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Dialysis dose and the effect of gender and body size on outcome in the HEMO Study

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Background. Gender and body size have been associated with survival in hemodialysis populations. In recent observational studies, overall mortality was similar in men and women and higher in small patients. The effect of dialysis dose in each of these subgroups has not been tested in a clinical trial.

Methods. The HEMO Study was a controlled trial of dialysis dose and membrane flux in 1846 hemodialysis patients followed up for 6.6 years in 15 centers throughout the United States. We examined the effect of dialysis dose on mortality and on selected secondary outcomes in subgroups of patients.

Results. Adjusting for age only, overall mortality was lower in patients with higher body weight ($P < 0.001$), higher body mass index ($P < 0.001$), and higher body water content determined by the Watson formula (Vw) ($P < 0.001$), but was not associated with gender ($P = 0.27$). The RR of mortality comparing the high dose with the standard dose group was related to gender ($P = 0.014$). Women randomized to the high dose had a lower mortality rate than women randomized to the standard dose (RR = 0.81, $P = 0.02$), while men randomized to the high dose had a nonsignificant trend for a higher mortality rate than men randomized to the standard dose (RR = 1.16, $P = 0.16$). Analysis of both genders combined showed no overall dose effect (R = 0.96, $P = 0.52$), as reported previously. Vw was greater than 35 L in 84% of men compared with 17% of women. However, the RR of mortality for the high versus standard dose remained lower in women than in men after adjustment for the interaction of dose with Vw or with other size parameters, including weight and body mass index. Conversely, the dose effect was not significantly related to size parameters after controlling for the relationship of the dose comparison with gender.

Conclusion. The data suggest that mortality and morbidity might be reduced by increasing the dialysis dose above the current standard in women but not in men. This effect was not explained by differences between men and women in age, race, or in several indices of body size. Because multiple comparisons were considered in this analysis, the role of gender on the effect of dialysis dose is suggestive and invites further study.

Key words: clinical trial, hemodialysis, gender, race, HEMO Study, survival, body size, weight, body water volume, Kt/V.

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The Hemodialysis (HEMO) Study was a prospective, randomized, multicenter clinical trial designed to determine if increasing the dose of hemodialysis or using high-flux membranes can affect mortality and morbidity. Patients with end-stage renal disease (ESRD) were randomly assigned to two different levels of dialysis dose, expressed as Kt/V, and to treatment with either a high-flux or a low-flux membrane. In intent-to-treat analyses of all patients, neither the high- nor the low-dose intervention significantly improved mortality or any of four prespecified main secondary outcomes, but a possible interaction with gender was identified [1].

Several observational studies have examined the relationship between dialysis dose and survival stratified by gender, race, or a measure of body size [2–5]. Owen et al [2] specifically suggested that the effects of dialysis dose can vary depending on race and gender. Several other observational studies have also reported that larger body size is associated with lower mortality, irrespective of dialysis dose [5–7]. Over the past decade, data from the United States Renal Data System (USRDS) have shown a lesser trend downward in the absolute mortality rate of women compared with men, resulting in reversal of the relative mortality rate, which is now higher in women. [8].

A J-shaped pattern to the overall dose-mortality curve, reported in several studies, has been attributed to effects of nutrition and body size, and to gender as well [2, 4, 8, 9]. Men are larger on average than women and may require more time on dialysis to achieve the same Kt/V. Therefore, gender and other linked variables can affect the dose-survival analysis. As a result, it has been difficult to separate the independent effects of gender, treatment time, and body size.

Using HEMO Study data, we examined the effects of race, gender, body size, and other variables as predictors of outcome, and we examined subgroups of patients in whom the dose intervention might have affected survival.

METHODS

Details of the study design, primary outcomes, and the characteristics of 1846 randomized patients have been published and are briefly summarized [1, 10]. Patients 18 to 80 years of age who were on dialysis at least 3 months, and had less than 1.5 mL/min/35 L residual urea clearance were enrolled between March 1995 and October 2000, and were followed up to 6.6 years. Half were dialyzed with a target equilibrated Kt/V (eKt/V) of 1.45, and half were treated with a target eKt/V of 1.05. Randomization was stratified by clinical center, age, and diabetic status. To qualify for randomization, each patient had to achieve an eKt/V greater than 1.30 within 4.5 hours of treatment during the baseline period. This criterion resulted in exclusion of very large patients (3% of randomized patients >100 kg). The dose was adjusted by changing either clearance (blood flow, dialysate flow, or dialyzer model) or treatment time, while encouraging the prescribing physician to shorten the dialysis as much as possible, but not below 2.5 hours, while maintaining fluid removal. Urea kinetics were modeled each month and tracked by an adherence committee. Serum tests for albumin (by nephelometry) and other commonly measured solutes were obtained at monthly intervals of predialysis. A patient's racial/ethnic classification was based on self reports.

The study protocol was approved by the institutional review board at each of the 15 clinical centers associated with a total of 72 participating dialysis clinics. Written consent was obtained from each patient at entry into baseline and before randomization.

Outcome measures

The primary outcome of the HEMO Study was all-cause mortality. The four main secondary outcomes were the rate of nonaccess hospitalizations, and three composite outcomes: first cardiac hospitalization or death from any cause, first infection-related hospitalization or death from any cause, and first 15% decline in serum albumin or death from any cause. Additional secondary outcomes considered in this report included death from cardiac causes, death from infection, the composite of first cardiac hospitalization or death from cardiac causes, the composite of first infection-related hospitalization or death from infection, the first access-related hospitalization, and the first access-related event. The first access event was defined as either the first recorded access-related hospitalization or the first access procedure of any type recorded monthly in the study database.

Size variables and other baseline measurements

Total body water volume (Vw) was determined by the Watson anthropometric formula [11]. Body mass index (BMI) was defined as body weight in kg divided by the square of height in cm. Urea distribution volume (V) was assessed monthly using single-pool urea kinetic analysis adjusting for the double-pool error [12–14]. Baseline postdialysis weight used to compute anthropometric volume, and the baseline modeled urea volume was averaged over two kinetic modeling sessions conducted on the patient's usual dialysis prescriptions.

Interactions

Seven baseline variables: age, gender, race, years on dialysis, diabetes, index of coexisting disease (ICED), and serum albumin, were prespecified by the HEMO investigators at the beginning of the trial as covariates in the primary statistical analyses and for subgroup analyses. The ICED score was defined as described previously [15], but excluding diabetes because diabetic status is a separate factor in analysis.

In this report we use the term "interaction" to describe differences in the effect of the dose intervention between different subgroups of patients. We applied statistical tests for interactions to see if the dose effect differed between subgroups defined by the above seven prespecified covariates and the size variables listed previously. In particular, the interaction between the dose intervention and gender refers to the difference between the effect of the dose intervention in females compared with males, and is quantitatively expressed as the ratio of the relative risk for the high versus standard dose group in women to the relative risk for the high versus standard dose group in men. Because the relative risk is itself a ratio, the principal expression of interaction shown in Tables 5 and 6 (columns headed "Ratio of RR") is a ratio of a ratio.

Statistical methods

The primary analysis of the effects of the dose and flux interventions on all-cause mortality was conducted with Cox regression stratified by clinical center and controlling for the seven prespecified baseline covariates, and for the interaction of baseline albumin with follow-up time.

Follow-up was censored after kidney transplants. Additional details regarding the primary analysis have been provided elsewhere [1, 2].

The interactions of the dose intervention with each of the seven prespecified baseline factors on mortality were individually tested by adding an interaction term between the dose intervention and the designated baseline factor to the basic Cox regression model described above. In the initial prespecified analyses, subgroups for continuous factors (age, albumin, and years on dialysis) were defined by their mean values.

After identification of a potential interaction between the dose intervention and gender on mortality, we performed similar analyses to test for interactions between dose and gender on the secondary outcome variables. These analyses were performed with overdispersed Poisson regression for the nonaccess hospitalization rate, and Cox regression analysis for each of the other composite outcomes. In the analyses of the secondary outcomes, follow-up was censored at transfer to nonparticipating dialysis units and at renal transplant. Follow-up time was also censored at death for the analyses of the nonaccess hospitalization rate, first access hospitalization, and first access event.

Additional Cox regression analyses were performed to individually test for interactions of the dose intervention with specific size parameters, while controlling for the seven prespecified covariates and the interaction of baseline albumin with follow-up time as in previous analyses. The size parameters were treated as continuous variables in these analyses, allowing tests of linear interactions. A further analysis was conducted by stratifying Vw into four quartiles to investigate the possibility of a nonlinear interaction. These models were next augmented to include two separate interaction terms, one of dose group with the size parameter being evaluated, and the other of dose group with gender. These analyses evaluated the extent to which trends for interactions between dose and the respective size parameters persisted after taking into account the interaction between gender and the size parameters, and conversely, the extent to which the interaction of dose group with gender persisted after taking into account any interaction between dose group and the size parameters. As in the primary analysis, all of the Cox regression analyses of mortality were stratified by clinical center and censored transplants.

All analyses in this report are based on comparisons of the randomized dose groups rather than the achieved levels of eKt/V. All reported *P* values are two-sided without adjustment for multiple comparisons.

RESULTS

Among the seven prespecified variables, gender was the only factor that had a significant interaction with the dose intervention on mortality ($P = 0.014$) (Table 1). Women appeared to respond to the high dose with a 19% reduction in mortality, whereas the mortality in men trended upward by 16% at higher doses. Kaplan-Meier survival curves comparing the dose interventions in men and women separately showed a similar lower mortality in women on the higher dose and the opposite effect in men (Fig. 1). The remainder of this report examines the relationship between gender and the effect of dose in greater detail, and in particular investigates if the interaction between dose and gender can be accounted for by body size or other factors that are associated with gender.

Table 1. Effects of seven prespecified baseline factors on the response to high Kt/V

Factor	Subgroup	Relative risk[a]	95% CI	*P* value[b]
Age[c]	≤58 years	0.95	(0.74–1.22)	0.92
	>58 years	0.97	(0.82–1.13)	
Gender	Men	1.16	(0.94–1.43)	0.014
	Women	0.81	(0.68–0.97)	
Race	Non-black.	1.13	(0.91–1.39)	0.060
	Black	0.87	(0.73–1.03)	
Diabetes	Nondiabetic	0.90	(0.74–1.09)	0.35
	Diabetic	1.02	(0.85–1.23)	
Years of dialysis[c]	≤3.7 years	1.03	(0.88–1.22)	0.12
	>3.7 years	0.83	(0.66–1.04)	
ICED[c]	≥2	0.92	(0.70–1.22)	0.96
	≤3	0.93	(0.76–1.15)	
Albumin[c]	≤3.6 g/dL	0.89	(0.75–1.06)	0.16
	>3.6 g/dL	1.08	(0.88–1.32)	

ICED, Index of Coexisting Diseases.

[a] Relative risk of mortality from any cause in high vs. standard Kt/V group.

[b] *P* values for interactions were based on comparisons without adjustment for multiple tests. Bonferroni limit for 7 variables = 0.0071.

[c] Interaction tests for continuous variables were based on dichotomization at their mean values.

Genders differences at baseline

Although randomization was not stratified by gender, female percentages were well-balanced, at 56% of patients in each of the treatment groups [1]. The women were slightly but significantly older than the men (Table 2). Blacks have a known survival advantage, and diabetes mellitus, a known survival disadvantage, were both over-represented in the women [2, 8]. The indices of body size listed in Table 2 were lower in women than in men. Histograms of body water in men compared with women, shown in Figure 2, revealed limited overlap. The type of vascular access, a factor previously shown to be associated with survival [16], appeared to disadvantage women who had more grafts and catheters than men at baseline (Table 2).

Each of these differences between the genders at baseline was investigated as a possible explanation for the relationship between gender and the effect of dose on outcome. None of the prespecified covariates, or the three baseline treatment parameters listed in Table 2 other than gender, had a statistically significant interaction with the

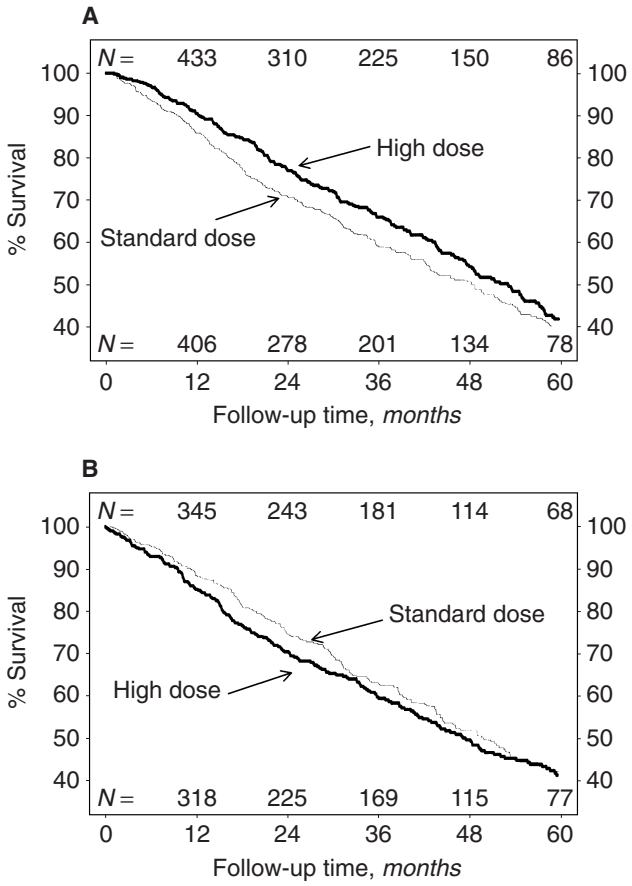

Fig. 1. Kaplan_Meier curves showing time to death in women by randomized treatment group (484 total deaths) (*A*). The high-dose group (dashed line) had a relative mortality risk of 0.81 compared with the standard dose group (solid line); 95% CI, 0.67–0.97, $P = 0.02$. Numbers of patients remaining in follow-up are provided for the high dose (top line) and standard dose (bottom line). Similar analysis showing time to death in men (387 total deaths) (*B*). In contrast to women, the high-dose group (dashed line) had a relative mortality risk of 1.16 compared with the standard dose group (solid line), 95% CI, 0.94–1.43, $P = 0.16$. Numbers of patients remaining in follow-up are provided for the standard dose (top line) and high dose (bottom line).

dose ($P > 0.05$ for all interaction tests), and the dose × gender interaction persisted after controlling for the interactions of dose with each of these other factors.

Causes of death in women

The higher dose in women was associated with fewer deaths caused by ischemic heart disease (53 in the high dose group vs. 65 in the standard dose group), cerebrovascular disease (15 vs. 25), congestive heart failure (5 vs. 10), and vascular access complications (12 vs. 21). Smaller differences were observed in women for deaths from other causes, including peripheral vascular disease (19 vs. 16) and malignancy (13 vs. 14).

Overall association of gender with mortality

Because of their smaller size, women required less time and lower urea clearances to achieve their targeted goals (Table 3). The absolute separation between standard and high-dose dialysis during follow-up was similar (0.37 and 0.38 eKt/V units in men and women, respectively), despite the higher average eKt/V and urea reduction ratio (URR) in women and the lower predialysis blood urea nitrogen (BUN). Adjusting only for treatment group, the relative risk of mortality (RR) in women compared with men in the two dose groups combined was 1.02 (95% CI, 0.89–1.16, $P = 0.83$). After controlling for age and treatment group, the RR decreased to 0.93 (95% CI 0.81–1.06, $P = 0.27$), and after controlling for all six remaining prespecified covariates and stratifying by clinical center, RR decreased to 0.85 (95% CI 0.74–0.98, $P = 0.02$). Thus, there appeared to be a moderate overall survival advantage of women compared with men with similar initial baseline risk factors. This perhaps reflects the longer life expectancy for women in the general population.

Overall association of body size and race with mortality

When averaged over both dose groups, a lower overall mortality rate was associated with larger body size and among blacks (Table 4; column 3). These relationships persisted after controlling for gender (Table 4; column 5). The data are consistent with previous reports of cross-sectional data [5] that showed a lower risk of mortality in larger patients and in blacks.

Interactions of dose with body size and their relationship to gender

The third and fourth columns of Table 5 summarize analyses of interactions between the dose intervention and various baseline parameters related to body size and race. A ratio of relative risks (RR) greater than 1 means that larger values of the baseline parameter are associated with a higher risk of death at the high dose compared with the standard dose intervention, while an RR ratio less than 1 means that larger values are associated with a reduced risk at the high dose. None of the examined indices of body size had significant interactions with dose ($P \geq 0.19$).

The final two columns of Table 5 show the interactions between the dose intervention and the same body size parameters after controlling for the interaction of dose with gender. The weak trends that were observed for higher mortality in the high dose compared with the standard dose group for higher height, Vw, and modeled volume (interaction P values 0.19 to 0.26), dissipated after controlling for the interaction of dose with gender. This is illustrated in greater detail for Vw in Figure 3.

Table 6 provides the converse of the analysis displayed in the final two columns of Table 5 by showing the strength of the interaction of dose with gender after adjusting for the interactions of dose with the respective size parameters. Several of the size parameters were strongly associated with gender (see Table 2), potentially making it difficult to distinguish between gender and body

Table 2. Description of randomized patients at baseline by gender

	All ($N = 1846$)	Men ($N = 808$)	Women ($N = 1038$)	P value[a]
Prespecified covariates				
Age *years*	57.6 ± 14.0[b]	56.6 ± 14.5	58.4 ± 13.6	0.005
% Black race	62.6%	55.0%	68.6%	<0.001
% Diabetic	44.6%	37.0%	50.5%	<0.001
Years on dialysis	3.75 ± 4.36	4.02 ± 4.58	3.54 ± 4.16	0.021
ICED score	1.97 ± 0.83	1.91 ± 0.85	2.02 ± 0.82	0.003
Albumin *g/dL*[c]	3.62 ± 0.36	3.70 ± 0.37	3.56 ± 0.34	<0.001
Baseline treatment parameters				
Equilibrated Kt/V *eKt/V*	1.43 ± 0.21	1.37 ± 0.19	1.48 ± 0.22	<0.001
Single-pool Kt/V *spKt/V*	1.60 ± 0.23	1.52 ± 0.20	1.66 ± 0.24	<0.001
URR	72.7 ± 4.9	71.0 ± 4.6	74.0 ± 4.7	<0.001
% with residual urea clearance >0	32.9%	35.1%	31.1%	0.07
Size parameters:				
Weight *kg*[d]	69.2 ± 14.7	72.1 ± 13.6	66.8 ± 15.1	<0.001
Height *cm*	165 ± 9.4	171 ± 7.7	159 ± 7.1	<0.001
BMI kg/cm^2	25.5 ± 5.3	24.5 ± 4.3	26.2 ± 5.8	<0.001
BSA m^2	1.75 ± 0.20	1.83 ± 0.18	1.68 ± 0.18	<0.001
Vw *L*	34.9 ± 6.1	39.6 ± 5.0	31.3 ± 4.0	<0.001
Creatinine *mg/dL*[c]	10.3 ± 2.9	11.2 ± 3.1	9.5 ± 2.5	<0.001
Vascular access[e]				
Native fistula	34.5%	48.9%	23.2%	<0.001
Synthetic graft	59.4%	47.8%	68.4%	<0.001
Catheter	5.6%	3.5%	7.3%	<0.001

Abbreviations are: ICED, Index of Coexisting Diseases; URR, urea reduction ratio; BMI, body mass index; BSA, body surface area; Vw, total body water volume.
[a]Comparison between men and women.
[b]Mean values ± SD.
[c]Predialysis.
[d]Postdialysis.
[e]0.5% of accesses classified as "Other."

size when interpreting interactions with the dose intervention. Nonetheless, when an adjustment was made for each of the size parameters, the gender interaction with dose remained, as shown in Table 6. These results indicate that within the HEMO Study the evidence suggesting a different dose effect between men and women was not explained by differences in body size between the two genders.

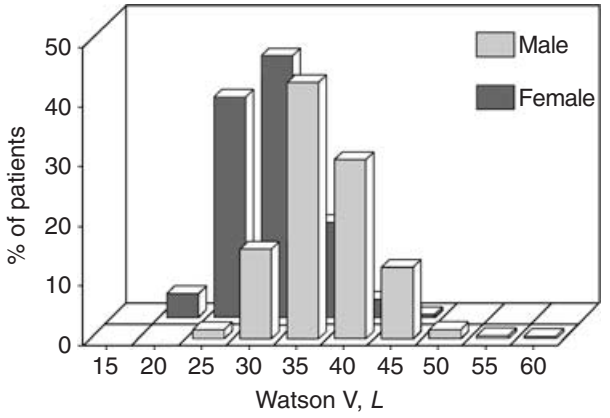

Fig. 2. Distribution of body water volumes (Vw) by gender. Vw, predicted by the Watson anthropometric formula [11], were in general much lower in female than in male patients assigned to randomized groups in the HEMO Study.

Interactions among race, gender, and dialysis dose

An interaction of borderline significance between racial/ethnic group and dose on mortality was detected ($P = 0.060$) (Table 1). Although weak, the interaction raised the possibility that the gender effect might be explained in part by race. However, the gender interaction with dose persisted after controlling for the interaction of race with dose (Table 6, bottom row), while the race interaction with dose weakened after controlling for the interaction of gender with dose (Table 5, bottom row).

The evidence for a different effect of dose between men and women was stronger in non-blacks in whom the RRs for the high- versus the standard-dose groups were 0.80 (95% CI 0.58–1.10) for women, compared with1.47 (95% CI 1.11–1.96) for men. Among blacks, the RRs for the high- versus the standard-dose groups were 0.84 (95% CI 0.68–1.04) for women, compared with 0.91 (95% CI 0.69–1.21) for men. Thus, it appears that the gender effect was driven by the response to the higher dose in non-blacks. Although the magnitude of the effect of race on the dose by gender interaction appears substantial, the difference in the dose by gender interactions between blacks and non-blacks did not reach statistical significance ($P = 0.064$). This reflects the very low power of this study (as is generally the case in clinical trials) to detect a three-way interaction.

Treatment time and other variables

The mean treatment time was shorter in women than in men, and even shorter in women randomized to the standard dose (Table 3). The HEMO Study was intentionally designed to allow time to vary within limits to reflect the standard of hemodialysis care in the United States. Centers were advised to select a prescription with

Table 3. Treatment parameters during follow-up by gender[a]

Parameter	All		Women		Men	
	Standard Dose	High Dose	Standard Dose	High Dose	Standard Dose	High Dose
Dialysis time (T) *minutes*	190 ± 23	219 ± 23	182 ± 21	210 ± 20	200 ± 21	231 ± 22
Blood flow rate *mL/min*	311 ± 51	375 ± 32	295 ± 51	367 ± 36	330 ± 43	385 ± 23
Urea clearance (K) *mL/min*	218 ± 25	251 ± 18	210 ± 24	247 ± 18	228 ± 21	257 ± 16
Urea K × T *L*	41.4 ± 7.0	55.1 ± 7.6	38.2 ± 5.9	51.7 ± 6.3	45.5 ± 6.1	59.6 ± 6.8
spKt/V	1.32 ± 0.09	1.71 ± 0.11	1.34 ± 0.10	1.73 ± 0.11	1.30 ± 0.07	1.68 ± 0.10
eKt/V	1.16 ± 0.08	1.53 ± 0.09	1.17 ± 0.09	1.55 ± 0.10	1.14 ± 0.06	1.51 ± 0.09
URR %	66.3 ± 2.5	75.2 ± 2.5	66.9 ± 2.6	75.7 ± 2.5	65.6 ± 2.2	74.5 ± 2.3
Predialysis BUN *mg/dL*	62.1 ± 13.6	54.3 ± 11.8	61.6 ± 12.9	54.0 ± 11.7	62.8 ± 14.4	54.8 ± 11.8

Summarized are the mean ± SD of these average values for all patients.
[a]Treatment parameters were first averaged over time for each patient with >4 months of follow-up.

Table 4. Association between various size parameters and the risk of mortality (RR) with or without adjustment for gender

Size arameter	Mean ± SD or %	Effect on mortality RR	95% Confidence Interval	Effect on mortality controlling for gender RR	95% Confidence Interval
Weight *kg*	69.2 ± 14.7	0.88[b]	(0.82–0.94)	0.87[b]	(0.81–0.94)
Height *cm*	164.6 ± 9.4	0.95	(0.89–1.02)	0.93	(0.93–1.01)
Vw *L*	34.9 ± 6.1	0.85[b]	(0.79–0.91)	0.73[b]	(0.66–0.81)
Modeled V *L*	31.1 ± 6.6	0.90[a]	(0.84–0.96)	0.88[b]	(0.81–0.95)
Body surface area m^2	1.75 ± 0.20	0.88[b]	(0.82–0.94)	0.86[b]	(0.80–0.93)
Body mass index kg/m^2	25.5 ± 5.3	0.90[a]	(0.84–0.96)	0.89[a]	(0.83–0.96)
Black race	62.6%	0.74[b]	(0.64–0.84)	0.73[b]	(0.64–0.84)

Except for race and gender, the relative risk (RR) of mortality is expressed for one SD increase in size parameter. In the third column, RR is controlled only for the randomized treatment group. In the fifth column, the RR is controlled for gender in addition to treatment group. In the last (bottom) line, blacks are compared with non-blacks. Race and each size parameter are evaluated independently, without adjustment for the other size parameters.
[a]$P < 0.05$; [b]$P < 0.001$.

the highest clearance, and therefore, the shortest treatment time consistent with the patient's assigned dose. Because of this design, the study was not optimized to evaluate the effect of treatment time, which was largely determined by the randomized dose assignment, volume of urea distribution, and the ability of the patient's access to sustain a high blood flow. Recognizing this major limitation, a series of multivariable time-dependent Cox regression analyses were performed to relate risk of mortality to the mean follow-up treatment time with several different strategies that adjusted for baseline and follow-up factors. No adverse effects of shorter treatment times were detected (data not shown).

Additional factors that had no apparent effect on the relationship of mortality to dose included the patient's native kidney urea clearance (Table 2), baseline serum phosphorus, baseline dialyzer flux, baseline eKt/V, and randomized flux group ($P > 0.30$). No change in the relative risk for the comparison of the high- versus the standard-dose groups was detected between the first two years after randomization and subsequent follow-up ($P = 0.97$).

Secondary outcomes and gender

Table 7 shows the relationship of gender to the effect of dose on ten secondary outcomes, including the four main secondary outcomes stipulated in the study protocol. Consistent with the analyses of mortality, the relative risk of the high- versus standard-dose was generally lower in women. However, the P value for the dose by gender interaction was smaller than 0.05 only for the following outcomes: first infection-related hospitalization or death from any cause; cardiac death; first 15% decline in serum albumin or death from any cause; and first access hospitalization. For the latter two outcomes, differences in the dose effect between genders were primarily caused by an adverse effect of the high dose in men rather than a beneficial effect in women.

DISCUSSION

Despite the overall lack of improvement in outcome from either a higher dose or higher flux, women in the HEMO Study appeared to have a 19% lower mortality risk ($P = 0.02$) when randomized to the higher dose of dialysis, whereas the mortality risk in the men actually rose 16% above that in men randomized to the standard dose of dialysis ($P = 0.16$) (Fig. 1). Gender was the only factor from among seven prespecified variables to exhibit such an effect (Table 1). Diabetics, older patients, patients with higher comorbidities, and non-blacks fared no better at the higher dose compared with the standard dose, despite the strong association of these variables with death (Table 4). Although the strong association of gender with body size makes it difficult to distinguish between the effects of these factors, differences in size did not appear in our analyses to account for gender effect (Table 6), whereas adjustment for gender reduced nearly all of the size parameter interactions to an insignificant level

Table 5. Effect of size on the mortality response to dialysis dose, with or without controlling for gender

Size parameter	Mean ± SD or %	Effect on response to dose Ratio of RRs	*P* value	Effect on response to dose, controlling for the interaction between dose and gender Ratio of RRs	*P* value
Weight *kg*	69.2 ± 14.7	0.98	0.83	0.95	0.53
Height *cm*	164.6 ± 9.4	1.09	0.19	0.98	0.78
Vw *L*	34.9 ± 6.1	1.09	0.26	0.96	0.64
Modeled V *L*	31.1 ± 6.6	1.10	0.20	1.02	0.77
Body surface area m^2	1.75 ± 0.20	1.02	0.84	0.95	0.48
BMI kg/m^2	25.5 ± 5.3	0.93	0.32	0.95	0.52
Black race	62.6%	0.77	0.063	0.81	0.15

Data shown in the third and fifth columns are the ratios of the relative risk (RR) of mortality for the high vs. standard dose groups per one SD increase in size parameter (except for race, where the ratio of the RR is expressed for blacks vs. non-blacks). The third column summarizes analyses of interactions between the dose intervention and various baseline parameters related to body size and race. Ratios of RR greater than 1 indicate a greater relative risk of the high compared to the standard dose at higher values of the size parameter than at smaller values. Ratios of RRs are provided without (third column) and with (fifth column) adjustment for the interaction of dose group with gender. All analyses are adjusted for the other six prespecified baseline covariates. *P* values are not adjusted for multiple analyses.

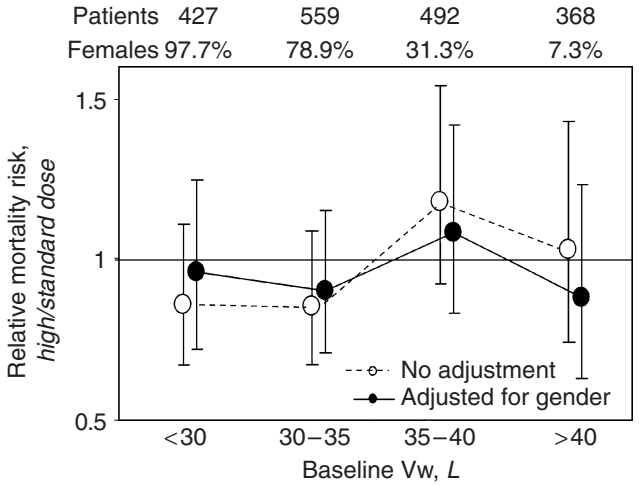

Fig. 3. The relative risk of death in the high dose compared with the standard dose group showed a weak relationship with baseline body water volume (Vw) (○) that disappeared after adjustment for gender (●). The number of women with Vw less than 30 L was 97.7% compared with 7.3% with Vw greater than 40 L.

(Table 5). The predominance of the gender effect independent of size suggests that other gender-specific characteristics influenced the response to the high dose. Analysis of secondary outcomes also suggested that the higher dialysis dose was effective in reducing morbidity in women but not in men (Table 7).

Table 6. Effect of gender on the mortality response to dialysis dose, modulated by size

Size parameter used to control the effect of gender	Effect of gender on response to high dose controlling for size parameter Ratio of RR	*P* value
None	0.71	0.014
Weight *kg*	0.73	0.023
Height *cm*	0.69	0.039
Vw *L*	0.70	0.047
Modeled V *L*	0.74	0.052
Body surface area m^2	0.70	0.019
BMI kg/m^2	0.75	0.037
Black race	0.74	0.032

Shown in the second column are the ratios of relative mortality risk (RR) in the high vs. standard dose groups in women compared with men after adjustment for the interaction of dose group with the specified size parameter. Ratios of RR <1 indicate a greater trend towards a benefit of the high dose in women than in men. All RRs were adjusted for the other six prespecified baseline covariates. *P* values are not adjusted for multiple comparisons.

Interpreting subgroup results in the context of multiple comparisons

For randomized clinical trials, the primary intent-to-treat analysis conducted in all randomized patients is given high priority, while results observed in subgroups of the full study population are interpreted with considerable caution. The data presented here, suggesting a benefit of the high-dose intervention in women, must be interpreted in this context. The *P* value for the hypothesis that the dose effect differed between women and men was 0.014, which is smaller than the 0.05 significance level typically used for testing an a priori hypothesis, but larger than the Bonferroni critical value of 0.0071, which is required to test separate interactions between the dose intervention and seven baseline factors. It is also important to note that the statistical significance of the dose by gender interaction depends in part on the trend for an adverse effect of the high dose in men. The degree to which this evidence supports a true dose by gender interaction depends on its biological plausibility, and the consistency of findings both within the HEMO Study database and in other studies. These issues are examined below.

Possible explanations for an improved outcome in women but not in men

An adverse effect of the high dose in men? In men there was not only a nonsignificant trend for increased mortality in the high-dose group compared with the standard dose group, but the high-dose intervention was associated with increased risk (with $P < 0.05$) for five of the 10 secondary outcomes summarized in Table 7. It is possible that both genders benefited equally from the improved solute removal expected at the high dose, but a separate adverse effect of the high dose in men reduced male survival, canceling the beneficial effect. Of interest, the reverse J-shaped curve of survival reported in

Table 7. Secondary outcomes: dose-gender interactions

	# Events *per* *100 patient years*	All patients			Men			Women			Interaction
		RR	95% CI	*P* value	RR	95% CI	*P* value	RR	95% CI	*P* value	*P* value[a]
All-cause mortality (acM)	871 (16.6)	0.96	(0.84–1.10)	0.53	1.16	0.94–1.43	0.16	0.81	0.67–0.97	0.02	0.014
Main secondary outcomes											
1st cardiac hospitalization or acM	1079 (28.5)	0.99	(0.88–1.12)	0.91	1.03	0.86–1.24	0.73	0.95	0.81–1.11	0.49	0.48
1st infection-related hospitalization or acM	1104 (29.9)	0.97	(0.86–1.09)	0.60	1.16	0.97–1.39	0.09	0.83	0.71–0.98	0.025	0.006
1st albumin event or acM	1011 (24.5)	1.03	(0.91–1.17)	0.66	1.23	1.02–1.49	0.028	0.88	0.75–1.04	0.14	0.009
All nonaccess hospitalizations	6087 (125)	0.95	(0.86–1.05)	0.35	0.98	0.84–1.16	0.84	0.94	0.83–1.06	0.30	0.63
Other secondary outcomes											
Cardiac death	343 (6.6)	1.03	(0.83–1.27)	0.80	1.39	1.01–1.90	0.042	0.81	0.61–1.09	0.16	0.014
1st cardiac hospitalization or cardiac death	835 (22.0)	1.00	(0.87–1.15)	0.99	1.04	0.85–1.28	0.68	0.97	0.81–1.16	0.75	0.60
Infection-related death	201 (3.8)	0.99	(0.75–1.31)	0.94	1.00	0.64–1.55	0.99	0.99	0.69–1.42	0.95	0.97
1st infection hospitalization or infection-related death	802 (21.7)	0.94	(0.82–1.09)	0.42	1.06	0.86–1.31	0.57	0.86	0.71–1.03	0.10	0.13
1st access hospitalization	685 (19.3)	1.05	(0.90–1.22)	0.56	1.37	1.07–1.75	0.013	0.90	0.74–1.09	0.27	0.008
1st access event	1085 (40.5)	1.07	(0.95–1.20)	0.29	1.25	1.03–1.51	0.022	0.98	0.84–1.14	0.77	0.050

[a]Tests interaction between dose (high vs. standard Kt/V) and gender (men vs. women).

observational data that shows higher mortality at high URR or Kt/V was seen only in men [2]. Although a common explanation for the lower survival at high doses seen in these observational studies is that a disproportionate number of clinically deteriorating small malnourished patients receives large doses of dialysis, this theory would not explain the exclusive effect in men. Another possible explanation is that hemodialysis has adverse effects that are accentuated at the higher clearances required to adequately dialyze men in comparison with women [4]. In the HEMO Study, this adverse effect was seen primarily in non-blacks, and as part of a post hoc analysis, so its significance is not certain.

Higher generation rate of uremic toxins in women? High toxin generation rates (G) counteract the beneficial effect of dialyzer clearance. In a steady state of generation and removal, $C = G/K$, where C is the concentration and K is the clearance. Toxin generation is assumed to vary with body size, so it is logical to normalize the effect of dialyzer clearance to an index of size such as V, a large component of which is muscle mass. However, the generation rate of uremic toxins may be more closely linked to another index of body size that does not include muscle mass [abstract; *J Am Soc Nephrol* 12:452A, 2001]. If this were true, then dosing dialysis based on Kt/V might result in a higher toxin concentration in women, which would shift their dose × concentration curve to the right, accounting for the higher sensitivity to dose. It is of interest that in hemodialysis patients mortality is affected by anthropometric V independent of the dialysis dose expressed as Kt/V (i.e., larger patients have a lower mortality than smaller patients treated with the same Kt/V) [2, 4, 5]. The reason for the independent effect of V is not clear but has been presumed, largely without evidence, to be nutritional. In the HEMO Study, women constituted the majority of patients with low Vw (97.7% of patients with Vw <30 L), and were under–represented in patients with high Vw (7.6% of patients with Vw >40 L) (see Fig. 2). So far, efforts to derive a function of body size that would eliminate the gender effect in the HEMO Study have been unsuccessful (Table 5).

Increased sensitivity to uremic toxicity in women? Failure to find a denominator that eliminates or normalizes the effect of gender suggests that women may be intrinsically more sensitive to equivalent toxin levels. This theoretical sensitivity to uremic toxicity contrasts with other life-threatening occurrences such as hemorrhage and infection, resistance to which is apparently enhanced in females, including those with ESRD [17, 18].

Treatment time

The effect of treatment time on morbidity and survival in thrice weekly hemodialyzed patients is controversial. Previous observational studies showing higher mortality rates associated with shorter treatment time most likely were caused by underdialysis [19]. More recent studies, including a report from the Dialysis Outcome Practice Pattern Study (DOPPS), showed no significant effect of treatment time on the risk of mortality when controlled for dose [20, 21], [abstract; *J Am Soc Nephrol* 12:343A, 2001]. Uncontrolled observational studies from Tassin, France, suggest that markedly prolonged treatment times are associated with improved survival [22]. In these studies the beneficial effects of a longer treatment time on control of extracellular fluid volume and/or blood pressure may play an important role. In the design of the HEMO Study, treatment time was closely coupled with the patients' randomized dose target, volume of urea distribution, and achievable blood flow. As a consequence, the HEMO Study did not provide a favorable setting for evaluating the effect of treatment time independently of these other factors, and cannot provide a

clear determination of whether the interaction of gender with dose may have resulted from shorter treatment times for women randomized to the standard dose group.

Other limitations

Because the HEMO Study was designed to test effects of the interventions in all randomized patients, it has limited power to address treatment effects in subgroups. In particular, while the HEMO Study results provide little or no evidence that the effect of dose depends on body size independently of gender, we cannot rule out the possibility of an undetected benefit of the high goal in smaller patients. The statistical power of the study to detect an interaction of dose with body size may also have been reduced by the exclusion of larger patients who were unable to achieve a target eKt/V of 1.45 within 4.5 hours.

Owing to an abundance of urban centers, the HEMO Study included a greater proportion of blacks than in the general United States ESRD population. As noted above in this study and by others [2], there was a trend for the gender-dose interaction to be stronger in non-blacks. Another similar study with more non-blacks might show an even greater gender interaction with dose than is shown here.

Clinical implications

The HEMO Study analysis of dialysis dose interactions suggests that women, independent of body size, constitute a subset of patients whose outcome is improved when treated with higher doses of dialysis. Because the level of significance must be considered borderline, a product of multiple comparisons, these results are suggestive, not proof of a gender effect. This notion is strengthened by analysis of some, but not all, secondary HEMO outcomes and by one previous observational report that was generally consistent with a greater effect of dose in women [2].

CONCLUSION

After the results of the HEMO Study became known, further analyses of national data from the USRDS identified similar interactions between dose and gender consistent with a greater benefit of increased dose in women within the range of doses investigated by the HEMO Study [abstract; *J Am Soc Nephrol* 13:20A, 2002] [8]. Modification of current standards for dialysis adequacy according to gender should be considered.

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