

EFFECT OF DIALYSIS DOSE AND MEMBRANE FLUX IN MAINTENANCE HEMODIALYSIS

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ABSTRACT

Background The effects of the dose of dialysis and the level of flux of the dialyzer membrane on mortality and morbidity among patients undergoing maintenance hemodialysis are uncertain.

Methods We undertook a randomized clinical trial in 1846 patients undergoing thrice-weekly dialysis, using a two-by-two factorial design to assign patients randomly to a standard or high dose of dialysis and to a low-flux or high-flux dialyzer.

Results In the standard-dose group, the mean (\pm SD) urea-reduction ratio was 66.3 ± 2.5 percent, the single-pool Kt/V was 1.32 ± 0.09 , and the equilibrated Kt/V was 1.16 ± 0.08 ; in the high-dose group, the values were 75.2 ± 2.5 percent, 1.71 ± 0.11 , and 1.53 ± 0.09 , respectively. Flux, estimated on the basis of β_2 -microglobulin clearance, was 3 ± 7 ml per minute in the low-flux group and 34 ± 11 ml per minute in the high-flux group. The primary outcome, death from any cause, was not significantly influenced by the dose or flux assignment: the relative risk of death in the high-dose group as compared with the standard-dose group was 0.96 (95 percent confidence interval, 0.84 to 1.10; $P=0.53$), and the relative risk of death in the high-flux group as compared with the low-flux group was 0.92 (95 percent confidence interval, 0.81 to 1.05; $P=0.23$). The main secondary outcomes (first hospitalization for cardiac causes or death from any cause, first hospitalization for infection or death from any cause, first 15 percent decrease in the serum albumin level or death from any cause, and all hospitalizations not related to vascular access) also did not differ significantly between either the dose groups or the flux groups. Possible benefits of the dose or flux interventions were suggested in two of seven prespecified subgroups of patients.

Conclusions Patients undergoing hemodialysis thrice weekly appear to have no major benefit from a higher dialysis dose than that recommended by current U.S. guidelines or from the use of a high-flux membrane. (N Engl J Med 2002;347:2010-9.)

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TWO treatment-related factors implicated in the substantial mortality and morbidity among patients undergoing maintenance hemodialysis¹ are the dose of dialysis delivered and the size of molecules removed. An index of the dialysis dose is the fractional clearance of urea (molecular mass, 60 D) which is commonly expressed as the intradialytic urea-reduction ratio² or as Kt/V, where K represents the rate of urea clearance by the dialyzer in milliliters per minute, t the duration in minutes of the treatment session, and V the volume of distribution of urea in the patient in milliliters.³ Current guidelines in the United States target a urea-reduction ratio of at least 65 percent or a single-pool Kt/V of at least 1.20.⁴ The urea-reduction ratio and single-pool Kt/V overestimate the delivered dose of dialysis, because they fail to account for blood urea rebound after dialysis. A more accurate measure of the dialysis dose, the equilibrated Kt/V, corrects for urea rebound and is usually 0.15 to 0.20 lower than the single-pool Kt/V⁵; by inference, current U.S. guidelines recommend a minimal equilibrated Kt/V of 1.00 to 1.05.

The National Cooperative Dialysis Study was to our knowledge the only randomized trial that evaluated the effect of the dose of dialysis on clinical outcomes.⁶ It established a beneficial effect of an increased dialysis dose on morbidity at dialysis doses well below the current standard and in patients with substantially fewer

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coexisting conditions than are found in the present population of patients undergoing hemodialysis. Some subsequent observational studies have reported continuing improvement in morbidity and mortality at dialysis doses well above those recommended in the current guidelines,⁷⁻⁹ whereas other studies have not found such improvement.¹⁰ Observational studies have also suggested that membranes with high porosity or flux, which clear larger solutes such as beta₂-microglobulin (molecular mass, 11,900 D), are associated with improved outcomes.^{11,12} To our knowledge, no randomized studies of the effects of membrane flux on clinical outcomes have been performed. Our study, the Hemodialysis (HEMO) Study, was a randomized clinical trial designed to determine whether increasing the dose of dialysis or using a high-flux dialyzer membrane alters survival or morbidity among patients undergoing hemodialysis.

METHODS

Study Design

The design of our study has been described previously.^{13,14} The study was approved by the institutional review board at each of 15 clinical centers associated with 72 participating dialysis units, and all patients gave written informed consent.

Eligible patients were randomly assigned in a 1:1 ratio with a two-by-two factorial design to either a standard-dose or a high-dose goal and to dialysis with either a low-flux or a high-flux dialyzer. Randomization was performed centrally with the use of random permuted blocks, with stratification according to clinical center, age, and diabetic status. The dose intervention was defined by the Kt/V. The single-pool Kt/V was determined by two-point urea modeling on the basis of the intradialytic reduction in blood urea and the intradialytic weight loss¹⁵ and was corrected to equilibrated Kt/V on the basis of the rate of dialysis (K/V).^{5,16} The standard-dose goal was an equilibrated Kt/V of 1.05, equivalent to a urea-reduction ratio of approximately 65 percent or a single-pool Kt/V of 1.25, depending on the amount of ultrafiltration. The high-dose goal was an equilibrated Kt/V of 1.45 (a urea-reduction ratio of about 75 percent or a single-pool Kt/V of approximately 1.65). The flux intervention was defined by the porosity of the dialysis membrane: the flux was classified as low if the mean beta₂-microglobulin clearance was less than 10 ml per minute and as high if the ultrafiltration coefficient was more than 14 ml per hour per millimeter of mercury and the mean beta₂-microglobulin clearance was more than 20 ml per minute. The beta₂-microglobulin clearance was determined on the basis of the intradialytic changes in the beta₂-microglobulin concentration and weight, under the assumption of a single-compartment model.¹⁷

A total of 8 types of low-flux dialyzers and 17 types of high-flux dialyzers were approved for use in the study. The most common dialyzers with low flux were the Fresenius F8 (used in 46 percent of sessions) and the Baxter CA210 (used in 43 percent); the most common dialyzers with high flux were the Fresenius F80 (used in 43 percent of sessions) and the Baxter CT190 (used in 48 percent). Use of dialyzers with unsubstituted cellulose membranes was not permitted. Reuse of dialyzers was permitted; however, the number of uses allowed was limited by the clearance profile of the dialyzer.¹⁸ The most frequent reprocessing methods involved the use of Renalin (Mintech) without bleach (in 40 percent of sessions), formaldehyde or glutaraldehyde (Diacide, Gulfstream) with bleach (in 32 percent of sessions), or heated citric acid (in 10 percent of sessions). Established standards of general medical care were monitored by a quality-of-care committee.¹⁹

Study Patients

Patients 18 to 80 years of age who were undergoing in-center hemodialysis thrice weekly and had been undergoing hemodialysis for three or more months were enrolled between March 1995 and October 2000. The patients' base-line dialysis prescriptions were maintained for three weeks after enrollment while base-line characteristics were ascertained. Subsequently, dialysis prescriptions were adjusted to evaluate the ability to achieve the high-dose goal in each patient. Patients were excluded from randomization if their residual urea clearance exceeded 1.5 ml per minute per 35 liters of urea, if their serum albumin level was less than 2.6 g per deciliter, or if an equilibrated Kt/V of more than 1.30 was not achieved within 4.5 hours during two of three consecutive monitored dialysis sessions in which the high-dose goal was targeted. On the basis of the last criterion, very heavy patients were excluded; 97 percent of the patients who underwent randomization weighed less than 100 kg.

Interventions and Follow-up

Centrally determined dialysis prescriptions were transmitted to investigators at the time of randomization and updated monthly throughout follow-up. The target equilibrated Kt/V was achieved by manipulating the duration of the treatment session and the dialyzer clearance commensurate with ultrafiltration requirements. Dialysis was provided in as short a time as possible but not less than 2.5 hours. Adherence was monitored by monthly modeling of urea kinetics.

Beta₂-microglobulin clearance was measured every two months in patients assigned to high-flux dialyzers and every six months in those assigned to low-flux dialyzers. Serum obtained monthly before dialysis was assayed for albumin by nephelometry. Blood urea nitrogen, serum beta₂-microglobulin, and albumin levels were centrally determined (Spectra East, Rockleigh, N.J.). Standardized assessments of coexisting conditions (with the use of the Index of Coexisting Disease)²⁰ were performed at base line and annually thereafter.¹⁹

Kinetic modeling, with multiple measurements of blood urea and beta₂-microglobulin during and after dialysis, was performed at months 4 and 36 for validation of kinetic models. On the basis of these modeling sessions, a modified rate equation (Table 1) involving a smaller adjustment for urea rebound after dialysis and yielding a higher equilibrated Kt/V value was developed for reporting the study results. The original rate equation was retained in the definition of dose groups in the study design.

Outcomes

The primary outcome was death from any cause. The main secondary outcomes were the rate of all hospitalizations not related to vascular access and three composite end points: the first hospitalization for cardiac causes or death from any cause, the first hospitalization for infection or death from any cause, and the first decline of more than 15 percent from base line in the serum albumin level or death from any cause. Four additional secondary outcomes were defined for the specific evaluation of cardiac or infectious events: death from cardiac causes, death from infectious causes, the composite of the first hospitalization for cardiac causes or death from cardiac causes, and the composite of the first hospitalization for infectious causes or death from infectious causes. Classifications of hospitalizations for cardiac or infectious causes and causes of death were determined locally and reviewed by an outcomes committee that was unaware of the treatment-group assignments.²¹

Statistical Analysis

The primary analysis was a Cox regression analysis²² of survival from the time of randomization. The effects of the dose and flux interventions were determined with stratification according to clinical center and were adjusted for the following prespecified base-line factors: age, sex, race, years of dialysis, presence or absence of di-

TABLE 1. BASE-LINE CHARACTERISTICS.*

FACTOR	ALL PATIENTS (N=1846)	STANDARD-DOSE GROUP (N=926)	HIGH-DOSE GROUP (N=920)	LOW-FLUX GROUP (N=925)	HIGH-FLUX GROUP (N=921)
Age (yr)	57.6±14.0	57.8±13.9	57.4±14.1	57.6±14.2	57.7±13.9
Female sex (%)	56.2	56.3	56.2	55.8	56.7
Black race (%)	62.6	64.1	61.1	62.6	62.6
Diabetes (%)	44.6	44.7	44.5	44.4	44.7
ICED score	2.0±0.8	2.0±0.8	2.0±0.8	2.0±0.8	2.0±0.8
Cardiac disease (%)	80.1	81.5	78.7	80.5	79.7
Yr of dialysis	3.7±4.4	3.9±4.5	3.6±4.3	3.7±4.2	3.8±4.5
Residual urea clearance >0 (%)	32.9	31.9	33.9	31.2	34.5
Weight after dialysis (kg)	69.2±14.7	69.6±14.8	68.7±14.6	69.0±14.7	69.3±14.7
Body water volume after dialysis (liters)†	34.9±6.1	35.1±6.2	34.8±6.0	34.9±6.1	34.9±6.0
Measurements before dialysis					
Blood pressure (mm Hg)					
Systolic	151.8±22.1	151.7±22.0	151.9±22.3	151.7±22.7	151.9±21.6
Diastolic	81.4±13.0	81.4±12.8	81.5±13.1	81.5±13.3	81.4±12.6
Serum creatinine (mg/dl)	10.3±2.9	10.3±2.8	10.3±3.0	10.3±2.9	10.2±2.9
Serum total cholesterol (mg/dl)	172.7±40.7	170.9±40.4	174.4±41.0	172.7±40.4	172.6±41.0
Serum albumin (g/dl)	3.6±0.4	3.6±0.4	3.6±0.4	3.6±0.4	3.6±0.4
Equilibrated normalized protein catabolic rate (g/kg/day)	1.03±0.24	1.04±0.24	1.03±0.24	1.03±0.24	1.03±0.24
Equilibrated Kt/V‡	1.43±0.21	1.43±0.21	1.43±0.21	1.43±0.21	1.44±0.21
High-flux membrane (%)	60.2	59.5	60.9	59.0	61.3

*Plus–minus values are means ±SD. There were no significant differences (at $P<0.05$) between the dose groups or the flux groups in any of the summarized characteristics. Index of Coexisting Disease (ICED) severity scores were computed with diabetes excluded; scores range from 0 to 3, with higher scores indicating a greater number and greater severity of coexisting diseases.²⁰ To convert values for creatinine to micromoles per liter, multiply by 88.4; to convert values for total cholesterol to micromoles per liter, multiply by 0.02586.

†Total body water volume was estimated on the basis of anthropometric measurements and demographic data.

‡The equilibrated Kt/V (where K represents the rate of urea clearance by the dialyzer in milliliters per minute, t the duration in minutes of the treatment session, and V the volume of distribution of urea in the patient in milliliters) was computed with the use of the following modified rate equation: equilibrated Kt/V = single-pool Kt/V – $0.4 \times 60 \times (K/V) + 0.01$, for patients in the high-dose group), where K/V is expressed in inverse minutes. Values for equilibrated Kt/V calculated with the original rate equation^{5,16} are 0.05 to 0.07 lower.

abetes, score for coexisting conditions excluding diabetes, albumin level, and the interaction of albumin level with time from randomization. For patients who received a kidney transplant, data were censored at the time of transplantation. However, in keeping with the intention-to-treat principle, data were not censored when patients were transferred to a nonparticipating center or switched to an alternative method of dialysis. Kaplan–Meier survival curves were constructed.²³ All reported P values are two-sided, without adjustment for multiple comparisons.

Interactions of the dose and flux interventions with the prespecified base-line factors were tested individually to determine whether the interventions had different effects on mortality in subgroups defined according to these factors. Subgroups defined according to continuous variables (age, albumin level, and years of dialysis) were defined by their mean values.

Secondary composite outcomes were analyzed by Cox regressions similar to that used in the primary analysis, but with data on patients who were transferred to nonparticipating centers censored because hospitalizations and decreases in albumin levels could not be monitored. The rate of hospitalizations not related to vascular access was analyzed by overdispersed Poisson regression.²⁴

We planned for randomization of 900 patients during an initial accrual period of 1.5 years, with 4 years of additional follow-up during which patients who died, received a kidney transplant, or were

transferred to a nonparticipating dialysis unit would be replaced by newly randomized patients until the final year of the trial. Thus, the planned follow-up ranged from 1 to 6.5 years, depending on the time of randomization. Under conservative assumptions, including a 20 percent reduction in mortality as compared with that in the general population of patients undergoing hemodialysis, a six-month treatment lag time, and no carryover effects of the interventions after transfer to an alternative method of dialysis or to another dialysis unit, the study had 84 percent power to detect a 25 percent reduction in mortality for each intervention.

An external advisory committee monitored the study with the use of six annual interim analyses conducted with O'Brien–Fleming stopping boundaries.²⁵ The nominal significance level for the final primary analysis of mortality was 0.042, in order to maintain an overall type I error rate of 5 percent for both interventions. The study was designed and conducted by a steering committee made up of academic investigators, who also held and analyzed the data.

RESULTS

Base-Line Characteristics of the Patients

A total of 2677 patients were screened, of whom 1846 underwent randomization. Randomized patients

had high rates of coexisting conditions: 96 percent had hypertension, 45 percent had either type 1 or type 2 diabetes, and 80 percent had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups (Table 1).

Characteristics of and Adherence to Treatment

Mean values for treatment variables (reported for 97 percent of monitored dialysis sessions) characterizing the treatment groups were attained by the first monthly measurement after randomization and remained stable throughout follow-up. The mean (\pm SD) equilibrated Kt/V during follow-up was 1.16 ± 0.08 in the standard-dose group and 1.53 ± 0.09 in the high-dose group (Table 2); the difference between the two was 0.37, or 92.5 percent of the targeted 0.40. The mean equilibrated Kt/V during follow-up was less than 1.25 for 93 percent of the patients in the standard-dose group and more than 1.35 for 92 percent of the patients in the high-dose group, indicating that there was little overlap between groups. The mean urea-reduction ratio was 66.3 ± 2.5 percent in the standard-dose group and 75.2 ± 2.5 percent in the high-dose group, and the mean single-pool Kt/V was 1.32 ± 0.09 in the standard-dose group and 1.71 ± 0.11 in the high-dose group.

The mean beta₂-microglobulin clearance during follow-up was 30.4 ml per minute higher in the high-flux group (33.8 ± 11.4 ml per minute) than in the low-flux group (3.4 ± 7.2 ml per minute). The mean beta₂-microglobulin clearance was less than 5 ml per minute

for each low-flux dialyzer, regardless of reprocessing method, and exceeded 30 ml per minute for each combination of dialyzer and reprocessing method used in the high-flux group, except for the CT190 reused with the Renalin method (25 ml per minute).

Death from Any Cause

For the 1846 randomized patients, the mean interval between randomization and the scheduled end of the study on December 31, 2001, was 4.48 years. However, attrition due to death and transplantation resulted in a mean follow-up time of 2.84 years, with 5237 total patient-years of follow-up. During follow-up, 392 patients left their dialysis center for reasons other than death, including 194 who received a transplant (95 in the standard-dose group and 99 in the high-dose group; 93 in the low-flux group and 101 in the high-flux group) and 198 others who switched methods of dialysis or transferred to nonparticipating facilities. Nonetheless, vital status was determined for all randomized patients. There were 871 deaths or 0.166 death per patient-year (Table 3 and Fig. 1). Cardiac diseases were the leading cause of death (343 of 871 [39 percent]).

All prespecified covariates were significant independent predictors of death (Table 4). The strongest predictors were age (a 41 percent increase in risk per 10-year increment), base-line serum albumin level (a 49 percent decrease in risk per increment of 0.5 g per deciliter), coexisting conditions (a 37 percent increase in risk per 1-unit increment in the score on the Index of Coexisting Disease), race (the risk of death was 23

TABLE 2. MEAN CHARACTERISTICS OF TREATMENT DURING FOLLOW-UP.*

TREATMENT VARIABLE	STANDARD-DOSE GROUP (N=926)	HIGH-DOSE GROUP (N=920)	LOW-FLUX GROUP (N=925)	HIGH-FLUX GROUP (N=921)
Duration of dialysis session (min)	190 \pm 23	219 \pm 23	206 \pm 28	203 \pm 27
Rate of blood flow (ml/min)	311 \pm 51	375 \pm 32	344 \pm 53	341 \pm 54
Rate of urea clearance (ml/min)	218 \pm 25	251 \pm 18	233 \pm 27	236 \pm 28
Total urea clearance/dialysis session (liters)	41.4 \pm 7.0	55.1 \pm 7.6	48.2 \pm 10.1	48.2 \pm 9.9
Single-pool Kt/V	1.32 \pm 0.09	1.71 \pm 0.11	1.51 \pm 0.22	1.52 \pm 0.22
Equilibrated Kt/V†	1.16 \pm 0.08	1.53 \pm 0.09	1.34 \pm 0.21	1.34 \pm 0.21
Urea-reduction ratio (%)	66.3 \pm 2.5	75.2 \pm 2.5	70.6 \pm 5.1	70.9 \pm 5.1
Blood urea nitrogen before dialysis (mg/dl)	62.1 \pm 13.6	54.3 \pm 11.8	58.6 \pm 13.5	57.9 \pm 13.1
Rate of beta ₂ -microglobulin clearance (ml/min)	18.9 \pm 19.0	18.3 \pm 16.8	3.4 \pm 7.2	33.8 \pm 11.4
Total beta ₂ -microglobulin clearance/dialysis session (liters)	3.5 \pm 3.6	4.0 \pm 3.6	0.7 \pm 1.5	6.8 \pm 2.3

*Treatment values were first averaged over time for each patient with more than four months of follow-up; plus-minus values are means \pm SD of these average values. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357.

†The equilibrated Kt/V was computed with the use of the following modified rate equation: equilibrated Kt/V = single-pool Kt/V - 0.4 \times 60 \times (K/V) (+0.01, for patients in the high-dose group), where K/V is expressed in inverse minutes. Values for equilibrated Kt/V calculated with the original rate equation^{5,16} are 0.05 to 0.07 lower.

percent lower for blacks), and years of dialysis (a 4 percent increase in risk per additional year of dialysis).

Neither the differences between the two dose groups nor the differences between the two flux groups were significant, and the 95 percent confidence intervals for both interventions included zero benefit. After adjustment for base-line factors, the high-dose group had a risk of death that was 4 percentage points lower (95 percent confidence interval, -10 to 16; P=0.53) than that in the standard-dose group, and the high-flux group had a risk of death that was 8 percentage points lower (95 percent confidence interval, -5 to 19; P=0.23) than that in the low-flux group. The effects of the dose and flux interventions were similar at both levels of the other variable (P for interaction=0.30). Results were similar when the data were analyzed without adjustment for the predefined covariates.

Secondary Outcomes

Results for the main secondary outcomes are shown in Figure 2. Risk reductions for the high-dose group were 1 percentage point (95 percent confidence interval, -12 to 12; P=0.91) for the composite cardiac outcome, 3 percentage points (95 percent confidence

interval, -9 to 14; P=0.60) for the composite infection-related outcome, and 4 percentage points (95 percent confidence interval, -6 to 13; P=0.38) for hospitalizations not related to vascular access. Effects of the high-flux as compared with the low-flux intervention ranged from an increase in risk of 1 percentage point (95 percent confidence interval, -9 to 11; P=0.87) for hospitalizations not related to vascular access to a decrease of 10 percentage points (95 percent confidence interval, -1 to 20; P=0.08) for the composite cardiac outcome, indicating that neither the dose intervention nor the flux intervention had statistically significant effects on any of the main secondary outcomes. Significant risk reductions (unadjusted P<0.05) in the risk of death from cardiac causes and in the combined outcome of first hospitalization for cardiac causes or death from cardiac causes were observed for the high-flux intervention.

Interactions of Treatment Interventions with Base-Line Characteristics

Among the seven prespecified base-line factors in the primary analysis, possible interactions were identified (unadjusted P<0.05) between the dose intervention and sex (P=0.01) and between the flux in-

TABLE 3. PRIMARY AND SECONDARY OUTCOMES.

OUTCOME	ALL PATIENTS (N=1846)	STANDARD-DOSE	HIGH-DOSE	LOW-FLUX	HIGH-FLUX
		GROUP (N=926)	GROUP (N=920)	GROUP (N=925)	GROUP (N=921)
no. of events (no./patient-yr of follow-up)					
Primary outcome					
Death from any cause	871 (0.166)	440 (0.171)	431 (0.162)	442 (0.171)	429 (0.162)
Main secondary outcomes					
First hospitalization for cardiac causes or death from any cause*	1079 (0.285)	545 (0.290)	534 (0.279)	550 (0.295)	529 (0.275)
First hospitalization due to infection or death from any cause†	1104 (0.299)	557 (0.307)	547 (0.292)	562 (0.312)	542 (0.287)
First >15% decrease in albumin level or death from any cause‡	1011 (0.245)	502 (0.244)	509 (0.245)	521 (0.251)	490 (0.238)
All hospitalizations not related to vascular access	6155 (1.27)	3107 (1.30)	3048 (1.24)	3018 (1.25)	3137 (1.28)
Additional secondary outcomes					
Death due to cardiac causes§	343 (0.066)	169 (0.066)	174 (0.065)	187 (0.072)	156 (0.059)
First hospitalization for cardiac causes or death due to cardiac causes¶	835 (0.220)	417 (0.222)	418 (0.219)	435 (0.233)	400 (0.208)
Death due to infection	201 (0.038)	99 (0.038)	102 (0.038)	104 (0.040)	97 (0.037)
First hospitalization due to infection or death due to infection	802 (0.217)	410 (0.226)	392 (0.209)	407 (0.226)	395 (0.209)

*Data include 735 hospitalizations for cardiac causes and 344 deaths.

†Data include 783 hospitalizations due to infection and 321 deaths.

‡Data includes 494 decreases of more than 15 percent in the albumin level and 517 deaths.

§Data for deaths and hospitalizations from cardiac causes include those due to angina, myocardial infarction, congestive heart failure, or arrhythmias.

¶Data include 735 hospitalizations for cardiac causes and 100 deaths from cardiac causes.

||Data include 783 hospitalizations due to infection and 19 deaths due to infection.

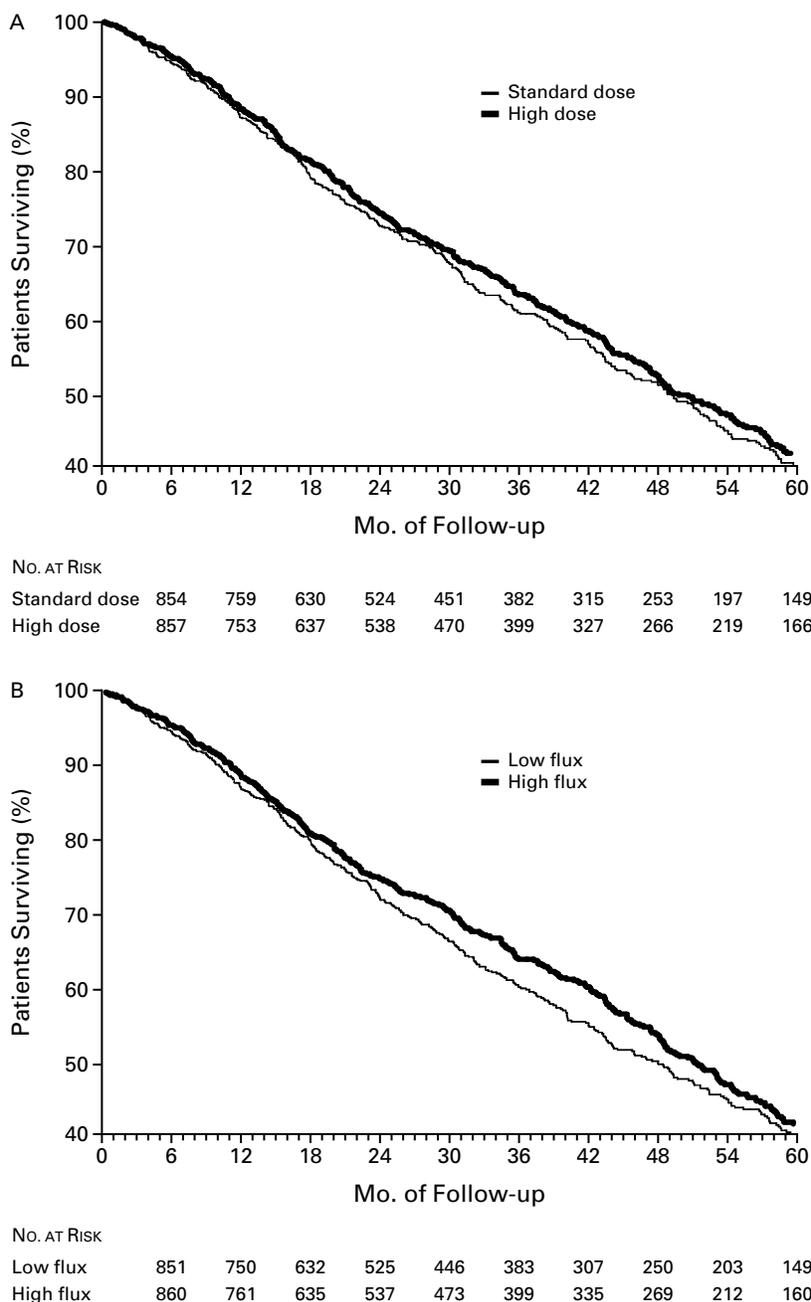


Figure 1. Survival Curves for the Treatment Groups. After adjustment for the base-line factors, mortality in the high-dose group was 4 percent lower (95 percent confidence interval, -10 to 16; P=0.53) than that in the standard-dose group (Panel A), and mortality in the high-flux group was 8 percent lower (95 percent confidence interval, -5 to 19; P=0.23) than that in the low-flux group (Panel B).

tervention and years of dialysis (≤ 3.7 years vs. > 3.7 years, $P=0.005$). In the high-dose group, the risk of death among women was 19 percentage points lower than that in the standard-dose group, but the risk of death among men was 16 percentage points higher

than that in the standard-dose group. The risk of death was 32 percentage points lower in the high-flux group than in the low-flux group among patients with more than 3.7 years of dialysis before randomization but was similar in the two flux groups among patients with

TABLE 4. PRIMARY COX REGRESSION ANALYSIS OF MORTALITY.*

PREDICTOR VARIABLE	COX REGRESSION COEFFICIENT	RELATIVE RISK OF DEATH (95% CI)	P VALUE
High dose	-0.04±0.07	0.96 (0.84–1.10)	0.53
High-flux membrane	-0.08±0.07	0.92 (0.81–1.05)	0.23
Age (per 10-yr increment)	0.34±0.03	1.41 (1.33–1.50)	<0.001
Female sex	-0.16±0.07	0.85 (0.73–0.98)	0.02
Black race	-0.26±0.08	0.77 (0.66–0.91)	0.002
Diabetes	0.25±0.08	1.29 (1.11–1.50)	0.001
Duration of dialysis (per 1-yr increment)	0.04±0.01	1.04 (1.02–1.06)	<0.001
Base-line ICED score (per 1-unit increment)	0.31±0.05	1.37 (1.25–1.50)	<0.001
Base-line serum albumin (per increment of 0.5 g/dl)	-0.67±0.09	0.51 (0.43–0.62)	<0.001
Interaction between base-line serum albumin and time from randomization†	0.10±0.03	1.11 (1.04–1.19)	0.003

*The analysis was stratified according to clinical center. The Index of Coexisting Disease (ICED) score was computed excluding diabetes; scores range from 0 to 3, with higher scores indicating a greater number and greater severity of coexisting disease. CI denotes confidence interval. Plus-minus values are means ±SE.

†The relative risk of 1.11 for the interaction between the base-line albumin level and the time from randomization indicates that there was a progressive weakening of the effect of the base-line albumin level over time, with its relative risk attenuating toward 1.0 by 11 percent per year of follow-up.

fewer years of prior dialysis. The interaction between the flux group and years of dialysis, but not that between the dose group and sex, remained significant at the level of 0.0071 determined with the Bonferroni method for seven tests of interaction. However, the strength of the interaction between the flux group and years of dialysis was reduced if the number of years of dialysis was treated as a continuous variable ($P=0.04$).

DISCUSSION

Among patients undergoing maintenance hemodialysis who were receiving thrice-weekly treatments lasting 2.5 to 4.5 hours each, neither a higher dose of dialysis nor the use of high-flux membranes significantly improved survival or reduced morbidity. This lack of effect was found despite a clear separation in fractional urea and beta₂-microglobulin clearances between the treatment groups. Study participants had a substantial prevalence of coexisting conditions similar to that in the overall population of patients in the United States undergoing hemodialysis. The study included a higher percentage of blacks (63 percent) than this overall population does, because of the predominance of urban centers, but patients with diabetes, elderly patients, and patients with cardiac disease were well represented. After the age-related entry criteria and race had been accounted for, mortality in our study was similar to that in the general population of patients in the United States undergoing hemodialysis.²⁶ These findings support the continued use of the current U.S. practice guidelines, which recommend a single-pool Kt/V of at least 1.2⁴ but make no recommendation for or against the routine use of high-flux membranes.

The mean achieved equilibrated Kt/V, single-pool Kt/V, and urea-reduction ratio in our standard-dose group were 1.16, 1.32, and 66.3 percent, respectively. Several observational studies, but to our knowledge no other randomized trials, have examined the relation between mortality and dialysis doses above these levels. Some,^{9,27} but not all,⁷ of these studies have reported reductions in mortality of approximately 20 percentage points with an increase in dose similar to that used in our study. The overall reduction in mortality in our high-dose group was 4.3 percentage points, with a 95 percent confidence interval of -10 percentage points to 16 percentage points. The upper confidence limits for risk reductions in secondary composite outcomes were lower, ranging from 9 percentage points for the composite albumin end point to 14 percentage points for the composite infection end point. Because randomization prevents many biases that can occur in observational studies,^{28,29} our study appears to rule out an average beneficial effect of a higher dose on survival similar to the larger estimates reported in some observational studies.

The high-flux group in our study had a risk of death from any cause that was 8 percentage points lower than that in the low-flux group, with an upper confidence limit of 19 percentage points. This finding contrasts with those of observational studies^{12,30} that have reported greater reductions in mortality of 20 to 24 percentage points associated with high-flux dialysis. Although, in our study, total mortality was not significantly reduced in the high-flux group, possible reductions in the rate of death and hospitalizations from cardiac causes were suggested (Fig. 2 and Table 3).

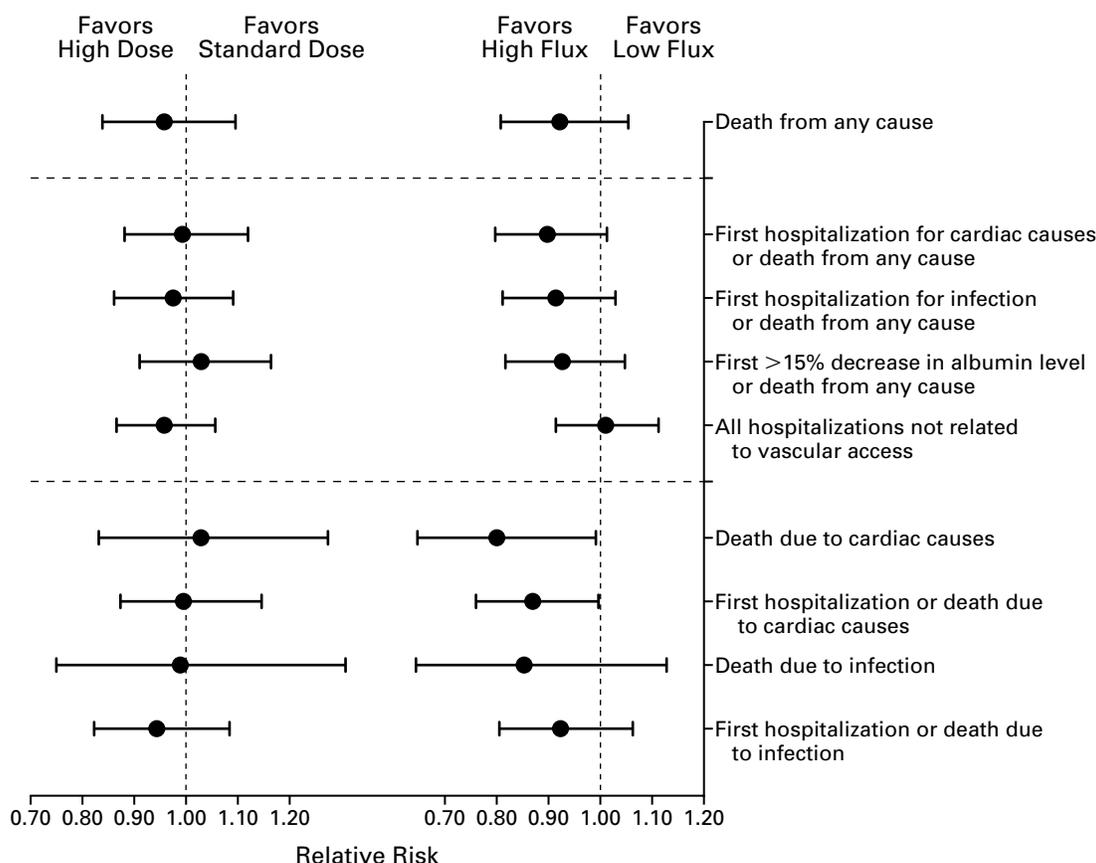


Figure 2. Effects of the Treatment Interventions on Primary and Secondary Outcomes.

Values are shown as relative risks and 95 percent confidence intervals associated with assignment to the high-dose group as compared with assignment to the standard-dose group and assignment to the high-flux group as compared with assignment to the low-flux group. Analyses were stratified according to clinical center and adjusted for base-line age, sex, race, duration of dialysis, presence or absence of diabetes, score for coexisting conditions excluding diabetes, serum albumin level, and the interaction of albumin level with time from randomization. Percentage risk reductions for the high-dose and high-flux groups given in the text are obtained by subtraction of the relative risk from 1 followed by multiplication by 100.

The primary intention-to-treat analysis pertains to the overall effect for all patients and does not rule out the possibility of different effects in specific subgroups. Several observational studies have proposed that an increased dose of dialysis may be of particular benefit in whites as compared with blacks,³¹ in white women as compared with black men,³² in smaller patients,³² and possibly in patients with diabetes as compared with nondiabetics.³³ Subgroup analysis in our study suggests that the high dose had a greater benefit in women but not in whites or patients with diabetes. Because of the strong association between sex and body size, the issue of possible dependence of the dose effect on size is complex and is not considered here. Our results also suggest a benefit of high-flux membranes for patients who had been undergoing dialysis for more than 3.7 years. Sex and years of dialysis were

among seven factors that were prespecified for investigation of subgroup effects. However, the risk of false positive results from multiple subgroup analyses must be considered, and the results of such analyses should be interpreted cautiously.

The difference between the doses achieved in the high-dose and standard-dose groups most likely represents the maximal practical difference under conditions of thrice-weekly dialysis, as currently practiced in the United States. The higher small-solute clearances that are achievable with much longer or more frequent treatments might result in a clinical benefit that was not attained by the high dose we used.^{34,35} By the same token, the higher beta₂-microglobulin clearances achievable with hemodiafiltration^{11,36} or sorbent techniques³⁷ might also improve outcomes.

In summary, although the effect of the dose and lev-

el of membrane flux may vary among selected subgroups of patients, the primary results of our study indicate that, with a schedule of thrice-weekly dialysis, neither an increased dose of dialysis nor use of a high-flux membrane substantially improves survival, reduces the rate of hospitalization, or maintains serum albumin levels as compared with a standard dose and use of low-flux membranes.

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APPENDIX

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