

Dialysis Dose Scaled to Body Surface Area and Size-Adjusted, Sex-Specific Patient Mortality

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Summary

Background and objectives When hemodialysis dose is scaled to body water (V), women typically receive a greater dose than men, but their survival is not better given a similar dose. This study sought to determine whether rescaling dose to body surface area (SA) might reveal different associations among dose, sex, and mortality.

Design, setting, participants, & measurements Single-pool Kt/V (spKt/V), equilibrated Kt/V, and standard Kt/V (stdKt/V) were computed using urea kinetic modeling on a prevalent cohort of 7229 patients undergoing thrice-weekly hemodialysis. Data were obtained from the Centers for Medicare & Medicaid Services 2008 ESRD Clinical Performance Measures Project. SA-normalized stdKt/V (SAN-stdKt/V) was calculated as $\text{stdKt/V} \times \text{ratio of anthropometric volume to SA}/17.5$. Patients were grouped into sex-specific dose quintiles (reference: quintile 1 for men). Adjusted hazard ratios (HRs) for 1-year mortality were calculated using Cox regression.

Results spKt/V was higher in women (1.7 ± 0.3) than in men (1.5 ± 0.2 ; $P < 0.001$), but SAN-stdKt/V was lower (women: 2.3 ± 0.2 ; men: 2.5 ± 0.3 ; $P < 0.001$). For both sexes, mortality decreased as spKt/V increased, until spKt/V was 1.6–1.7 (quintile 4 for men: HR, 0.62; quintile 3 for women: HR, 0.64); no benefit was observed with higher spKt/V. HR for mortality decreased further at higher SAN-stdKt/V in both sexes (quintile 5 for men: HR, 0.69; quintile 5 for women: HR, 0.60).

Conclusions SA-based dialysis dose results in dose-mortality relationships substantially different from those with volume-based dosing. SAN-stdKt/V analyses suggest women may be relatively underdosed when treated by V-based dosing. SAN-stdKt/V as a measure for dialysis dose may warrant further study.

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Introduction

In the National Institutes of Health–sponsored Hemodialysis (HEMO) Study (1), the primary results demonstrated no significant overall effect of dialysis dose as measured by equilibrated (eKt/V) or single-pool (spKt/V) (where K is urea clearance of the dialyzer, t is dialysis time, and V is volume of distribution area) (2). However, in a prespecified subgroup analysis, women randomly assigned to the conventional (lower) dose had higher mortality than women randomly assigned to the higher dose. An opposite trend toward higher mortality in men assigned to the higher dose was observed (3). These results not only suggested that the relationship between dose expressed as per session Kt/V versus mortality might be different among women and men but also pointed to a potential limitation in the assessment of dialysis adequacy using spKt/V.

One problem with the way hemodialysis adequacy is assessed is use of V, which is the volume of distribution of urea and is an approximation of total body water, to normalize the dose (4–6). Alternatives to V-based scaling of Kt have been proposed; these include

the use of Kt without normalization to any body size measure (4) or normalization of Kt to body surface area (SA) (5,6). Use of an SA-normalized measure is physiologically appealing because GFRs in the normal population scale to SA rather than to V (7). Furthermore, smaller patients, including children and women, will have a relatively low ratio of V to SA (6–8). Thus, any system for measurement of dialysis adequacy that normalizes dose to V will result in less dialysis given to these subpopulations than does a system that normalizes dose to SA.

This paper examines the associations among sex, dialysis dose, and mortality when dialysis dose was expressed using an alternative SA-normalized metric and compares these associations with results found using V-based measures of dose.

Materials and Methods

Patients and Study Design

We analyzed a cohort of prevalent hemodialysis patients from the Centers for Medicare & Medicaid (CMS) 2008 ESRD Clinical Performance Measures

project who had ESRD for at least 6 months and received dialysis thrice weekly ($n=7229$) (9). Patients who were alive on December 31, 2007, and had been undergoing dialysis at least 6 months before October 1, 2007, were selected from a national random sample stratified by the ESRD Network. Data were collected during a 3-month period, from October to December 2007. Data collection and analysis for quality improvement purposes do not need institutional review board approval, as detailed in the U.S. Department of Health and Human Services' guidance regarding quality improvement projects (10). Data collection forms were passed through the National Institutes of Health clinical exemption process.

Monthly measurements were averaged over the 3-month period, but a patient was required to have only 1 month of data to be included in the analyses. Dialyzer brand, dialyzer mass transfer area coefficient, and dialysate flow rate were not available in the Clinical Performance Measures database. The primary outcome was mortality during the follow-up calendar year (2008). Patients were censored at transplantation if they received a transplant during the follow-up period or on December 31, 2008, if they were still living.

Formal Modeling

Standard Kt/V (stdKt/V), spKt/V, and eKt/V were computed using a two-pool variable volume urea kinetic model of dialysis implemented in the Solute Solver program (11). Anthropometrically estimated urea distribution volume (Vant), pre- and post-dialysis BUN levels, dialysis session length, and weight change during dialysis were used as inputs. The equation used to estimate Vant was derived from the HEMO Study (12,13). The HEMO Study estimating equation is a modification of the Watson equation (14) that adjusts for diabetic status and race and gives values approximately 85% of those for the Watson V equation. This method of solving urea kinetics using volume, rather than estimated dialyzer clearance as an input, was first proposed by Casino *et al.* (15) and is implemented in Solute Solver (11).

Residual renal function was not reliably measured or present in the database and was assumed after exclusion of patients in their first 6 months of dialysis to be zero. SA was estimated by the equation of Dubois and Dubois (16). SA-normalized stdKt/V (SAN-stdKt/V) was computed by multiplying stdKt/V by the ratio of Vant to SA divided by the population mean value of Vant/SA as previously described (6,13). According to the HEMO Study estimating equation for Vant, the population mean for Vant/SA was approximately 17.5 in the HEMO Study patient group (13), and the mean value was very similar in the present patient group.

Cohorts for Data Analysis

Extreme data values were excluded from analyses. For pre- and post-dialysis BUN, extreme values were based on the 1st and 99th percentiles (642 dialysis sessions were excluded). Also excluded were dialysis sessions <120 minutes ($n=51$) and those for which listed weight loss was >2 kg/hr ($n=160$). The final cohort included 7229 patients, in which 77% ($n=5578$) had valid data reported for three

dialysis sessions, 18% ($n=1287$) had two valid sessions, and 5% ($n=364$) had one valid session.

Statistical Analyses

Baseline descriptive statistics were compared between women and men using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous measures. Cox proportional hazards models assessed the association between sex-specific dose, time quintiles, and 12-month mortality. Patients were censored at time of transplantation or at the end of the 1-year follow-up period (December 31, 2008). All Cox models were adjusted for baseline patient characteristics, including age, race, Hispanic ethnicity, years with ESRD, diabetes as ESRD cause, catheter use, and a comorbidity index (17) that is based on comorbid conditions reported for incident patients on the ESRD Medical Evidence Form (CMS 2728). These conditions include atherosclerotic heart disease, congestive heart failure, inability to ambulate, cancer, and diabetes among others. The 1-year hazard ratios (HRs) for sex-specific volume quintiles, adjusted for baseline patient characteristics, were calculated using the first dose quintile of each sex as reference groups. Because Vant was associated with mortality, we adjusted for Vant in our analyses and removed Vant adjustment in sensitivity analyses. Results from Cox models for all analyses evaluating dialysis dose and mortality are presented as adjusted 1-year HRs, with men in the first quintile as the reference group. Model fit was assessed by the likelihood ratio chi-squared statistic and the c-statistic (18).

Results

Patient and Treatment Characteristics

Women were slightly older, more likely to be African American, and more often had diabetes as the cause of ESRD compared with men (Table 1). Men were significantly taller and heavier and consequently had higher estimated Vant and SA than women. The mean ratio of Vant/SA was 18.5 ± 1.4 in men versus 16.2 ± 0.89 in women, with a population mean value of 17.5 ± 1.63 . Body mass index was slightly greater for women (mean, 28.7 ± 8.0 versus 27.4 ± 6.7 kg/m²). Dialysis sessions were significantly longer in men (mean, 226 versus 210 minutes), but mean urea reduction ratio, spKt/V, eKt/V, and stdKt/V were all greater in women than in men. In contrast, mean SAN-stdKt/V dose was lower in women than in men (Table 1).

Relationship of spKt/V versus SAN-stdKt/V by Sex

Figure 1 shows a scatterplot of spKt/V versus SAN-stdKt/V by sex. The slope of rise in spKt/V for women is steeper than in men. Thus, at higher doses of spKt/V, the equivalent dose of SAN-stdKt/V is lower in women compared with men.

Association between Vant and Dialysis Dose

Table 2 shows the relationship of Vant, estimated using the HEMO Study equation, with various measures of dialysis dose. In both sexes, high quintiles of V-based dialysis dose including spKt/V, eKt/V, or stdKt/V were all associated with low Vant values. On the other hand, high

Table 1. Patient and treatment characteristics by sex

Characteristic	Men	Women	P Value
Participants (<i>n</i>)	3943	3286	<0.001
Age (yr)	61.0 (50.0–72.0)	64.0 (53.0–73.0)	<0.001
Race, <i>n</i> (%)			<0.001
White	2295 (58.3)	1718 (52.3)	
African American	1330 (33.7)	1300 (39.6)	
Other	316 (8.0)	268 (8.2)	
Hispanic ethnicity, <i>n</i> (%)	525 (13.3)	459 (14.4)	0.39
Time with ESRD (yr)	2.7 (1.3–5.4)	2.8 (1.3–5.6)	0.15
Diabetes, <i>n</i> (%)	1646 (41.7)	1570 (47.8)	<0.001
Catheter, <i>n</i> (%)	720 (18.2)	863 (26.3)	<0.001
Postdialysis weight (kg)	78.7 (67.7–93.6)	70.0 (58.5–86.2)	<0.001
Height (cm)	174.0 (168.0–180.3)	160.0 (155.0–165.1)	<0.001
Body mass index (kg/m ²)	26.2 (22.8–30.7)	27.3 (23.0–32.9)	<0.001
SA (m ²)	1.9 (1.8–2.1)	1.7 (1.6–1.9)	<0.001
HEMO Vant ^a (L)	35.4 (31.6–40.3)	27.9 (25.1–31.8)	<0.001
HEMO Vant ^a /SA	18.4 (17.5–19.3)	16.2 (15.6–16.8)	<0.001
Dialysis session length (min)	226.7 (210.0–241.7)	210.0 (184.7–230.0)	<0.001
Modeled dialyzer clearance from Solute Solver (ml/min)	262.6 (235.5–288.8)	246.2 (219.1–272.9)	<0.001
Urea reduction ratio (%)	72.3 (68.7–75.4)	75.5 (71.9–78.7)	<0.001
Single-pool Kt/V	1.5 (1.4–1.7)	1.7 (1.5–1.8)	<0.001
Equilibrated Kt/V	1.3 (1.2–1.5)	1.4 (1.3–1.6)	<0.001
Standard Kt/V	2.4 (2.3–2.5)	2.5 (2.4–2.6)	<0.001
SA-normalized standard Kt/V	2.5 (2.3–2.7)	2.3 (2.2–2.5)	<0.001

Values expressed with a range are the median (interquartile range). HEMO, Hemodialysis; Vant, anthropometric volume; SA, body surface area.

^aHEMO Vant is the anthropometrically estimated urea distribution volume calculated using the HEMO Study equation.

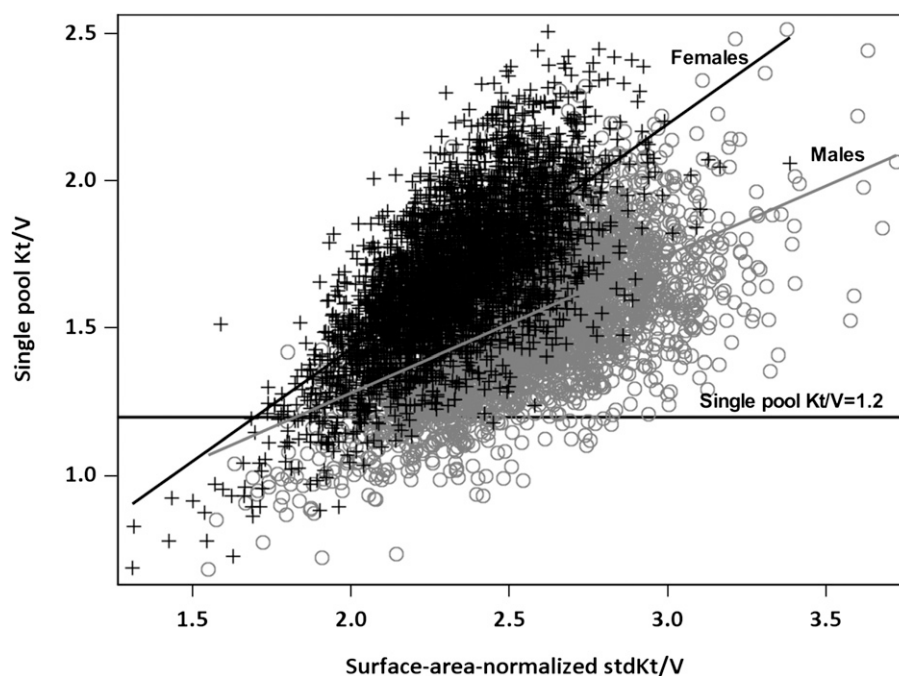
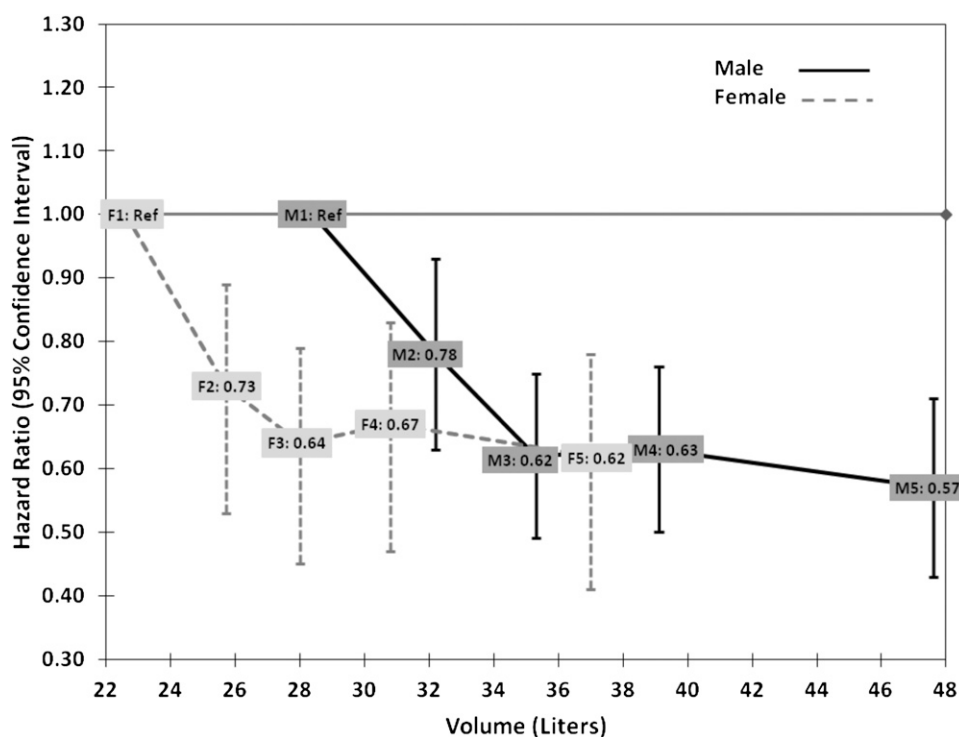
**Figure 1. | Single-pool Kt/V plotted against body surface area–normalized standard Kt/V by sex.**

Table 2. Mean anthropometric volume (HEMO Study equation) by Quintiles of various measures of dialysis dose

Measure	Mean Vant by Measure-Specific Quintile $\pm$ SD (L)				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Men					
Single-pool KtV	39.9 $\pm$ 7.9	38.2 $\pm$ 7.1	36.4 $\pm$ 6.6	35.3 $\pm$ 6.1	33.0 $\pm$ 5.4
Equilibrated KtV	39.3 $\pm$ 7.8	37.9 $\pm$ 7.3	36.2 $\pm$ 6.6	35.8 $\pm$ 6.4	33.6 $\pm$ 5.6
Standard KtV	38.7 $\pm$ 7.5	37.7 $\pm$ 7.6	36.6 $\pm$ 7.0	35.8 $\pm$ 6.3	34.1 $\pm$ 6.0
SA-normalized standard KtV	33.1 $\pm$ 5.6	34.8 $\pm$ 5.7	35.8 $\pm$ 5.8	37.6 $\pm$ 6.5	41.3 $\pm$ 8.4
Dialysis session length	32.7 $\pm$ 5.2	33.9 $\pm$ 5.1	36.4 $\pm$ 6.0	37.5 $\pm$ 6.6	42.1 $\pm$ 8.0
Women					
Single-pool KtV	32.0 $\pm$ 6.0	30.0 $\pm$ 5.2	28.6 $\pm$ 4.7	27.6 $\pm$ 4.3	26.0 $\pm$ 3.8
Equilibrated KtV	31.4 $\pm$ 5.9	29.7 $\pm$ 5.4	28.7 $\pm$ 5.0	27.9 $\pm$ 4.4	26.4 $\pm$ 3.9
Standard KtV	31.0 $\pm$ 5.9	29.3 $\pm$ 5.4	28.8 $\pm$ 5.2	28.3 $\pm$ 4.8	26.8 $\pm$ 4.0
SA-normalized standard KtV	27.6 $\pm$ 4.9	27.7 $\pm$ 4.7	28.6 $\pm$ 4.6	29.1 $\pm$ 5.2	31.0 $\pm$ 6.0
Dialysis session length	26.2 $\pm$ 4.2	27.2 $\pm$ 4.3	28.6 $\pm$ 4.5	29.9 $\pm$ 5.2	32.2 $\pm$ 5.8

HEMO, Hemodialysis; Vant, anthropometric volume; SA, body surface area.

**Figure 2.** | Estimated urea distribution volume quintiles calculated using the HEMO Study equation versus mortality by sex, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, and incident comorbidity. M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

quintiles of dose expressed as SAN-stdKt/V were associated with higher values for Vant. High quintiles of session length also were associated with higher values for Vant.

Association between Vant and Mortality

Figure 2 shows the adjusted 1-year mortality HRs by quintiles of Vant for men and women. Relative to the first

quintile in each sex, mortality risk was markedly reduced among both men and women in Vant quintiles 2 and 3; risk then leveled off at the two highest quintiles.

Association between Mortality and spKt/V, stdKt/V, or SAN-stdKt/V

Figures 3, 4, and 5 show the 1-year mortality HRs in men and women for sex-specific quintiles of spKt/V,

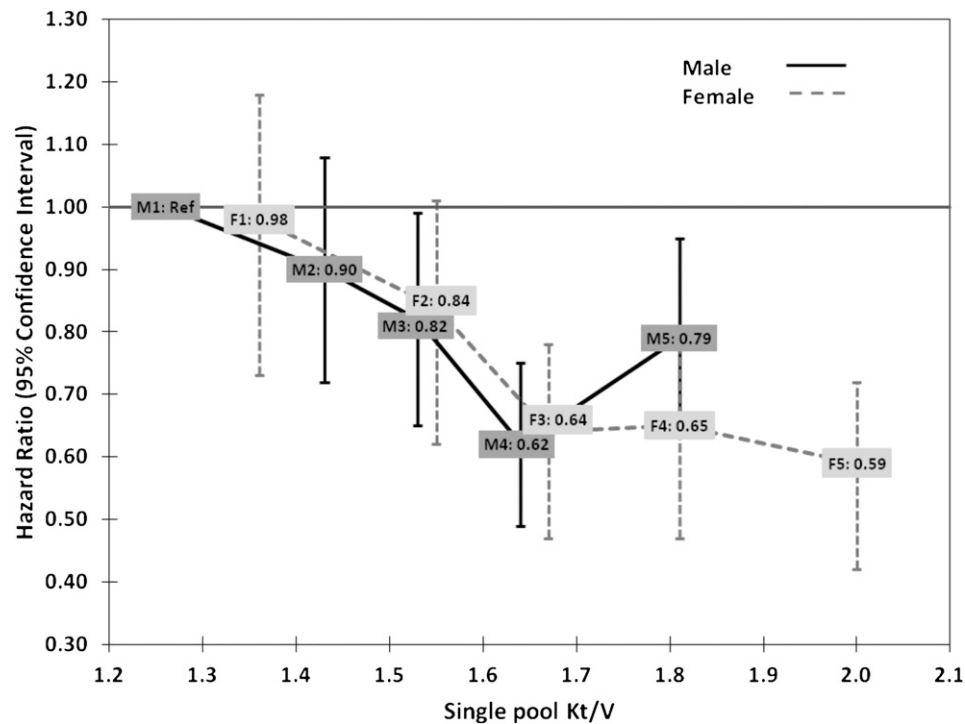


Figure 3. | Single-pool Kt/V quintiles versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, incident comorbidity, and Vant (HEMO Study equation). M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

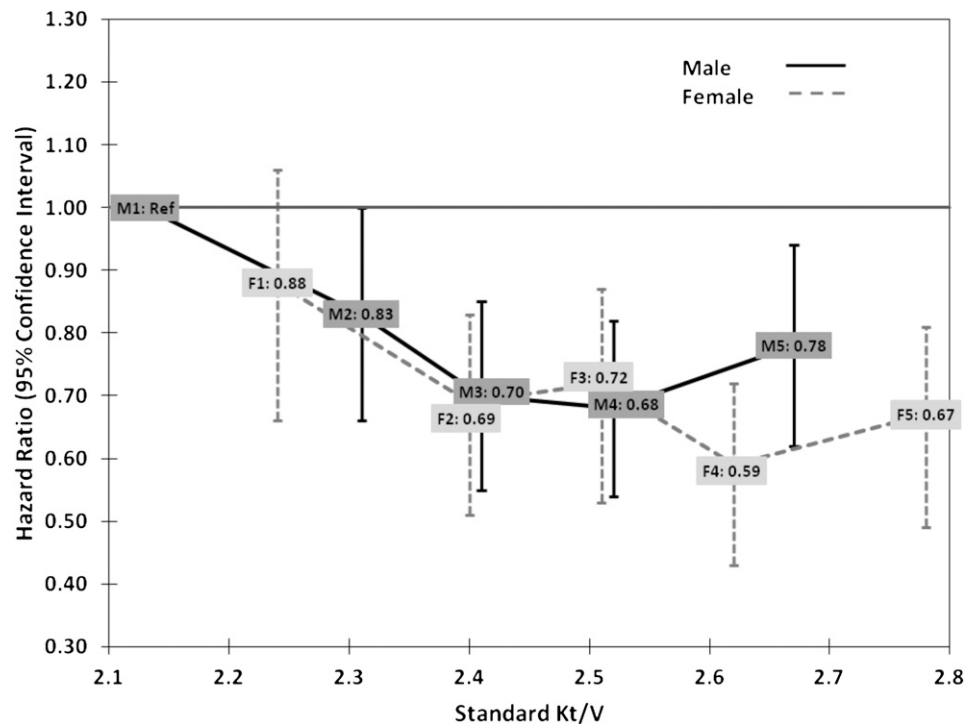


Figure 4. | Standard Kt/V quintiles versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, incident comorbidity, and Vant (HEMO Study equation). M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

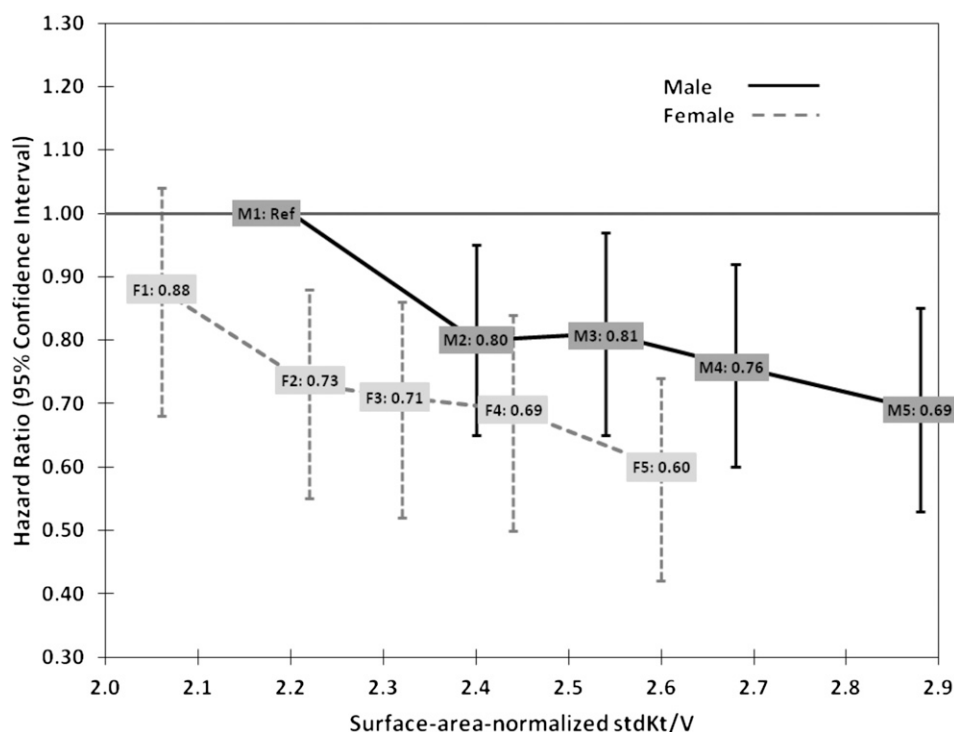


Figure 5. | Body surface area–normalized standard Kt/V quintiles versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, incident comorbidity, and Vant (HEMO Study equation). M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

stdKt/V, and SAN-stdKt/V, respectively, adjusted for demographic and clinical characteristics, and Vant. Excluding adjustment for Vant gives similar results (Figures A1, A2, and A3; Appendix). For spKt/V (Figure 3), the adjusted mortality hazard ratio decreased as spKt/V increased until a dose of approximately 1.6–1.7 was reached. Among men, mortality HR appeared to increase at the highest quintile as compared with the fourth quintile of spKt/V, whereas among women the HR was lower by 6% at the highest quintile. The relationship between eKt/V (data not shown) or stdKt/V (Figure 4) and mortality yielded similar results, with a flattening of the mortality risk observed at higher levels of dialysis dose.

In contrast, adjusted analyses using SAN-stdKt/V (Figure 5) demonstrated that the HR for mortality decreased progressively as SAN-stdKt/V increased, and mortality risk continued to decrease even at the highest quintiles for both men and women. At the highest dose quintiles, mortality risks were reduced by approximately 31% and 40% for men and women, respectively. Figure 5 also shows that women received a lower SAN-stdKt/V dose and had a lower mortality risk than men. This finding persisted when the adjustment for Vant was removed (Figure A3).

The likelihood ratio chi-squared statistics were similar between spKt/V (LR chi-square = 550, 23 df; $P < 0.001$) and SAN-stdKt/V (LR chi-square = 530, 23 df; $P < 0.001$). C-statistics were also similar across all three dose models (0.67, 0.68, and 0.68 for models using spKt/V, stdKt/V, and SAN-stdKt/V, respectively).

Association of Mortality with Session Length (Time)

The Vant-adjusted results depicted in Figure 6 showed no significant association between dialysis session length quintiles and mortality.

Discussion

We found that women receive a higher V-based dose of dialysis than men (Table 1). This is in agreement with U.S. Renal Data System data, which show that women who undergo dialysis in the United States typically have a higher urea reduction ratio than men (19). Observational studies that have looked at dose versus mortality associations have shown that higher doses of dialysis appear to benefit women more than men (20,21), and the randomized HEMO trial results also suggest that women receiving a conventional minimum spKt/V of approximately 1.3 may be relatively underdialyzed (3). Furthermore, there is evidence that small patients (*e.g.*, patients with a low Vant) have an increased risk for death (22). When we rescaled dose to SA, women had lower doses of dialysis than men. Thus, it is possible that V-based scaling of dialysis dose leads to relative underdialysis of women and smaller patients, partially accounting for their poor survival.

Our results suggest that associations among sex, dialysis dose, and mortality differed markedly depending on how dose is normalized. In the present dataset, when dose was normalized to body water (V) as Kt/V, whether spKt/V, eKt/V, or stKt/V was used, mortality HR curves differed somewhat in shape between men and women, and death

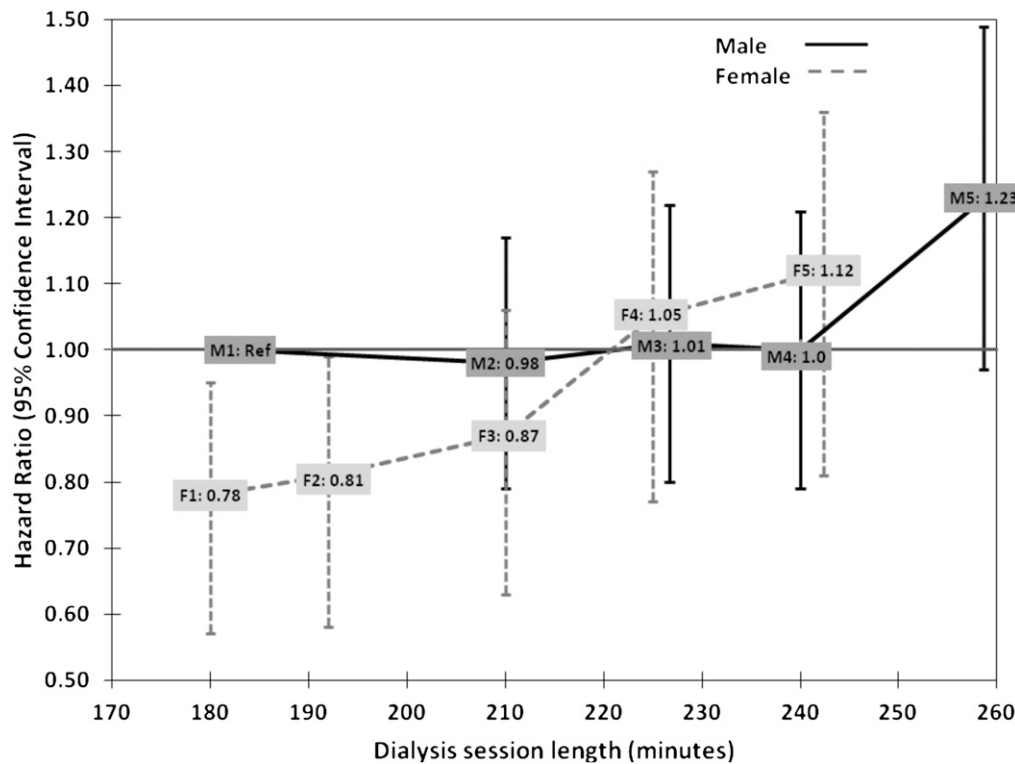


Figure 6. | Dialysis time quintiles versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, incident comorbidity, and Vant (HEMO Study equation). M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

risk actually increased in the highest dose quintile in men, in analyses with or without (Appendix) adjustment for Vant. Each of these V-based dose measures was, on average, higher in women than in men. When mortality between men and women was considered at similar V-based dialysis doses, mortality tended to be similar in men and women; in contrast, among populations with good renal function, women survive substantially longer than men. However, when dialysis dose was normalized to SA, the dose-mortality curves were similar in shape for men and women. When the dose measure used was SAN-stdKt/V, survival appeared to continue to improve as SAN-stdKt/V increased. Comparing survival between men and women at a similar dose of SAN-stdKt/V, it appeared to be better for women, reminiscent of the survival advantage enjoyed by women with normal renal function over men.

The fact that SAN-stdKt/V provided a more consistent relationship between dialysis dose and mortality in men versus women than V-based dosing does not indicate *per se* that SAN-stdKt/V is the more biologically correct measure of dose. It is possible that at higher levels of dialysis doses, a plateau effect for survival may be observed. In the HEMO Study, increasing spKt/V, from 1.3 to 1.7 on average, failed to result in an overall survival benefit. Similarly, it is not clear whether women retain their normal survival advantage as renal function falls. The factors associated with increased mortality risk among ESRD patients compared with patients with normal renal function

may affect both sexes equally, thereby reducing the female survival advantage seen in the general population.

With the exception of the National Cooperative Dialysis Study (23) and the HEMO Study (2), most efforts to determine optimal dialysis dose have come from examination of the relationship between dose and mortality in observational studies. One problem with analyzing datasets from observational studies is confounding of the dose of dialysis, be it urea reduction ratio, spKt/V, eKt/V, or stdKt/V, with body size. Higher doses of dialysis tend to be given to patients with lower Vant. For example, Table 2 shows that as spKt/V increases, the mean Vant (as estimated from the HEMO Study equation) of each spKt/V quintile is progressively reduced. Because low Vant is strongly associated with mortality (22) (Figure 2), the confounded relationship between Vant and dose may obscure a potential benefit of higher dialysis doses. The flattening, and even reversal, of survival advantage at higher quintiles of V-based dialysis may potentially be explained by the fact that patients receiving high dialysis doses tend to have low Vant. To account for this, we adjusted the analyses for Vant within each sex. The Vant adjustment did not markedly change the results, although it did seem to attenuate the flattening of the survival curve at high levels of V-based dosing, where patients with a low V tend to congregate.

Dialysis time is both a component of conventional dialysis dose expressed as Kt/V and a measure of dialysis by itself. Kt/V measures the removal of small solutes, such

as urea. After the first few hours, additional time does not contribute much to urea removal because during longer dialysis sessions, the blood urea level is quite low. Compared with urea, other solutes, such as phosphate and middle molecules, show markedly improved removal when total dialysis time is prolonged. Dialysis time also contributes to lowering the rate of fluid removal, allowing more time for vascular refilling and greater degrees of volume removal. Although substantially better outcomes have been noted when 8- to 10-hour dialysis sessions are given thrice weekly or every other night (24), the role of dialysis time in conventional dialysis is less clear. Some studies have shown benefit to extending time to >4 hours (25–27), whereas others have found little effect beyond 3.5 hours in women and beyond 3 hours in men (28). In our dataset, when we examined the association between time and survival, no significant relationship was observed. There was a slight non-statistically significant suggestion for higher mortality with longer time (Figure 6), which is probably due to confounding by indication. In other words, longer dialysis times may have been prescribed for clinical conditions that may be associated with increased mortality, such as difficulty with volume control or decreased tolerance to shorter dialysis due to intradialytic hypotension.

Is there a biological argument to choose between V-based and SA-based dialysis dose scaling? At the same height and weight, SA is similar in men and women. However, total body water, a surrogate for V, is higher in men because of greater muscle mass. There is no good evidence that muscle is an important source of uremic toxins, and so if dialysis dose is scaled to V, men will be prescribed more dialysis than women of the same height and weight, despite having similar levels of SA. In one study, healthy men and women of the same SA had similar levels of GFR (29), although in another study GFR/SA was slightly (4.5%) higher in men than in women. Still, GFR scaled to SA between men and women is more similar than GFR scaled to V (29,30). For this reason, it has been suggested that V-based dialysis dosing be rescaled to SAN-stdKt/V (6). The effect of such rescaling would be to increase the dose of dialysis to women, to smaller patients (in whom V/SA tends to be lower), and to children younger than 10 years of age (in whom V/SA is low and decreases progressively with younger age).

There are clinical reasons to search for a better candidate measure of dialysis adequacy. The most recent Kidney Disease Outcomes Quality Initiative adequacy guidelines (2006) recapitulated the previous guidelines' recommendation of a minimum spKt/V of 1.2 for both sexes (31). However, in the clinical practice recommendations, a higher dose was recommended for women and smaller patients, although the amount of recommended increase was not specified. These additional recommendations were added in view of observational data suggesting that women appear to benefit more from increased levels of urea reduction ratio (20) or spKt/V (21) compared with men. It also is well known that smaller hemodialysis patients, with a lower Vant, have worse survival than larger patients (21). Although the reasons for this may be multifactorial, relative underdialysis of smaller patients might be a contributing cause.

In interpreting the effects of our findings, the following limitations must be considered. First, we used an observational dataset in which dose of dialysis and mortality may be confounded by dose-targeting bias (32,33). This bias suggests that delivered dose of dialysis may be linked to mortality by factors other than the biologic effect of increased solute removal. In addition, although most observational studies suggest potential benefit to improving dialysis dose in the spKt/V range of 1.3 versus 1.8, the randomized HEMO Study showed no benefit; this is an important limitation of any observational dose-mortality analysis done at the patient level.

In summary, the results of our analyses suggest that rescaling of dialysis dose from volume-based stdKt/V (or spKt/V) to an SA-based dose results in dose-mortality relationships that are substantially different. In the absence of future randomized clinical trials, decisions regarding adoption of new dialysis dosing standards may need to be based on cautious analysis of observational data, taking into account possible size and other dose-targeting biases, as well as examination of sex-based subgroups results in the HEMO Study. Cost implications of any such change in dosing standards should also be considered given that the cost data underlying the dialysis payment systems in the United States and elsewhere were derived from a regimen in which dosing was not SA normalized. Nevertheless, the use of the SAN-stdKt/V measure deserves further study as it may be a reasonable alternate candidate standard for dialysis dose that might allow better quantification of dialysis dose for both men and women and potentially improve outcomes.

Appendix

Detailed Methods

The HEMO Study anthropometric volume equation was as previously described (14):

$$V_{\text{HEMO}} = 0.824 \times V_{\text{Watson}} \times (1 + 0.033[\text{if diabetic}]) \\ \times (1 + 0.033[\text{if female}]) \times (1 + 0.043[\text{if black}]) \\ \times (1 - [0.002 \times ([\text{Age} - 50]/10)])[\text{if male}] \\ \times (1 - [0.015 \times ([\text{Age} - 50]/10)])[\text{if female}]$$

Results from Sensitivity Analyses

Dose versus mortality data without adjustment for Vant (HEMO): Figures A1, A2, and A3 show spKt/V, stdKt/V, and SAN-stdKt/V associations versus mortality, where no correction was made for body size.

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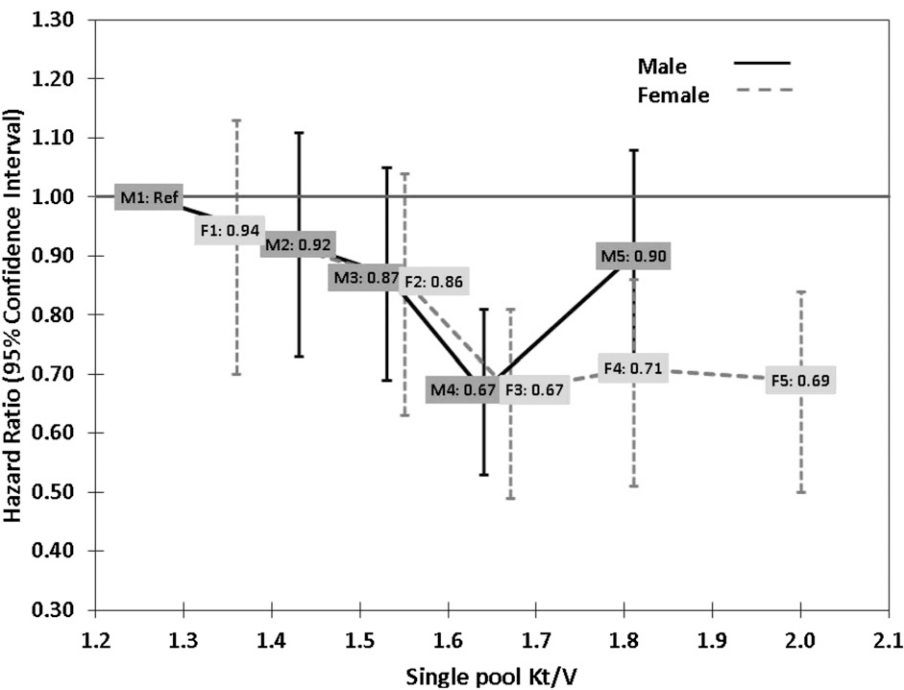


Figure A1. | Single-pool Kt/V quintiles versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, and incident comorbidity. In contrast to Figure 3, results are not adjusted for body size. M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

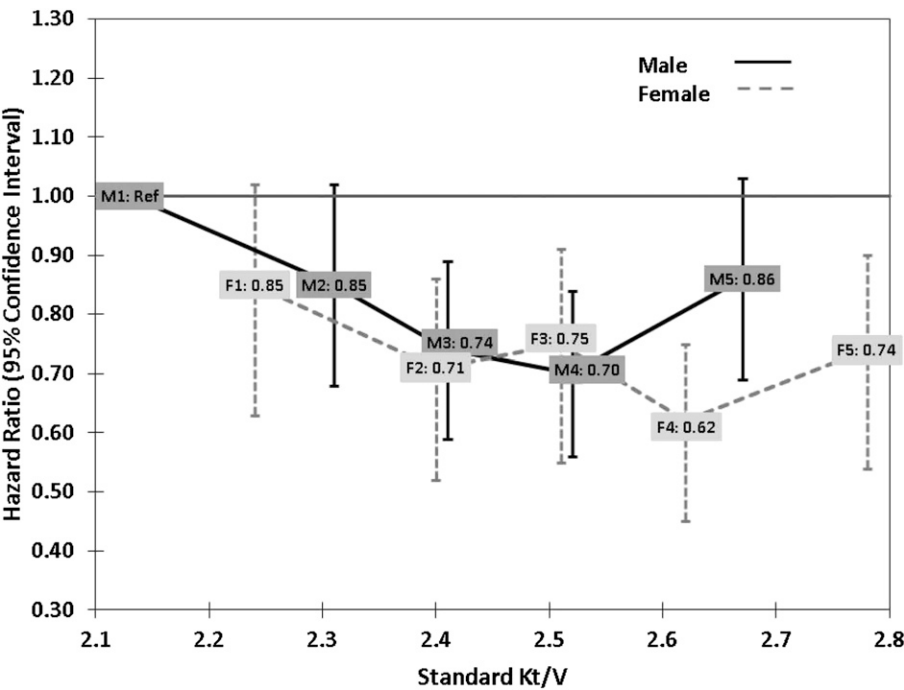


Figure A2. | Standard Kt/V versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, and incident comorbidity. In contrast to Figure 4, results are not adjusted for body size. M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

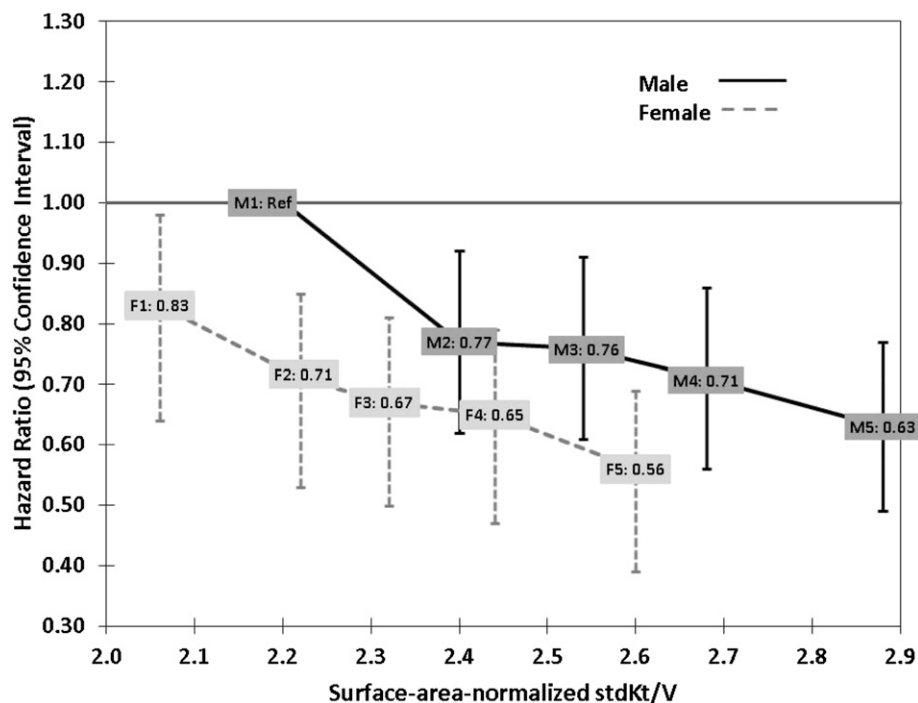


Figure A3. | Body surface area-normalized standard Kt/V versus mortality, adjusting for age, race, Hispanic ethnicity, diabetes as ESRD cause, catheter use, years with ESRD, and incident comorbidity. In contrast to Figure 5, results are not adjusted for body size. M1–M5 denotes quintile 1 through quintile 5 of men; F1–F5 denotes quintile 1 through quintile 5 of women. Hazard ratios are plotted at the median of the corresponding quintile.

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