High Dialysis Dose Is Associated With Lower Mortality Among Women But Not Among Men

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• ***Background:*** **Several observational studies reported lower mortality risk among hemodialysis patients treated with doses greater than the standard dose. The present study evaluates, with observational data, the secondary randomized Hemodialysis (HEMO) Study finding that greater dialysis dose may benefit women, but not men.** ***Methods:*** **Data from 74,120 US hemodialysis patients starting end-stage renal disease therapy were analyzed. Patients were classified into 1 of 5 categories of hemodialysis dose according to their average urea reduction ratio (URR), and their relative risk (RR) for mortality was evaluated by using Cox proportional hazards models. Similar analyses using equilibrated Kt/V were completed for 10,816 hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) in 7 countries.** ***Results:*** **For both men and women, RR was substantially lower in the URR 70%-to-75% category compared with the URR 65%-to-70% category. Among women, RR in the URR greater-than-75% category was significantly lower compared with the URR 70%-to-75% group ($P < 0.0001$); however, no further association with mortality risk was observed for the greater-than-75% category among men ($P = 0.22$). RR associated with doses greater than the Kidney Disease Outcomes Quality Initiative guidelines (URR ≥ 65%) was significantly different for men compared with women ($P < 0.01$). Similar differences by sex were observed in DOPPS analyses.** ***Conclusion:*** **The agreement of these observational studies with the HEMO Study supports the existence of a survival benefit from greater dialysis doses for women, but not for men. Responses to greater dialysis dose by sex deserve additional study to explain these differences.** ***Am J Kidney Dis*** **43:1014-1023.**

INDEX WORDS: Sex; hemodialysis (HD) dose; Kt/V; urea reduction ratio (URR); relative mortality risk; Hemodialysis (HEMO) Study; Dialysis Outcomes and Practice Patterns Study (DOPPS); Centers for Medicare and Medicaid Services (CMS).

PORT ET AL[1] and Wolfe et al[2] reported that mortality was substantially lower at urea reduction ratio (URR) doses greater than the standard dose for 3 weight-group tertiles defined by body mass index, although the benefit of the highest dose appeared to be smaller in the heaviest weight group. Recently, the Hemodialysis (HEMO) Study Group reported no significant mortality difference between hemodialysis patients in standard- and high-Kt/V dose groups. However, the HEMO Study also reported that a greater dialysis dose may significantly benefit women, but not men.[3,4] Owen et al[5] reported differential dose-response relationships by race. In the present study, the association of dose (measured as URR or equilibrated Kt/V [eKt/V]) and mortality is evaluated separately for men and women based on 2 large databases: those of (1) the US Centers for Medicare and Medicaid Services (CMS) and (2) the international Dialysis Outcomes and Practice Patterns Study (DOPPS).

Several observational studies have shown that a greater dose of hemodialysis is associated with lower mortality risk.[1-12] Most of these studies used data before the large shift toward greater doses of dialysis and the use of high-flux dialyzers that has occurred since 1990[13,14]; few of these observational studies focused on results specifically by sex. At present, the guidelines of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (K/DOQI) recommend that URR, a measure of dialysis dose for small molecules, exceed 65%.[15] This guideline

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was motivated by the strong evidence of increased mortality risk with dialysis doses less than a URR of 65%. Many studies have attempted to determine the dose level above which additional increases have limited benefit,[6,10,16,17] but this topic has remained controversial.

The authors of the present study previously showed that the correlation between lower dialysis dose and greater mortality must be adjusted for body size through strata or statistical adjustment because larger doses (in units of URR or Kt/V) tend to be given to smaller persons.[1,2,18] Furthermore, both low dialysis dose (Kt/V) and small body size were found to be independent risk factors for mortality in long-term hemodialysis patients.[2] This study examines whether results from the national CMS data and international DOPPS data agree with the unexplained trend observed in the HEMO Study that women, but not men, benefit from a dose substantially greater than the level recommended by the K/DOQI guidelines.

METHODS

Data Sources

CMS. National data from the CMS Medical Evidence Form (CMS 2728) and Patient Claims (CMS UB-92) were used for this study. The study population was selected from 242,658 patients who began treatment for end-stage renal disease (ESRD) in the United States between April 1, 1997, and December 31, 1999. To minimize the influence of residual renal function on mortality risk for this study, we included only patients who were alive on hemodialysis therapy after 15 months of ESRD. Patients who, during the first 15 months of ESRD, either received a transplant (n = 14,298; 6%) or died (n = 67,875; 28%) were excluded from the study population. Patients having fewer than 3 Medicare dialysis claims with reported URR categories (<60%, 60% to 65%, 65% to 70%, 70% to 75%, and >75%) during months 10 to 15 of dialysis therapy (primarily non-Medicare and peritoneal dialysis patients) also were excluded (n = 77,484; 32%). Additionally, patients whose Medicare claims indicated on average fewer than 2.5 dialysis sessions per week during months 10 to 15 of dialysis therapy were excluded (n = 4,612; 2%). An additional 4,269 patients (2%) were excluded because height or weight data were unavailable. The final study population consisted of 74,120 patients, which represents Medicare-insured patients with ESRD treated with hemodialysis at the end of month 15 of ESRD. Follow-up for these patients started at the end of month 15 of dialysis therapy, ie, between July 1, 1998, and March 31, 2001. Comorbid conditions, height, and weight came from the CMS 2728, which is filled out for each patient at the start of ESRD. Follow-up ended June 30, 2001.

Medicare dialysis bills report dialysis dose in 5 URR categories. URR is the fractional reduction in blood urea nitrogen (BUN) concentration during dialysis: [100% * (pre-BUN−post-BUN)/pre-BUN]. URR values of 57.5%, 62.5%, 67.5%, 72.5%, and 77.5% were assigned to the 5 reported categories of less than 60%, 60% to 65%, 65% to 70%, 70% to 75%, and greater than 75%, respectively. The average values assigned to the Medicare dialysis bills for months 10 to 15 of dialysis were used. Patients were then classified into the 5 URR categories based on this average value.

To make the study sample comparable to the dose levels of the HEMO Study, some analyses included only patients for whom URR averaged greater than the K/DOQI recommendation of URR of 65% or greater. In these analyses, the sample is reduced to 64,372 patients with a URR of 65% or greater.

DOPPS. An independent international data source also was analyzed, with data from patients in the DOPPS from 7 countries (France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States). Data collection began in 1997 in the United States, 1998 in Europe, and 1999 in Japan and ran through 2001. The study population was selected from the 17,034 prevalent hemodialysis patients recruited into the DOPPS. To minimize the effect of residual renal function on mortality risk for this study, we excluded the first 12 months of ESRD treatment. Patients who died (n = 1,037), received a transplant (n = 202), changed modalities (n = 285), withdrew from dialysis therapy (n = 166), recovered renal function (n = 149), transferred (n = 1026), or were dropped from the study (n = 1,193) before month 12 of ESRD were excluded from analyses. Patients whose predialysis and postdialysis BUN levels were not measured or not reported (n = 2,160) also were excluded. The final study population included 10,816 hemodialysis patients who had been treated for ESRD for at least 1 year. eKt/V was calculated according to the second-generation formula of Daugirdas[19] at the first dialysis session during follow-up with measured dialysis dose data occurring after the patient had completed at least 12 months of ESRD treatment.

Albumin and weight were measured at the time of dialysis dose measurement in the DOPPS. Height and all comorbid conditions were measured at time of entry into the DOPPS.

To make the study sample comparable to the dose levels of the HEMO Study, some analyses excluded patients for whom eKt/V at study start was less than the K/DOQI recommendation of 1.05. This group of patients accounted for 22% of the study sample. In these analyses, the sample was reduced to 8,438 patients with an eKt/V greater than 1.05.

Statistical Methods

CMS. Cox proportional hazards models were used to analyze the time from study start date (ie, the end of month 15 of ESRD for each patient) to death (censored at transplantation or June 30, 2001, whichever came first). The 74,120 patients had a total follow-up of 90,075 patient-years. The average URR during months 10 to 15 was related to the relative mortality risk during follow-up by sex by using a Cox proportional hazards model with adjustments for age at incidence, race, diabetes as the cause of ESRD, 18 comorbidity measures, weight, height, and year of incidence. These measures were collected at the start of ESRD on CMS 2728 (15 months before the study start). Results from Cox models

Table 1. Patient Characteristics by Sex

	CMS (United States) (N = 74,120)		DOPPS (7 countries) (N = 10,816)	
	Men (51.4%)	Women (48.6%)	Men (57.0%)	Women (43.0%)
Age at incidence (y)	63.3	65.4	59.1	60.6
Diabetes as ESRD cause (%)	42.4	53.7	28.8	35.3
Asian (%)	2.9	3.2	25.8	21.5
Black (%)	31.1	38.8	17.2	23.4
Native American (%)	1.6	2.1	0.5	0.6
White (%)	63.0	54.8	54.3	51.8
Other race (%)	1.4	1.1	2.2	2.7
Low dose at study start (%) (URR $<$ 65% or eKt/V $<$ 1.05)	18.7	7.3	28.9	14.4
Comorbid conditions (%)*				
Diabetes	49.4	61.7	33.1	39.7
Diabetes with insulin	21.0	27.4	21.4	27.5
Congestive heart failure	31.8	35.8	25.8	30.8
Ischemic heart disease/Coronary artery disease	26.3	22.9	53.6	55.3
Peripheral vascular disease	16.5	13.3	22.1	18.6
Myocardial infarction	9.7	7.3	14.7	13.0
Chronic obstructive pulmonary disease	8.0	5.6	10.8	8.0
Cardiac dysrhythmia	5.8	5.0	24.1	23.3
Smoker	6.8	3.7	58.2	24.6
Cancer	5.4	3.6	9.8	8.2
Inability to ambulate	2.8	3.4	5.3	8.7
Alcoholism	2.2	0.6	5.6	2.5
Drug dependence	1.4	0.4	3.2	2.3
Pericarditis	1.0	0.9	3.2	3.2
Inability to transfer	0.7	1.0	12.7	19.2
Cardiac arrest	0.7	0.6	2.1	2.1
Human immunodeficiency virus	0.9	0.3	1.1	0.6
Aquired immunodeficiency syndrome	0.5	0.1	0.8	0.3

*CMS comorbid conditions are measured at the start of ESRD (15 months before study start). DOPPS comorbid conditions are measured at entry into the DOPPS (0 to 12 months before study start).

are presented as relative mortality risks and 1-year death rates adjusted to the overall average patient characteristics.

Patients were classified into 5 dialysis-dose groups according to sex, for a total of 10 categories. Sensitivity analyses excluding patients with a history of congestive heart failure or coronary artery disease also were performed because these conditions may lead clinicians to prescribe low blood flows or shorten treatments because of hypotensive episodes. In addition, interactions between the dose-by-sex effect and age, race, diabetes, and body size were examined.

DOPPS. Survival among DOPPS patients was evaluated by using Cox models of time to death (censored at transfer to another facility, recovery from dialysis, transplantation, or the end of their facility follow-up period, whichever came first). Time at risk for these Cox models began with the date of the measured dialysis dose at the start of follow-up. The 10,816 patients had a total follow-up of 19,318 patient-years. Cox models were adjusted for age at incidence, race, diabetes as cause of ESRD, 18 comorbid factors, weight, height, vascular access type at time of dose measurement, education, nursing home status, and skipped or shortened treatments in the month before eKt/V measurement and stratified by country. Time from measurement of comorbid factors (entry into the DOPPS) and measurement of dialysis dose (entry into the analysis) was less than 6 months for 67% of patients and 6 to 12 months for the remaining 33% of patients.

Statistical adjustment for patient years of ESRD before entry into the study was made by using left truncation.[20] This technique allows for estimation of Cox regression coefficients accounting for differences in duration of previous dialysis at the study start. Clustering effects were addressed by using robust standard estimates based on the sandwich estimator.[20] All analyses were performed using SAS software (SAS Institute Inc, Cary, NC).

RESULTS

The 2 study populations consisted of 74,120 US patients based on CMS data and 10,816 international patients based on DOPPS data. Table 1 lists average patient age at incidence, race, percentage with diabetes as the cause of ESRD,

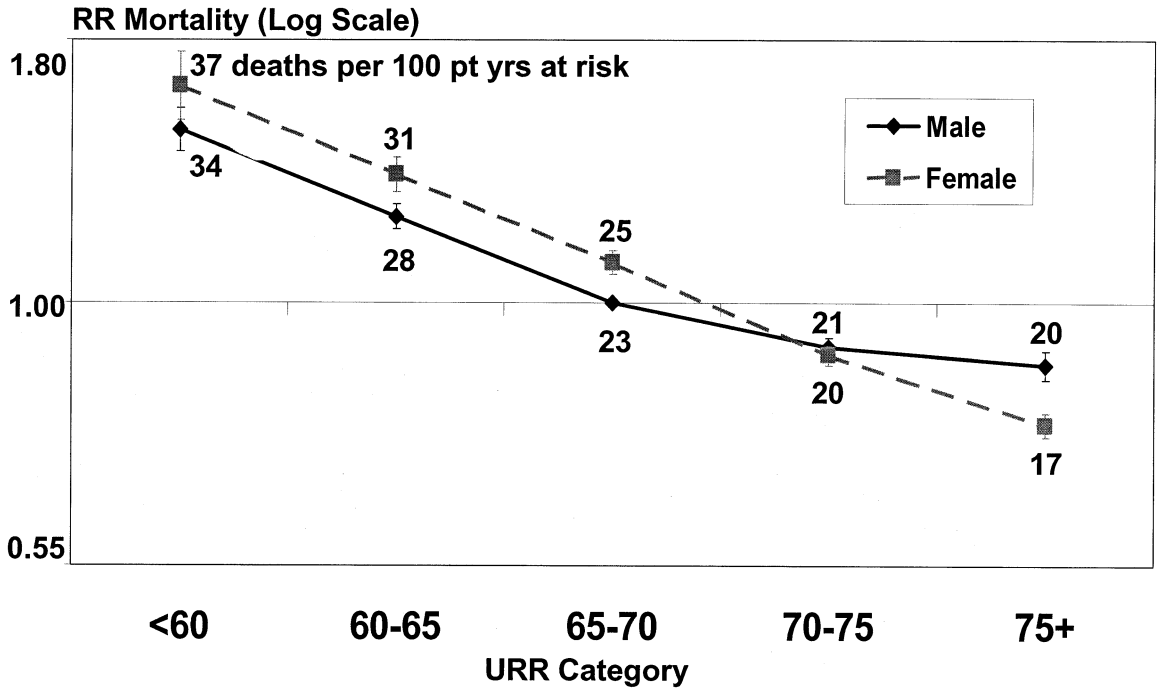

Fig 1. Mortality RR (on a log scale) and standard error bars by sex and dialysis dose, measured in URR categories for CMS patients. The reference group is men with a URR of 65% to 70%. Adjustments include the factors listed for CMS in Table 1, in addition to weight, height, and year of incidence. Lines connect RRs in the respective URR categories at the midpoints of the categories. Each group is labeled with its 1-year adjusted death rate per 100 patient-years at risk (adjusted to the overall average values for all factors except URR and sex).

and the 18 comorbidities reported in each of the study populations for men and women. Of the comorbidities recorded in the CMS database, percentages ranged from diabetes as the most frequent (55% overall) to acquired immunodeficiency syndrome as the least frequent (0.3% overall). These characteristics differed somewhat between the study populations, but are not atypical for the populations studied. Regression models were used to account for the differences observed between men and women in Table 1.

Figure 1 shows results of the CMS data analysis. The vertical axis represents relative risk (RR) for mortality. Numerical values shown near each point in the graph are the adjusted (all else equal) death rates. For both men and women, there is a steep decline in mortality risk with increasing URR, and the rate of decline is similar for men and women for a URR less than 70%. For both men and women, patients with a URR less than 60% have significantly greater mortality risk than those in the 65%-to-70% category ($P < 0.0001$ for both). However, results for patients with a URR of 65% or greater differ by sex, seen by the different slopes in Fig 1 at a URR greater than 65%.

Results from the DOPPS analyses are limited here to the 8,438 patients with an eKt/V greater than 1.05 (single-pool Kt/V [spKt/V], ~>1.2). The overall death rate in the DOPPS analyses was 23.4%. Figure 2 shows mortality RR separately for men and women by sex-specific means within eKt/V quartiles. Women benefit more from a greater eKt/V ($P < 0.001$) than men ($P = 0.23$). It appears that the decline in mortality risk among women also may become less steep for doses greater than an eKt/V of 1.4, although the change in slopes was not statistically significant.

Table 2 lists mortality RRs for men and women in the CMS analysis in each of the upper 2 URR categories compared with the 65%-to-70% category. Women in the 70%-to-75% category had a 19% lower mortality risk (RR, 0.81; $P < 0.0001$) and women in the greater-than-75% category had a 31% lower mortality risk (RR, 0.69; $P < 0.0001$) compared with women in the 65%-to-

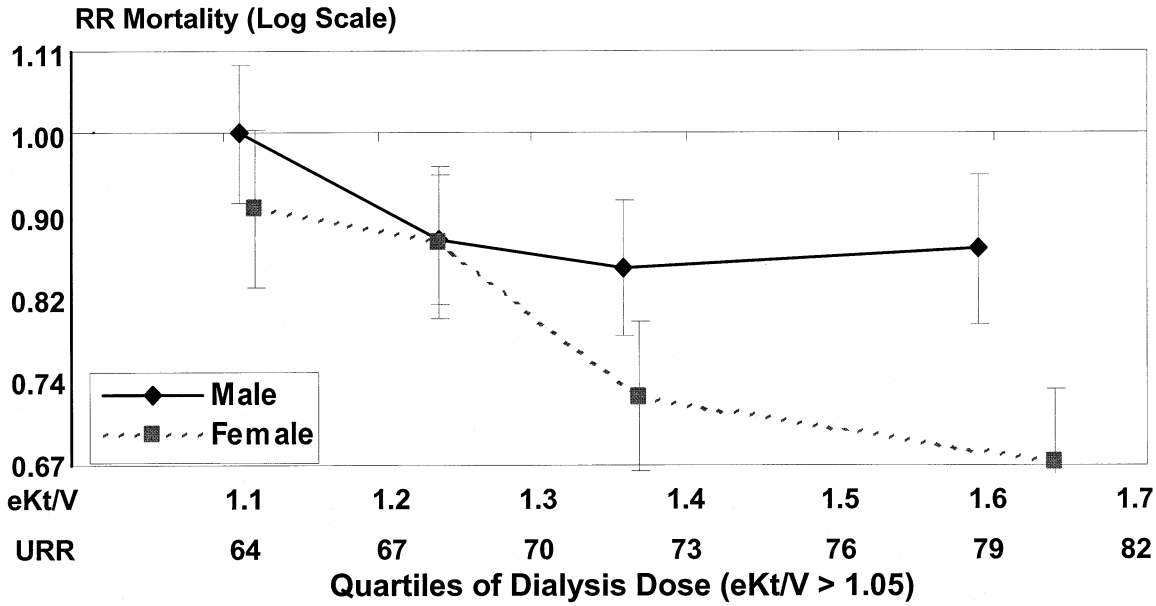

Fig 2. Mortality RR (on a log scale) and standard error bars by sex and dialysis dose, measured by eKt/V for DOPPS patients. Data points are for quartiles of patients after excluding those with an eKt/V less than 1.05. The reference group is men in the lowest eKt/V quartile. Adjustments include the factors listed for the DOPPS in Table 1, in addition to weight, height, vascular access type at time of dose measurement, education, nursing home status, skipped or shortened treatments in the month before eKt/V measurement, and country and accounting for facility clustering effects. Lines connect RRs in the respective eKt/V quartiles at the average values for sex group within the quartile. The smallest sample sizes were for lowest-dose female and highest-dose male groups (n = 694 and 740, respectively).

70% category. For men, the reduction in mortality risk was smaller, but substantial, being 10% lower in the 70%-to-75% category (RR, 0.90; $P < 0.0001$) and 13% lower in the greater-than-75% category (RR, 0.87; $P < 0.0001$) compared with the 65%-to-70% category. The decline in mortality continued in the highest dose group for women, whereas the highest dose group offered little additional benefit for men.

Table 3 lists reductions in mortality risk associated with greater dose for men and women in the HEMO Study, DOPPS, and CMS. Comparisons for the CMS data set are for URR greater than 75% compared with URR of 70% to 75%. A significant reduction in mortality was seen for women in the greater-than-75% category, with a 15% lower mortality risk (RR, 0.85; $P < 0.0001$) in the URR category of greater than 75% compared with a URR of 70% to 75%. For men, no additional risk reduction extended to the greater-than-75% category (>75% versus 70%-to-75% category; RR, 0.96; $P = 0.22$). These comparative results by sex were consistent with those of the HEMO Study, which reported a 19% reduction in mortality risk for women in the high-dose group and a 16% greater mortality risk (no ben-

Table 2. Mortality RR and Number of Patients According to Sex by URR Category at Study Start Compared With 65% to 70% for CMS Patients With URR ≥65%

Sex	$RR_{URR\ 65\%-70\%}$	$RR_{URR\ 70\%-75\%}$	$RR_{URR\ >\ 75\%}$
Male	1.00 (n = 13,509)	0.90* (n = 13,482)	0.87* (n = 4,015)
Female	1.00 (n = 7,732)	0.81* (n = 14,651)	0.69*† (n = 10,983)

*$P < 0.0001$ compared with URR of 65% to 70% for the same sex.
†$P < 0.0001$ compared with URR of 70% to 75%.

Table 3. Association Between Greater Dose and RR for Mortality for Men and Women

	Mortality RR for Higher *v* Lower Dose*				
	Women		Men		
	RR	*P*	RR	*P*	Dose Effect by Sex† (*P*)
HEMO Study‡	0.81	0.02	1.16	0.16	<0.014
DOPPS (per 0.37 eKt/V)§	0.80	<0.001	0.93	0.23	0.08
CMS (URR > 75% *v* 70%-75%) overall	0.85	<0.0001	0.96	0.22	0.003
Younger (<50 y)	0.73	0.006	1.00	0.98	0.09
Older (50+ y)	0.86	<0.0001	0.98	0.55	0.001
Nondiabetic	0.84	<0.0001	0.98	0.65	0.002
Diabetic	0.86	<0.0001	0.93	0.21	0.18
White race	0.82	<0.0001	0.94	0.08	0.005
Black race	0.96	0.32	1.06	0.48	0.27
Small body size‖	0.83	<0.0001	0.95	0.19	0.005
Big body size‖	0.90	0.008	1.00	0.97	0.17

*Tests whether high dose is associated with a reduction in mortality for each sex.

†Tests whether the RR for women equals the RR for men. A significant difference indicates that high dose is associated with a larger reduction in mortality for women than men.

‡Compares average eKt/V of 1.53 and 1.16 and average URR of 75.2% and 66.3%[3,4]

§Linear estimate of RR of 0.94 per 0.1 eKt/V for women and RR of 0.98 per 0.1 eKt/V for men applied to a difference of 0.37 eKt/V (equals average difference in HEMO Study groups).

‖Patients were classified as big or small within sex by the ratio of weight to height, dividing patients at the median sex-specific weight-height ratio.

efit) for men. Because of the smaller sample size in the DOPPS data, the dose-response relationship was evaluated for Table 3 as an average trend for each sex, ie, as a continuous variable for each sex. Among women, RR for mortality declined significantly with increasing eKt/V greater than 1.05 (6% lower per 0.1 higher eKt/V; $P < 0.001$). Among men, RR for mortality did not change significantly with increasing eKt/V (2% lower per 0.1 higher eKt/V; $P = 0.23$). For women, DOPPS findings parallel those of the HEMO Study, which showed an RR of 0.81 for an eKt/V that was 0.37 greater than in their reference group.[3,4] The significant DOPPS finding for women of an RR of 0.94 per 0.1 eKt/V yields an RR of 0.80 per 0.37 eKt/V ($0.94^{3.7}$). The HEMO Study, DOPPS, and CMS study failed to find a benefit of the high dose for men, whereas all 3 studies found a benefit for women. The difference in benefit between sexes was statistically significant in the CMS ($P < 0.01$) and HEMO ($P < 0.014$) studies and approached significance in the DOPPS ($P = 0.08$).

In the CMS data set, we also evaluated possible differences in the dose-by-sex effect by age (<50 and >50 years), race (white and black ["other" not shown]), diabetes as cause of ESRD, and body size. For the extra examination of body size, patients were classified as big or small within sex by the ratio of weight to height, dividing patients at the median sex-specific weight-height ratio. These analyses were restricted to the 64,362 patients with a URR of 65% or greater, with results shown for only the highest 2 URR groups. Table 3 lists mortality risk by sex for a URR of 75% compared with 70% to 75% overall and for these subgroups of the CMS data set. Dose-by-sex results were qualitatively similar, showing a more substantial decline in mortality at the greatest URR dose among women than among men in every age, race, diabetes, and body-size category. There was a significant benefit for women in the highest dose range for all except black women (RR, 0.96; $P = 0.23$). For men, no subgroup showed more than a 7% lower mortality risk for the highest dose range, and none of the effects was statistically significant, although white men had a reduced risk that nearly reached statistical significance (RR, 0.94; $P = 0.08$). The difference between the male and female benefit for a URR of 75% compared with 70% to 75% interaction was significant in many subgroups.

Additional Analyses

Sensitivity analyses also were performed. We excluded all patients who had a history of coronary artery disease or congestive heart failure to consider the possibility that very high dose affects differently those with and without heart disease. Using CMS data, this sensitivity analysis included 41,658 of the 74,120 patients included in the main analysis. Results were very similar regardless of whether these patients were included in the analysis.

DISCUSSION

The K/DOQI guidelines[20] are based on consensus opinion that inadequate dialysis can be defined by a URR less than 65% or eKt/V less than 1.05 (corresponding approximately to spKt/V $<$ 1.2). The results here confirm that dose levels less than the K/DOQI guidelines are associated with greater mortality risk. The present discussion focuses on results from the higher dose ranges, which were the focus of the HEMO Study.

Results from both the CMS and DOPPS data sources suggest differing responses by sex to higher dialysis dose ranges. In the present study of CMS data, the highest URR group ($>$75%) showed a clearly lower RR for mortality than the 70%-to-75% URR group in women (RR, 0.85; $P < 0.0001$), but not men (RR, 0.96; $P = 0.22$). Similarly, the international DOPPS data indicated a substantial and significant inverse association of dose and mortality for dose ranges greater than an eKt/V of 1.05 in women (RR, 0.95 per 0.1 higher eKt/V; $P < 0.001$), but not men (RR, 0.99; $P = 0.48$). In the CMS data, the dose-by-sex effect is consistent for major groups of age, race, diabetes, and body size.

These findings agree with those of the randomized HEMO Study, which also showed a benefit of high dose for women, but not men, a result that differed significantly by sex ($P < 0.014$). However, in the HEMO Study protocol, this finding was considered nonsignificant with Bonferroni correction for multiple comparisons.[3,4] The new findings from CMS and DOPPS data confirm a statistically significant interaction. The strikingly consistent results in all 3 studies indicate that survival benefit from high-dialysis dose levels differs for men and women.

Whereas a randomized trial like the HEMO Study can evaluate a cause-and-effect relationship between dialysis dose and mortality, observational studies can document significant correlations, but cannot directly prove causation.[22] Observational studies are likely to be biased toward showing a stronger benefit than truly exists because healthier patients can tolerate higher doses of dialysis and access failures were classified as "low dose," lacking specific information about access. Despite the potential bias, observational studies agree with the HEMO Study results of a differing effect of dose by sex. The remaining discussion addresses potential explanations for this dose-by-sex interaction.

The strength of the CMS data set is its large sample size. Dose data were reported to the CMS in 5 ranges of URR without detailed URR or Kt/V values or their relevant components. Despite this limitation in dose measurement, the 3 categories of interest (URR of 65% to 70%, 70% to 75%, and $>$75%) yielded important insights for the 64,372 patients who had likely lost residual renal function by the end of month 15 of ESRD when the study was started. These results were consistent with the HEMO Study results, for women in particular.[3,4]

The DOPPS data provide a cross-sectional international sample of more than 10,000 patients and allowed for a more detailed analysis of dose by eKt/V as a continuous variable within the range of the HEMO Study. However, because dose data were collected only once every 4 months, it was necessary to use a single measure of dialysis dose, rather than an average of several monthly doses, as in the CMS data. Subsequent changes in dialysis dose over time and a single measurement would tend to give a lower estimate of associated risks because of misclassification or "noise" in the data. The effect of unrecorded residual renal function was minimized by excluding the first year of ESRD, with the average patient having had more than 3 years of ESRD therapy at entry into the DOPPS.

A bias toward a less steep mortality-by-dose relationship may be introduced by imprecise or nonstandardized measurement of URR. The technique of drawing the postdialysis BUN sample has been variable in the past.[23] However, the K/DOQI guidelines may already have contributed to a more standardized sampling technique

and a reduction in noise for the URR measure. Yet, in the international DOPPS, such blood drawing may have been less well standardized, which could have led to less significant findings. However, it is not clear why such noise could have been substantially stronger in men than women.

Potential explanations for the relatively steep and consistent correlation of high dose and low RR for mortality for women were explored through additional analyses. This led to the first hypothesis that a high URR likely is achieved with high-flux membranes, and the low mortality risk results from the improved middle-molecule clearance, rather than from the small-molecule clearance that URR considers.[24] We adjusted the CMS analysis for frequency of high-flux dialyzer use at each patient's dialysis unit. Because this adjustment did not modify the results, it provided no support for the hypothesized role of middle molecules.

The second hypothesis was that central venous catheters may be associated with a lower dialysis dose and, independently, with increased mortality risk.[25] Such a mechanism could explain the steep correlation of URR and RR for mortality at lower ranges of URR. Using again the percentage of use of central venous catheters at the patient's dialysis unit as a proxy, virtually no modification of the overall correlation was found in the CMS data, although this proxy measure for catheters was significantly associated with mortality risk. To address this question in the DOPPS data, analyses were performed controlling for central venous catheter use and, separately, by excluding these patients entirely. Results in these 2 cases did not differ appreciably: RR for mortality per 0.1 eKt/V for women stayed at 0.94, whereas the RR for men changed from 0.98 for all patients to 0.97 for patients without central venous catheters.

Explanations for the observed differences by sex for the association of dialysis dose and mortality are lacking. A greater prevalence of shortening or skipping dialysis treatments in men than women could contribute to this observation because of greater misclassification of the monthly average dialysis dose in men (biasing the results toward the null, ie, finding no association). However, Leggat et al[26] showed only a small nonsignificant difference in this direction in the United States. Similarly, Saran et al[27] found internationally more noncompliance to dialysis prescription among men than women; but again, this difference by sex was small.

As another potential explanation for the observed differences by sex, it was hypothesized that hormonal differences may have a role. This possibility was broadly evaluated under the assumption that women older than 50 years are postmenopausal because only a small fraction ($<$7%) of hemodialysis patients in this age group have been shown to receive hormone replacement therapy.[28] However, the pattern of mortality risk by dose level in this older subgroup was similar for both the CMS and DOPPS data, showing that the association with mortality risk was stronger for women than men, although the difference was somewhat smaller in this older age group. Other potential explanations must be sought. One might consider the possible role of different body composition, particularly fat, for men and women. An earlier analysis by the authors of the current study regarding causes of death by dialysis dose level showed that low dialysis dose was associated with all groups of causes of death and did not identify a uremia-associated cause of death.[29] One could speculate that more severe preexisting heart disease among men or selection of higher risk male patients to receive a higher dose could have a role. However, such selection should not have occurred in the randomization of the HEMO Study, which yielded a similar result. This dose-by-sex interaction gives a plausible explanation for a previously reported greater benefit among small patients compared with larger patients.[2]

Observational studies shed light on the level of dialysis dose actually delivered. Trends in the past decade show a remarkable increase in average dialysis dose in the United States according to national random samples.[14,30] The US Renal Data System Case Mix Adequacy Study[10] had shown a substantially lower dose in 1990, with an average URR of only 60.1%. The reduction in mortality during the 1990s can be explained to some extent by the steady increase in dialysis dose.[14,30] An optimal dose of hemodialysis, the level above which no improvement in outcomes can be observed, has not been clearly identified. The present study agrees with the HEMO Study in suggesting that this level may be higher for

women than men. Because the group of men in the United States with a URR greater than 75% was only a very small minority of patients (5.4%), the lack of an association with lower mortality risk remains uncertain. In the United States and the other DOPPS countries, average delivered dose was similar.[31] However, for an important fraction of patients, it was less than the recommended minimal level per K/DOQI guidelines, at least after more than 12 months of ESRD, when most patients have lost their residual renal function.

The 2 studies presented here may be viewed as hypothesis generating, which is a characteristic of observational studies. However, the agreement of these observational studies with the randomized trial of the HEMO Study suggests a survival benefit from greater dialysis doses for women, but not for men. This indicates the need for new explanatory hypotheses and additional study into this consistent, but puzzling, finding.

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