Additional sensitivity analyses used stratification by sampled dialysis unit to control for possible "center effects" in estimating the slope of dose with mortality. Diabetic status was the focus of several analyses. These analyses included stratification by the presence of diabetes (either as the primary cause of ESRD or as a comorbid factor), as well as separate proportional hazards models separately for diabetic and non-diabetic patients. Additional analysis tested if the effect of dose of dialysis varied significantly by the presence of diabetes.

In order to identify the dose level (URR or Kt/V) beyond which there is no beneficial effect on mortality of increasing dialysis dose, proportional hazards models were fitted using a linear slope change model (spline function) [27] at each of several predetermined cut points. These statistical models test whether a horizontal line (slope = 0) relating dialysis dose (URR or Kt/V) and log (risk of death) at dose values above the cut point would give a significantly better fit to the data. The 95% confidence interval (CI) for the dose above which the slope changed to 0 (that is, no relationship) was calculated based on the likelihood ratio test. The 95% confidence interval includes all dose values which were not rejected at the 5% level.

Results

Basic descriptive statistics for all covariates used in the analysis are presented in Table 1. (Factors not used as covariates in the proportional hazards modeling are indicated with a superscript e.) Two subsamples are shown, both on ESRD therapy for more than one year and receiving bicarbonate dialysis. The first is the Analysis Sample of 2,311 patients for whom we had available information on the delivered dialysis dose. The second is the subsample of 1,713 patients who were matched to the USRDS data base, but were excluded from the analysis primarily because the dose of delivered dialysis could not be calculated. A comparison of these two subsamples suggests that they are similar except for differences in geographic distribution. A proportional hazards test for differences in patient mortality between the two subsamples showed that the Excluded Sample had a reported relative risk of 1.04 compared to the Analysis Sample, but this was statistically insignificant (P = 0.55). Thus, covariate controls and stratification by geographic region help to make the results generalizable beyond the Analysis Sample.

Prescribed Kt/V (data not shown) averaged 1.08, which is within 2% of the average delivered Kt/V of 1.10 [5]. URR averaged 60.1%.

Shown in Figures 1 and 2 are results of the four main analyses estimating the relationship of delivered dose (URR in Fig. 1 and Kt/V in Fig. 2) and relative mortality risk. All four analyses use a proportional hazards model with 21 covariates and stratification by geographic region. The two bar charts represent categorical estimates of the correlation of dialysis dose and mortality. The two line charts presented as insert in Figures 1 and 2 represent separately estimated continuous linear specifications of the correlation of dose with mortality. The line chart in Figure 1 indicates that a 5 percentage point higher URR (such as 65% vs. 60%) is associated with an 11% lower mortality risk (RR = 0.89, P = 0.001). Using Kt/V as a measure of dialysis dose indicates that a

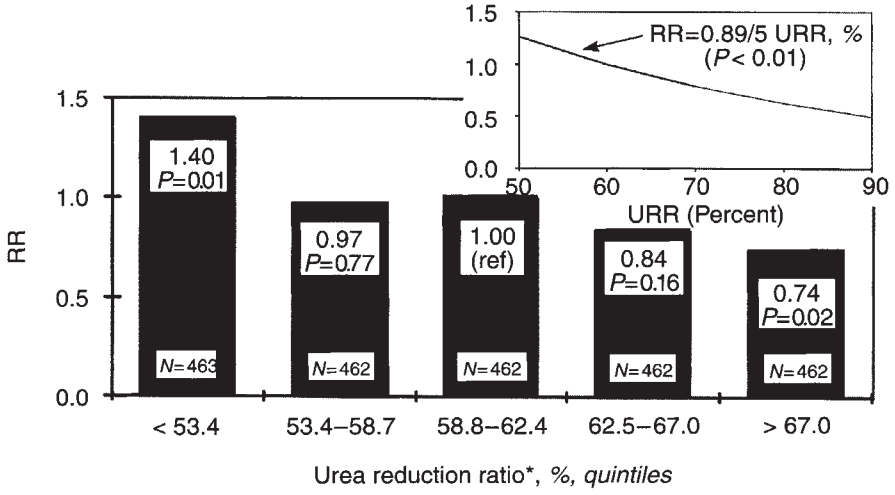

Fig. 1. *The relative risk of mortality by delivered dose of dialysis measured as Urea Reduction Ratio (in percent) among a random sample of U.S. patients prevalent on dialysis for more than one year on Dec. 31, 1990 (N = 2,311).* The line represents the relationship of delivered URR and mortality risk, with URR as a continuous variable and with the mean URR (60.1) set as the reference (RR = 1.00). The thin portion of the line indicates the segment in which the correlation may be less steep. The bars represent the risk of mortality for different categories (quintiles) of delivered URR with URr = 58.8 to 62.4 arbitrarily set as the reference (RR = 1.00). *From the pre/post-BUN and pre/post-weight. *N* = 2,311, thrice weekly only.

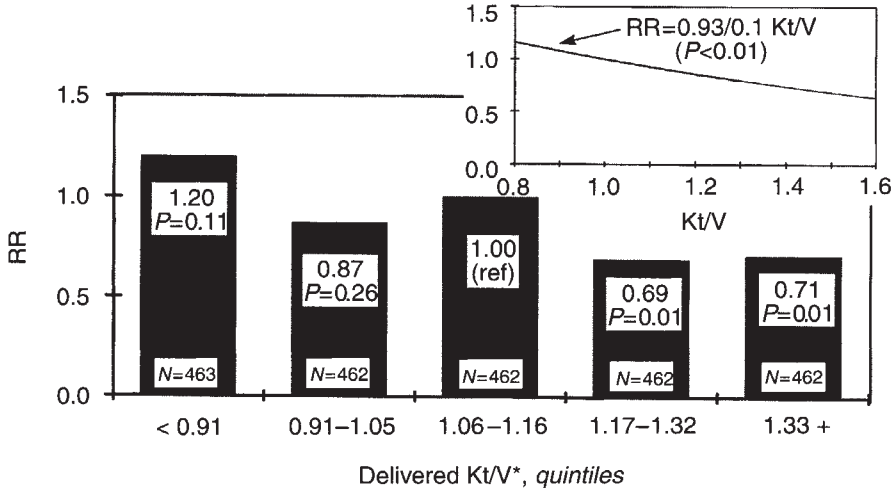

Fig. 2. *The relative risk of mortality by delivered dose of dialysis (measured as Daugirdas corrected Kt/V) among a random sample of U.S. patients prevalent on dialysis for more than one year on Dec. 31, 1990 (N = 2,311).* The line represents the relationship of delivered Kt/V and mortality risk, with Kt/V as a continuous variable and with the mean Kt/V (1.10) set as the reference (RR = 1.00). The thin portion of the line indicates the segment in which the correlation may be less steep. The bars represent the risk of mortality for different categories of delivered Kt/V with Kt/V = 1.0–1.2 arbitrarily set as the reference (RR = 1.00). *From (1 − post/pre)BUN. *N* = 2,311, thrice weekly.

0.1 higher Kt/V is associated with a 7% lower mortality risk (RR = 0.93, $P = 0.01$). The correlation of Kt/V and URR was very high ($r = 0.96$), and therefore the similarity of the two continuous estimates of the correlation of dose with mortality would be expected.

The categorical estimates in Figures 1 and 2 are compared to the mortality risk experienced by the middle quintile group (ref = 1.00) and show a clear downward trend in mortality with higher doses of delivered therapy. Generally, the categorical results were very consistent with the linear models, and yielded statistically significant results at either extreme of dose.

In sensitivity analyses, we changed the acceptable range of Kt/V from 0.4 to 2.0 to narrower ranges of 0.6 to 1.6 and 0.4 to 1.6. The linear relationship between mortality risk and Kt/V remained statistically significant ($P < 0.001$ for both) and appeared to be stronger with 9% lower mortality risk per 0.1 higher Kt/V (RR = 0.91).

The impact of "skipped" dialysis treatments on reducing the mortality dialysis dose was assessed by adding a covariate for this occurrence during the first month of study. Although "skipped" treatments did not affect the slope of the mortality curves shown in Figures 1 and 2, the measured mortality risk associated with "skipped" treatments supports the general finding that a lower dialysis dose implies higher mortality. One "skipped" treatment in a month of 13 treatments yields an 8% reduction in the monthly Kt/V and accounted for a 14% higher mortality risk (RR = 0.01). By comparison the slope of the linear estimates of Kt/V and mortality in Figure 2 would imply a substantially lower impact of one skipped treatment. This suggests that the effect of a missed treatment was approximately twice the linear effect reported in Figure 2.

To identify the dialysis dose level beyond which there is no beneficial effect of increasing dose, proportional hazards models (one for each indicator of dialysis dose) were fitted using a linear slope change model [27] at each of several predetermined cut points. A range of potential cut points were considered, with a horizontal line (slope = 0) above the cut point, for the linear relationship between dose and log (risk of death). The models with the best fit had a horizontal relationship above 70% for URR and 1.3 for Kt/V, respectively. The slopes below these points were steeper than those reported in the primary analyses with a reduction in mortality risk by 9% per 0.1 Kt/V or 12% per 5

percentage points higher URR. Allowing the slope to be 0 above these values (that is, Kt/V of 1.3 or URR of 70%) led to a marginally significant improvement in the fit of the overall model ($P = 0.065$) without accounting for the multiple tests that were performed to select the best model. If there is a horizontal relationship we are 95% confident that it starts no lower than a Kt/V of 1.15 or a URR of 62%. This 95% confidence interval has no upper bound because the improvement in fit with the slope change model was not significant at a P value of less than 0.05.

Sensitivity analyses

Several different specifications of models were tested as a prior study has suggested that death rates of diabetics and non-diabetics are not proportional, which would violate the basic assumption of proportional hazards. Patient diabetic status was added as a stratification parameter along with geographic region. The linear estimate of the relative mortality with Kt/V was very similar to the estimate presented in Figure 2.

In addition to stratification on diabetic status, separate models were estimated for diabetic and non-diabetic patients. The estimated RR of mortality, per 0.10 higher Kt/V, was 0.907 for diabetic patients ($P < 0.001$) and 0.952 for non-diabetic patients ($P = 0.048$). These sensitivity estimates suggest that Kt/V and mortality may have a steeper slope for diabetics than for non-diabetics (RR = 0.907 vs. 0.952) but the slopes were not statistically different from each other ($P = 0.18$). A final test of sensitivity of the influence of diabetes was to estimate an interaction effect between Kt/V and diabetic status. This test was not statistically significant ($P = 0.83$).

Additional sensitivity analyses tested the influence of dialyzer membrane (categorized as cellulose, modified cellulose, and synthetic) on estimates of the impact of Kt/V on mortality. The type of dialyzer membrane did not significantly modify the association of Kt/V with mortality as reported in Figures 1 and 2, although the type of dialyzer membrane appeared to have some influence; this is the subject of our ongoing research [28, 29]. The sensitivity test for center effects suggested that some of the apparent effect of dialysis dose on mortality may be explained by a general center effect.

An alternative specification of one of the main models (linear estimate using URR) was estimated using as indicators of the dialysis dose four separate measurements: prescribed sessions per week, prescribed minutes per session, URR and percentage weight change. Of the four measures, only URR was statistically significant in association with mortality ($P = 0.001$) and quantitatively similar to the estimates reported in Figure 1. The effect of prescribed treatments per week on mortality was protective (RR = 0.93 per session; $P = 0.60$). At the same URR, the effect of prescribed minutes per session on mortality was quantitatively small and possibly adverse although statistically insignificant ($P = 0.62$). A greater weight change during dialysis appeared adverse but far from significant ($P = 0.71$).

Finally, the quantitative effects of comorbid conditions on patient mortality were similar to those previously reported [22]. Statistically significant and quantitatively notable effects on mortality (not shown) included age, race, diabetes, nutritional status (both undernourished and serum albumin), inability to ambulate, congestive heart failure, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and chronic obstructive pulmonary disease. Comorbid factors that were not statistically significant ($P > 0.05$) were: cirrhosis, neoplasms, smoking, bilirubin, cholesterol, obesity, and left ventricular hypertrophy.

To determine if the 18 comorbid factors might confound the estimation of the association of mortality with dialysis dose, an analysis was performed using only age, sex, race, and cause of ESRD as covariate controls. With this shortened list of covariates the estimated mortality risk was 12.6% lower per 5 percentage point higher URR compared to 11% lower in the complete model.

Discussion

The statistical results reported in this study provide a strong indication that higher doses of dialysis are associated with lower levels of mortality. This analysis of dialysis dose has several features that make this paper unique. This is the first paper to use a randomly selected national sample of all Medicare patients. Secondly, this is the first report to control for such a long list of covariates. Thirdly this analysis used two alternative measures of the dialysis dose, URR and Kt/V. The two linear estimates (Figs. 1 and 2) provide good approximations of the categorical estimates shown in the same Figures. The categorical estimates do not impose a constraint on the functional form of the relationship. These linear estimates of a 7% lower mortality risk per 0.10 higher Kt/V and 11% lower mortality risk per 5 percentage points higher URR are similar to the estimates provided by Owen et al [3]. The conclusions of this analysis clearly support the results of previous studies and provide a more precise relationship between the dose of dialysis and mortality.

This study clearly shows the close correspondence between the two dialysis dose measures URR and Kt/V for use in population based analyses of mortality. Since both dialysis dose measures are either totally or mostly derived from pre- and post-dialysis BUN, this should not be a surprise (the correlation coefficient between Kt/V and URR was 0.96).

One can assume that at very high delivered dialysis dose, (more replacement of renal function), a smaller benefit may be achieved per unit of increase in dose. The current study suggests that the dose where the slope of the mortality by dose curve turns flat occurs near a URR of 70% or a Kt/V of 1.3. This analysis also indicated that up to a URR of 70% and a Kt/V of 1.3, the slope was linear and somewhat steeper than shown in Figures 1 and 2 for all ranges. We note that analysis of NCDS data suggested no relationship of mortality to dose above a Kt/V of 1.0 [2], although this estimate was challenged by Keshaviah [30]. Both the linear and categorical estimates reported in Figures 1 and 2 suggest that a substantial reduction in mortality risk (approximately 20%) may be possible at a delivered therapy of 1.3 versus 1.0 Kt/V (URR of 70 vs. 60%). Owen et al [3] estimate that the mortality curve turns flat above a URR of 65%. Given the wide confidence interval, our estimate of 70% URR is consistent with Owen et al [3].

As recently reported [14] the dose of delivered hemodialysis therapy (Kt/V) provided to US patients fell short of the dose of dialysis derived from the National Cooperative Dialysis Study [2]. Thirty-eight percent of patients who had been on dialysis for at least one year were receiving a Kt/V of 1.0 or less in 1991. The NCDS suggested a minimum dose of 1.0 to achieve satisfactory short-term outcome.

This low dose of delivered dialysis probably results from several factors. Perhaps the most important is that the dose of dialysis was not routinely measured until recently. There are indications that

the dose of dialysis continues to improve [23, 31, 32]. In 1986 to 1987, the time of the former USRDS study of delivered dialysis therapy, only 10% of the incident patients had a pre and post BUN [14], a necessary requirement for calculating delivered dialysis dose. For the 1991 prevalent patients of the present study, the fraction of patients with a pre- and post-BUN has increased to 55%. This has to be seen as a substantial improvement in treatment monitoring.

Prescribed treatment time was not found to be either qualitatively plausible or statistically significant in explaining mortality when controlling for dose of dialysis. While this finding appears to be consistent with Owens et al [3], future studies should obtain data on the actual rather than prescribed duration of the dialysis treatment.

The analyses also indicate a substantial geographic variation in the practice of measuring the dose of dialysis in 1991. By Census Region (Table 1) and by Network (not shown), it is clear that at the time of the current study there was substantial variation in the proportion of patients having their dose of dialysis monitored by pre and post dialysis BUN measurements.

This paper reports for the first time on the impact of "skipped" dialysis treatments on patient survival. Our analyses suggest that the results of each "skipped" treatment per month confirm the general finding that lower dose correlates with higher mortality. The quantitative effect of the skipped treatment appears to be larger than the prorated monthly dose effect predicted by the linear slope in Figure 2. It is likely that this larger effect of skipped treatments may be the consequence of the fact that "skipping" treatments might be an indicator for other adverse patient behaviors, or that missed treatments result in more adverse effects than simply a reduction in monthly dialysis dose.

Limitations of this research

Since there was no standardized procedure for timing and techniques of collecting the post BUN sample, there is a potential for non-comparable readings across dialysis facilities and patients. While this type of error would usually lead to "errors in variables" and bias towards no effect, the observed dialysis dose correlations with mortality risk were strong and statistically significant. If there is a bias in our results because of differences in post-dialysis BUN collection, it probably leads to understating the correlation of Kt/V with mortality. A suggestion for a steeper correlation was provided in the sensitivity analysis which excluded the highest and lowest Kt/V ranges. Also reported above was a possible "center effect" which could explain part of the apparent impact of higher dose on patient mortality. Wolfe et al [33] have shown a significant inverse correlation of the mean Kt/V by facility with the facility SMR. Thus, studies based on patients suggest that the center effect level data and facility level data have consistently shown an important role of the dialysis dose on mortality. All of these studies are observational in design so some component of the relationship could be due to either patient selection or center effects.

This study did not account for the effects of residual renal function as this datum was not collected. For this reason, we selected patients who had been on dialysis for at least one year (with the duration of prior ESRD averaging 4.6 years), under the hypothesis that most patients would have little if any residual renal function left *after* one year [21]. Ideally, future analyses should consider more direct measurements of residual renal function.

The comorbid and risk factor measurements available to this project include many measures of the presence but limited indication of the severity of the comorbid condition. Future analyses may include this additional detail, but it is unlikely to substantially affect the current results. In the analysis of the potential change in slope in the mortality risk by dialysis dose the break point was selected statistically from among several possible values. The validity of this marginally significant slope change estimate should be tested in the future with data that include a larger fraction of patients receiving a high dialysis dose.

In conclusion, this national study of a large random sample of U.S. hemodialysis patients shows a large and statistically significant inverse correlation of the delivered dose of dialysis and mortality risk. A strength of this study is that it adjusted for numerous comorbidity and risk factors. Sensitivity analyses show that the estimated linear slope of dialysis dose and mortality is robust and remarkably stable to numerous alternative specification of the main effect. Survival benefits from higher dialysis dose appear to be present up to a Kt/V level of approximately 1.3, with a 7% lower mortality risk per 0.1 higher Kt/V and an 11% lower mortality risk per 5 percentage points higher URR. Future studies may document an even larger benefit through more accurate determination of dialysis dose.

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