Effects of High-Flux Hemodialysis on Clinical Outcomes: Results of the HEMO Study

ALFRED K. CHEUNG,* NATHAN W. LEVIN,† TOM GREENE,‡ LAWRENCE AGODOA,§ JAMES BAILEY,‖ GERALD BECK,‡ WILLIAM CLARK,¶ ANDREW S. LEVEY,# JOHN K. LEYPOLDT,* DANIEL B. ORNT,** MICHAEL V. ROCCO,†† GERALD SCHULMAN,‡‡ STEVE SCHWAB,§§ BRENDAN TEEHAN,‖‖ and GARABED EKNOYAN,,¶¶ FOR THE HEMO STUDY GROUP

**Veterans Affairs Salt Lake City Healthcare System and Department of Medicine, University of Utah, Salt Lake City, Utah; †Renal Research Institute, New York, New York; ‡Department of Epidemiology and Biostatistics, Cleveland Clinic Foundation, Cleveland, Ohio; §National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; ‖Department of Medicine, Emory University, Atlanta, Georgia; ¶Baxter Corporation, McGaw Park, Illinois; #Department of Medicine, Tufts-New England Medical Center, Boston, Massachusetts; **Department of Medicine, University of Rochester, Rochester, New York; ††Department of Medicine, Wake Forest University, Winston-Salem, North Carolina; ‡‡Department of Medicine, Vanderbilt University, Nashville, Tennessee; §§Department of Medicine, Duke University, Durham, North Carolina; ‖‖Department of Medicine, Lankenau Hospital, Philadelphia, Pennsylvania; and ¶¶Department of Medicine, Baylor College of Medicine, Houston, Texas.*

Abstract. Among the 1846 patients in the HEMO Study, chronic high-flux dialysis did not significantly affect the primary outcome of the all-cause mortality (ACM) rate or the main secondary composite outcomes, including the rates of first cardiac hospitalization or ACM, first infectious hospitalization or ACM, first 15% decrease in serum albumin levels or ACM, or all non-vascular access-related hospitalizations. The high-flux intervention, however, seemed to be associated with reduced risks of specific cardiac-related events. The relative risks (RR) for the high-flux arm, compared with the low-flux arm, were 0.80 [95% confidence interval (CI), 0.65 to 0.99] for cardiac death and 0.87 (95% CI, 0.76 to 1.00) for the composite of first cardiac hospitalization or cardiac death. Also, the effect of high-flux dialysis on ACM seemed to vary, depending on the duration of prior dialysis. This report presents secondary analyses to further explore the relationship between the flux intervention and the duration of dialysis with respect to various outcomes. The patients were stratified into a short-duration group and a long-duration group, on the basis of the mean duration of dialysis of 3.7 yr before randomization. In the subgroup that had been on dialysis for >3.7 yr, randomization to high-flux dialysis was associated with lower risks of ACM (RR, 0.68; 95% CI, 0.53 to 0.86; $P = 0.001$), the composite of first albumin level decrease or ACM (RR, 0.74; 95% CI, 0.60 to 0.91; $P = 0.005$), and cardiac deaths (RR, 0.63; 95% CI, 0.43 to 0.92; $P = 0.016$), compared with low-flux dialysis. No significant differences were observed in outcomes related to infection for either duration subgroup, however, and the trends for beneficial effects of high-flux dialysis on ACM rates were considerably weakened when the years of dialysis during the follow-up phase were combined with the prestudy years of dialysis in the analysis. For the subgroup of patients with <3.7 yr of dialysis before the study, assignment to high-flux dialysis had no significant effect on any of the examined clinical outcomes. These data suggest that high-flux dialysis might have a beneficial effect on cardiac outcomes. Because these results are derived from multiple statistical comparisons, however, they must be interpreted with caution. The subgroup results that demonstrate that patients with different durations of dialysis are affected differently by high-flux dialysis are interesting and require further study for confirmation.

The annual mortality rate among patients undergoing maintenance hemodialysis is approximately 18%, with cardiovascular events being the most common cause of death. Morbidity is also substantial, with an average of 1.94 hospitalizations and approximately 14 d of hospitalization each year (1). The HEMO Study was a randomized, prospective, clinical trial designed to examine the effects on clinical outcomes of two treatment parameters, *i.e.*, hemodialysis dose based on the clearance of urea (molecular mass, 60 D) and membrane porosity or flux, which serves as an index of the clearance of middle molecules (2).

Compared with low-flux dialysis, high-flux dialysis more efficiently removes middle molecules ranging in size from 1000 to >15,000 D (3,4). These molecules include β_2-micro-

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Correspondence to Dr. Alfred K. Cheung, Dialysis Program, 85 North Medical Drive East, University of Utah, Salt Lake City, UT 84112. Phone: 801-581-6427; Fax: 801-581-4750; E-mail: alfred.cheung@hsc.utah.edu

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globulin (β_2M) (11,800 D), which was the marker used for the flux evaluations in the HEMO Study. Substances with lower molecular masses might behave kinetically as middle molecules because of properties such as steric configuration, electric charge, hydrophobicity, or binding to plasma proteins. Limited controlled clinical studies demonstrated that synthetic high-flux dialyzers were associated with improvements in neutrophil functions (5) and plasma lipolytic activities (6), compared with low-flux cellulosic membranes. In addition, in observational studies, high-flux dialyzers were associated with lower rates of amyloidosis (7,8) and death (8–11), compared with low-flux dialyzers. Potential disadvantages of high-flux dialyzers include loss of albumin into the dialysate when bleach is used for reprocessing (12,13) and back-transfer of dialysate contaminants into the blood (14), although some high-flux membranes also adsorb and thus inhibit the back-transfer of endotoxins (15). Many previous studies, however, exclusively compared a synthetic high-flux membrane with an unsubstituted cellulosic low-flux membrane, thus confounding the effects of middle-molecule clearance with those of membrane biocompatibility. Furthermore, there have been no randomized trials examining the effects of membrane flux on long-term clinical outcomes.

The primary analysis of the HEMO Study demonstrated that randomization to high-flux dialysis thrice-weekly (2.5 to 5.0 h/session) did not significantly alter the primary outcome of all-cause mortality (ACM) and the four main secondary outcomes (the composite of first cardiac hospitalization or ACM, the composite of first infectious hospitalization or ACM, the first decrease in serum albumin levels of ≥15% or ACM, and non-vascular access-related hospitalizations) (2). There was, however, a statistically significant 20% decrease in cardiac deaths associated with high-flux dialysis. In addition, the data suggested that high-flux dialysis had a larger effect among patients who had been undergoing long-term dialysis before entry into the HEMO Study, compared with those who had undergone shorter-term dialysis. This report describes the effect of high-flux dialysis on additional secondary outcomes in the cohort. Furthermore, the interaction between flux and the number of years on dialysis was critically examined.

Materials and Methods

HEMO Study Design

The HEMO Study was a prospective, randomized, multicenter, clinical trial with a 2 × 2 factorial design and equal allocation to each treatment arm (2). Among the eligibility criteria was a residual kidney urea clearance of <1.5 ml/min per 35 L of urea distribution volume. A total of 1846 patients were randomized to either a standard dose of dialysis, targeting an equilibrated dose (eKt/V of urea) of 1.05, or a high dose, targeting an eKt/V of 1.45, and to either low-flux or high-flux membrane dialyzers. Randomization was performed with random permuted blocks and was stratified according to clinical center, diabetic status, and age (2). Patients were not blinded to their assigned interventions.

The average duration of dialysis was 3.7 yr and 60.2% of the patients were treated with high-flux dialyzers before entry into the study. A total of 925 patients were randomized to low-flux dialyzers, whereas 921 patients were randomized to high-flux dialyzers.

Dialyzers

All dialyzers used during the follow-up phase of the HEMO Study were categorized as follows. Low-flux dialyzers were defined as those with mean β_2M clearances of <10 ml/min (see calculation below). High-flux dialyzers were defined as those with β_2M clearances of >20 ml/min, averaged over the lifespan of the dialyzer, and an *in vitro* or *in vivo* ultrafiltration coefficient of ≥14 ml/h per 1 mmHg. Dialyzers with β_2M clearances between 10 and 20 ml/min were excluded from the study. In addition, all dialyzers were required to have *in vitro* urea mass transfer-area coefficients of >500 ml/min, at a dialysate flow rate of 500 ml/min. A variety of dialyzers and reprocessing techniques were used in the participating dialysis units, resulting in highly variable β_2M clearances in the high-flux arm. The β_2M clearances associated with the majority of the dialyzers and specific reprocessing techniques were described in detail in an earlier publication from the HEMO Study (3).

Two dialyzers connected in series were used in 2.5% of all follow-up sessions among patients randomized to the high-dose arm. To maintain β_2M clearances of comparable magnitudes among patients using two dialyzers in series and those using single dialyzers, two low-flux dialyzers were used for patients randomized to the low-flux arm and a combination of a high-flux dialyzer and a low-flux dialyzer was used for patients randomized to the high-flux arm. The allowable double-dialyzer combinations were limited to two F8 (Fresenius Medical Care-North America, Lexington, MA) or two CA210 (Baxter Healthcare Corp., McGaw Park, IL) dialyzers in the low-flux arm and an F8 dialyzer followed in series by an F80 dialyzer (Fresenius) or a CA210 dialyzer followed in series by a CT190 dialyzer (Baxter) in the high-flux arm. A single combined value for β_2M clearance was determined for each of the double-dialyzer combinations.

Sample Collection and Assays

Data for calculating β_2M clearances and urea kinetics were obtained during monthly modeling sessions. Blood samples were collected from the vascular access immediately before dialysis and from the arterial blood tubing 20 s after dialysis, after the dialyzer blood flow rate had been reduced to <80 ml/min. All blood samples were centrifuged, and the serum and plasma samples were shipped to a central laboratory (Spectra East, Rockleigh, NJ) for analysis. The concentrations of β_2M were measured with a solid-phase competitive RIA, with reagents supplied by Abbott Laboratories (Abbott Park, IL), and radioactivity was determined with a Micromedic Apex automatic counter (model 10600; ICN Biomedicals, Costa Mesa, CA). The intra-assay and interassay coefficients of variation were 3.6 and 5.0%, respectively.

Dialyzer Clearances of β_2M

Dialyzer clearances of β_2M were determined on the basis of the changes in serum β_2M concentrations during the dialysis session, with the assumption that β_2M was equally distributed within a single compartment, which was assumed to be the extracellular volume or one-third of the urea distribution volume (16). The urea distribution volume was calculated as the running mean of the previous four values obtained in monthly kinetic modeling sessions. Monthly values of urea distribution volume were corrected for double-pool effects from single-pool urea kinetics derived from predialysis and postdialysis blood urea nitrogen concentrations (17), treatment time, and calculated dialyzer clearances of urea, using *in vivo* urea mass transfer-area coefficients (18). With these assumptions, β_2M clearance could be calculated as $Q_f \times [1 - \log(C_{post}/C_{pre})/\log(1 + Q_f \times T/V\beta_{2M})]$, where Q_f denotes the average net ultrafiltration rate, cal-

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culated as the difference between the predialysis and postdialysis body weights divided by treatment time (T) (16). C_{post} and C_{pre} denote the postdialysis and predialysis serum β_2M concentrations, respectively, and $V\beta_{2M}$ denotes the postdialysis volume of extracellular fluids. This equation assumes no intradialytic generation of β_2M, ignores residual kidney and nonkidney/nondialyzer clearances of β_2M, and does not account for postdialysis rebound of serum β_2M concentrations.

For high-flux dialyzers, the clearance of β_2M was determined at the first and second month and then every other month during the follow-up phase. For low-flux dialyzers, β_2M clearance was determined at the first month and yearly thereafter. The Kt/V for β_2M was calculated by multiplying the dialyzer clearance of β_2M by the treatment time and dividing the result by the postdialysis volume of extracellular fluid.

The mean follow-up β_2M clearance, Kt/V for β_2M, Kt/V for urea, and predialysis serum β_2M level were defined for each patient by averaging all available follow-up values. To avoid confounding from different reuse limits for different dialyzer/reprocessing method combinations, summaries of β_2M clearances for different dialyzer/reprocessing method combinations were based on averages of predicted β_2M clearance levels at each follow-up kinetic modeling session. The predicted β_2M clearances were obtained with a multiple-regression analysis of the observed β_2M clearances with respect to the type of dialyzer, reuse number, and type of reprocessing method, based on the sessions in which serum β_2M levels were measured.

Follow-up Monitoring and Outcomes

The planned duration of follow-up monitoring ranged from 0.8 to 6.6 yr (mean, 4.24 yr), depending on the time of randomization. Because of deaths and transplantation, however, the mean actual follow-up duration was 2.84 yr. Classifications of outcomes were made at the clinical centers and were reviewed by an outcome committee composed of study investigators who were unaware of the treatment assignments (2). The primary outcome variable was ACM. The prespecified main secondary outcomes were (*1*) the composite of first cardiac hospitalization or ACM, (*2*) the composite of first infectious hospitalization or ACM, (*3*) the first decrease in serum albumin levels of ≥15% from baseline levels or ACM, and (*4*) the rate of all hospitalizations unrelated to vascular access. Additional secondary outcomes that specifically targeted cardiac and infectious events included (*1*) cardiac death, (*2*) the composite of first cardiac hospitalization or cardiac death, (*3*) infectious death, and (*4*) the composite of first infectious hospitalization or infectious death.

Statistical Analyses

Baseline characteristics are presented as means ± SD or as the proportions of patients in designated subgroups. Comparisons were performed with *t* tests, ANOVA, or chi-squared tests as appropriate. All reported *P* values are two-sided, without adjustment for multiple comparisons. All analyses described here were performed with SAS version 8 (SAS Institute Inc., Cary, NC).

Primary and Secondary Analyses of Clinical Outcomes

The primary analysis of the effects of the flux interventions on ACM was conducted with a Cox regression (19), stratified according to clinical center and controlling for the seven prespecified baseline factors, *i.e.*, age, gender, race, diabetes mellitus, years on dialysis, serum albumin levels, and comorbidity score (index of coexistent disease score) (20), calculated with the exclusion of diabetes mellitus. The interaction of baseline albumin levels with follow-up time was also included as a covariate, to account for a reduction in the association of baseline albumin levels with mortality rates with follow-up time. Kidney transplantation was treated as a censoring event in the primary analysis. However, in accordance with the intent-to-treat principle, deaths after transfer to centers not participating in the HEMO Study or transfer to alternative dialysis modalities were counted as outcomes and allocated to the patients' randomized arm. An additional sensitivity analysis was performed to examine the effect of the flux interventions on ACM rates, without censoring at transplantation.

Overdispersed Poisson regression analysis (21) was used to evaluate the effects of the treatment interventions on the non-access-related hospitalization rate, whereas Cox regression analysis was used to test the effects of the interventions on the remaining secondary outcomes. These analyses were also performed by controlling for the same prespecified baseline covariates as in the primary analysis. Kidney transplantation, transfer to a nonparticipating dialysis center, and transfer to an alternative dialysis modality were all considered censoring events in the secondary analyses.

Interactions of Flux Interventions with Covariates

Interactions of the flux interventions with each of the seven prespecified baseline factors and other factors were tested individually. Those tests determined whether the randomized flux assignments had different effects on mortality rates or the secondary clinical outcomes among subgroups defined on the basis of those factors. The interactions were tested with extensions of the Cox regression or overdispersed Poisson regression models described above, in which a term for the interaction between the flux assignment and the designated baseline factor was added to the basic model containing main effect terms for the treatment assignment and the seven prespecified covariates. Subgroups for the continuous variables (age, albumin levels, and years of dialysis) were initially defined according to the mean values. With this procedure, a potential interaction between the flux intervention and prestudy years on dialysis was identified when the prestudy years on dialysis values were dichotomized according to the mean value of 3.7 yr (see the Results section). To determine whether the interaction of the flux intervention with years on dialysis could be explained on the basis of one of the other baseline factors, an additional series of analyses that jointly evaluated separate interactions between flux assignment and both prestudy years on dialysis and the other baseline factor were performed. Additional sensitivity analyses were performed to examine the interactions between the flux intervention and the seven prespecified baseline factors with respect to ACM, without censoring at transplantation.

Further analyses were performed for more detailed assessments of the dependence of the effect of the flux intervention on years of dialysis. The model described above for the interaction of the flux intervention with prestudy years of dialysis coded as a dichotomous variable was modified to test the interaction of the flux intervention with prestudy years of dialysis coded as a continuous variable or categorized into quintiles. Time-dependent Cox regression analyses were conducted with the same covariate adjustment, to determine whether the relative risk (RR) for the flux comparison changed during the follow-up period for patients within different ranges of prestudy years of dialysis. Time-dependent Cox regression analysis with the same covariate adjustment was also used to examine the interaction of the flux intervention with the total years of dialysis, defined as the sum of the years of dialysis before the study and additional years of dialysis accrued during the follow-up period.

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Results

Patient Characteristics

The characteristics of the patients, categorized according to either prestudy years on dialysis or randomized flux arms, are presented in Table 1. There were no significant differences between the low-flux and high-flux arms with respect to any of the examined variables, indicating that the cohort was well randomized. There were, however, substantial differences in characteristics between the two groups dichotomized according to years on dialysis. Most notably, fewer patients who had undergone dialysis for >3.7 yr demonstrated measurable residual urinary urea clearance, compared with the short-duration group (10.7% *versus* 42.9%, $P < 0.001$). In addition, the long-duration group was more likely to be male (47.1% *versus* 42.2%, $P = 0.049$) and black (66.6% *versus* 60.8%, $P = 0.019$) and was less likely to be diabetic (29.1% *versus* 51.6%, $P < 0.001$).

Dialyzers, Reprocessing Methods, and β_2M Clearances

Eight different models of low-flux dialyzers and 17 different models of high-flux dialyzers were used in the study. CA210 and F8 dialyzers were used in 43 and 46% of all low-flux sessions and CT190 and F80 dialyzers were used in 48 and 43% of all high-flux sessions, respectively. The mean β_2M clearances for all dialyzers and reprocessing methods in the low-flux arm were low and were therefore collectively reported as a single value (2.7 ml/min) in Table 2. Single-use dialyzers were used in only 14.4% of the high-flux sessions. Mean β_2M clearances with high-flux dialyzers varied significantly, depending on the dialyzer model and the reprocessing method (Table 2). The highest mean β_2M clearance was observed with F80A dialyzers (Fresenius) reprocessed with heated citric acid (46.0 ml/min), which were used in 7.6% of all high-flux sessions. The lowest clearance was observed with CT190 dialyzers (Baxter) reprocessed with Renalin (22.9 ml/min), which were used in almost 30% of the high-flux sessions.

Clearances of β_2M and Urea

The dialyzer clearances of β_2M in the high-flux and low-flux arms during the follow-up period are presented in Figure 1. The mean dialyzer β_2M clearances for the entire follow-up period were 33.8 ± 11.4 ml/min for the high-flux arm and 3.4 ± 7.2 ml/min for the low-flux arm (Table 3). The β_2M Kt/V values for the two arms were 0.67 ± 0.23 and 0.07 ± 0.15, respectively. Therefore, the mean predialysis serum β_2M levels during the follow-up period were 41.5 ± 13.0 mg/L in the low-flux arm and 33.6 ± 9.1 mg/L in the high-flux arm ($P < 0.0001$, high-flux *versus* low-flux dialysis). The eKt/V values for urea (1.34) in the two flux arms were virtually identical. Within each of the arms, there were no significant differences in mean β_2M clearances, mean β_2M Kt/V values, or mean urea eKt/V values between the patients with ≤3.7 yr of dialysis and those with >3.7 yr of dialysis before the study. These data indicate that any differences in clinical outcomes in response to flux interventions between the groups with different prestudy durations of dialysis were not attributable to differences in dialyzer clearances of β_2M and urea.

Table 1. Baseline characteristics of the 1846 randomized patients[a]

Factors	All	Prestudy Years on Dialysis		Randomized Arms	
		≤3.7 yr[b]	>3.7 yr	Low Flux	High Flux
No. of patients	1846	1269	577	925	921
Age (yr)	57.6 ± 14.0	58.9 ± 13.6	54.9 ± 14.7	57.6 ± 14.2	57.7 ± 13.9
Female (%)	56.2	57.8	52.9	55.8	56.7
Black (%)	62.6	60.8	66.6	62.6	62.6
Diabetic (%)	44.6	51.6	29.1	44.4	44.7
Years on dialysis	3.7 ± 4.4	1.5 ± 1.0	8.6 ± 4.9	3.7 ± 4.2	3.8 ± 4.5
Postdialysis weight (kg)	69.2 ± 14.7	70.3 ± 14.9	66.6 ± 14.0	69.0 ± 14.7	69.3 ± 14.7
Urea volume[c] (L)	31.1 ± 6.6	31.3 ± 6.5	30.7 ± 6.7	31.2 ± 6.8	31.1 ± 6.3
Urinary urea clearance of >0 (%)	32.9	42.9	10.7	31.2	34.5
Urinary urea clearance of >0.75 ml/min per 35 L (%)	14.0	19.2	2.6	13.2	14.9
On high flux (%)	60.2	58.4	64.3	59.0	61.3
ICED score[d]	2.0 ± 0.8	2.0 ± 0.8	2.0 ± 0.8	2.0 ± 0.8	2.0 ± 0.8
Cardiac disease (%)	80.1	79.5	81.5	80.5	79.7
Serum albumin level (g/dl)	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	3.6 ± 0.4	3.6 ± 0.4

[a] All data are presented as mean ± SD or percentages. All factors differed significantly ($P < 0.05$) between the subgroup with ≤3.7 yr and the subgroup with >3.7 yr on dialysis, except for the ICED score and cardiac disease. In contrast, there were no differences between the high-flux and low-flux arms in any of the presented factors, indicating that the cohort was well randomized.

[b] The mean time for which the randomized cohort had been on dialysis before entry into the study was 3.7 yr.

[c] Urea distribution volume, as determined by kinetic modeling.

[d] ICED score, index of coexistent disease score ((20)), computed with diabetes mellitus excluded.

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Table 2. Combinations of dialyzers and reprocessing methods

Dialyzer	Reprocessing Method[a]	No. of Patients[b]	% of Sessions[c]	Mean β_2M Clearance (ml/min)[d]
Low-flux		913	100	2.7
High-flux				
various	No reuse	190	14.4	38.3
CT190	Renalin	288	29.7	22.9
CT190	Bleach + formaldehyde/glutaraldehyde	183	11.1	38.6
F80A	Renalin	136	10.1	33.2
F80A	Heated citric acid	86	7.6	46.0
F80B	Bleach + formaldehyde/glutaraldehyde	251	15.0	39.0
F80B	Bleach + Renalin	58	4.8	30.3
others	Various	259	7.3	42.5

[a] Refer to reference (3) for details of reprocessing methods.
[b] Number of patients using that particular dialyzer/reprocessing method combination at least once.
[c] Percentage of modeling sessions within the particular flux arm in which the specific dialyzer/reprocessing method combination listed was used and data were not missing.
[d] Refer to the Materials and Methods section for the calculation of β_2-microglobulin (β_2M) clearance.

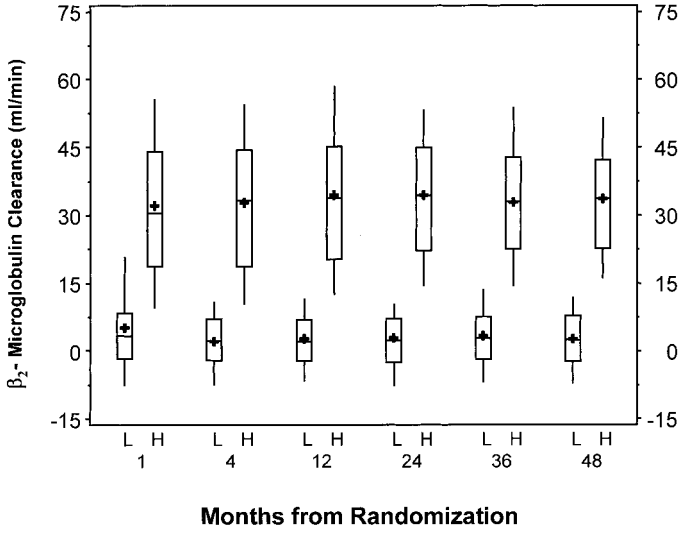

Figure 1. Distributions of individual measurements of β_2-microglobulin (β_2M) clearance at selected follow-up visits. The plus sign inside each box plot represents the mean, and the center horizontal line represents the median. The lower and upper horizontal lines at the bottom and top of the box represent the 25th and 75th percentiles, respectively. The lower and upper vertical lines extend to the 10th and 90th percentiles, respectively. High-flux dialysis (H) was associated with higher dialyzer β_2M clearances ($P < 0.001$) than was low-flux dialysis (L).

Interactions of Baseline Factors with Flux Interventions

In the entire cohort, randomization to the high-flux arm was not significantly associated with death in the primary analysis, in which the follow-up period was censored at the time of transplantation [RR, 0.92; 95% confidence interval (CI), 0.81 to 1.05], or in a sensitivity analysis without censoring at transplantation (RR, 0.91; 95% CI, 0.80 to 1.04). However, it is conceivable that the responses of different subgroups to high-flux dialysis might not be uniform. Further analyses were therefore performed to evaluate whether the effects of flux intervention on ACM differed between subgroups defined according to the seven baseline factors that were prespecified in the study protocol or between subgroups defined according to seven additional factors selected after the study, for the purposes of this report. Among the seven prespecified baseline factors, only an interaction between flux and years of dialysis was identified (Table 4). The *P* value for the difference in the effects of high-flux assignment on ACM rates for the two duration subgroups (interaction between flux and years on dialysis) was 0.005, which is lower than the Bonferroni critical value of 0.0071 that is appropriate for the evaluation of seven different prespecified factors. For patients with >3.7 yr of dialysis before the study, randomization to the high-flux arm was associated with a 32% reduction ($P = 0.001$) in the risk of ACM, compared with the low-flux arm. In contrast, for patients with ≤3.7 yr of dialysis before the study, there was no significant difference ($P = 0.56$) in the risk of ACM between the two flux arms (Table 5). The results of the analyses of interactions between the flux intervention and the seven prespecified baseline factors demonstrated similar results when the analyses was performed without censoring for transplantation; the interaction of the flux intervention with the prestudy duration of dialysis remained statistically significant ($P = 0.005$), and no other interactions were identified ($P > 0.10$ for the interaction of the flux intervention with each other factor).

There was no evidence that the effects of the flux intervention differed between subgroups defined according to any of the seven additional factors selected for this report (Table 4). Although the patients who had been undergoing dialysis for a long time tended to exhibit lower residual kidney function, there was no difference in the effect of high-flux assignment on ACM rates between patients with residual urea clearance values of ≤0.24 ml/min (RR, 0.90; 95% CI, 0.77 to 1.05) and

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Table 3. Clearance and Kt/V for β_2M and eKt/V for urea during the follow-up period, according to the treatment arm and the duration of dialysis before the study

Subgroups	Mean Clearance of β_2M (ml/min)	Mean Kt/V of β_2M[a]	Mean eKt/V of Urea
High flux			
all	33.8 ± 11.4	0.67 ± 0.23	1.34 ± 0.21
standard-dose arm	35.2 ± 11.9	0.65 ± 0.22	1.16 ± 0.08
high-dose arm	32.3 ± 10.6	0.69 ± 0.24	1.53 ± 0.10
≤3.7 yr[b]	33.9 ± 11.0	0.67 ± 0.23	1.35 ± 0.21
>3.7 yr[b]	33.6 ± 12.0	0.66 ± 0.24	1.34 ± 0.21
Low flux			
All	3.4 ± 7.2	0.07 ± 0.15	1.34 ± 0.21
≤3.7 yr[b]	3.3 ± 7.1	0.07 ± 0.14	1.34 ± 0.21
>3.7 yr[b]	3.6 ± 7.6	0.07 ± 0.16	1.33 ± 0.20

[a] The volume of distribution for β_2M was assumed to be equal to the extracellular volume and was calculated as the volume of distribution for urea (by kinetic modeling) divided by 3.

[b] Years on dialysis before entry into the study. There were no significant differences ($P > 0.05$) between the group with ≤3.7 yr and the group with >3.7 yr on dialysis in any of the presented variables.

those with residual urea clearance values of >0.24 ml/min (RR, 1.08; 95% CI, 0.83 to 1.41; $P = 0.24$ for interaction). There was also no significant interaction between the flux intervention and the presence or absence of anuria (>50 ml or <50 ml of urine/d, $P = 0.30$). Therefore, the differences in residual kidney function did not seem to explain the interaction between flux and the duration of dialysis. In addition, although dialyzer β_2M clearances in the high-flux arm tended to be lower when dialyzers were reprocessed with Renalin than when dialyzers were not reprocessed with Renalin (Table 2) (3), there was no evidence that the effects of the flux intervention differed between the dialysis units using Renalin and those not using Renalin.

As indicated in Table 1, the number of prestudy dialysis years was significantly associated with a number of other patient characteristics at baseline. This raised the question of whether the apparently greater benefit of high-flux dialysis among patients with >3.7 yr of dialysis could be explained on the basis of one or more of the other characteristics. To directly address this possibility, additional analyses of the interaction between flux and years of dialysis were performed, controlling for interactions between flux assignment and the other designated factors presented in Table 4. The adjusted *P* values for the interaction between flux and years of dialysis ranged from 0.003 to 0.007 (individual values not shown) with controlling for the interactions of flux with the other factors; those values are close to the *P* value of 0.005 obtained when the interaction between flux and years of dialysis was considered alone. Therefore, there is no evidence that the relationship between the flux effect and prestudy years of dialysis is attributable to one of the other factors considered in Table 4.

Finally, we considered whether the strength of the interaction between flux assignment and prestudy years of dialysis was related to the use of low-flux *versus* high-flux dialysis at the time of entry into the study. The interaction tended to be stronger for patients who were undergoing low-flux dialysis than for patients who were undergoing high-flux dialysis at the time of entry, but this three-way interaction was not statistically significant ($P = 0.21$). For patients who were undergoing low-flux dialysis at the time of entry, the RR of ACM for high-flux *versus* low-flux assignment during the follow-up period was 0.59 (95% CI, 0.40 to 0.86) for patients who had been on dialysis for >3.7 yr, compared with the RR of 1.12 (95% CI, 0.87 to 1.46) for patients who had been on dialysis for ≤3.7 yr ($P = 0.006$ for the difference between these two RR). In contrast, for patients who were undergoing high-flux dialysis at the time of entry, the difference in the effects of assignment to the high-flux arm during the follow-up period for the groups with different prestudy durations of dialysis (RR, 0.79; 95% CI, 0.59 to 1.05, for >3.7 yr; RR, 1.04; 95% CI, 0.84 to 1.28, for ≤3.7 yr) was not statistically significant ($P = 0.14$).

Effects of Flux Assignment on Secondary Outcomes and Interactions with Prestudy Years on Dialysis

Although randomization to high-flux dialysis did not significantly reduce the ACM rate or the four main secondary outcomes in the entire cohort, it was associated with reduced risks of cardiac death (RR, 0.80; 95% CI, 0.65 to 0.99) and of the composite outcome of first cardiac hospitalization or cardiac death (RR, 0.87; 95% CI, 0.76 to 1.00) (Table 5). When the patients with >3.7 yr of dialysis before the study were compared with those with ≤3.7 yr of dialysis, high-flux dialysis generally seemed to have a beneficial effect in the long-duration group but not in the short-duration group. Among patients with >3.7 yr of dialysis, the RR were consistently <1.0 for all nine outcomes presented in Table 5. Among these nine outcomes, however, statistically significant differences in the effects of the flux interventions between the two dialysis duration subgroups (interaction between flux and years of

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Table 4. Interactions of baseline factors with flux interventions for ACM[a]

Factor	Subgroup	RR[b]	95% CI	*P* Value for Interaction[c]
Age[d,e]	≤58 yr	0.98	0.76 to 1.26	0.69
	>58 yr	0.92	0.79 to 1.08	
Gender[d]	Male	1.03	0.84 to 1.26	0.27
	Female	0.88	0.74 to 1.06	
Race[d]	Non-black	1.04	0.84 to 1.28	0.24
	Black	0.88	0.74 to 1.04	
Diabetes mellitus[d]	Absent	0.95	0.78 to 1.15	0.87
	Present	0.93	0.77 to 1.11	
Years of dialysis[d,e]	≤3.7 yr	1.05	0.89 to 1.24	0.005
	>3.7 yr	0.68	0.53 to 0.86	
ICED score[d,e,f]	≤2 units	0.95	0.72 to 1.24	0.94
	>2 units	0.93	0.76 to 1.14	
Serum albumin level[d,e]	≤3.6 g/dl	0.91	0.76 to 1.09	0.65
	>3.6 g/dl	0.97	0.79 to 1.19	
Postdialysis weight[e,g]	≤69 kg	0.97	0.81 to 1.16	0.70
	>69 kg	0.92	0.75 to 1.13	
Urea distribution volume[e,g,h]	≤31 L	0.91	0.76 to 1.09	0.64
	>31 L	0.97	0.80 to 1.19	
Residual kidney urea clearance[e,g]	≤0.24 ml/min per 35 L	0.90	0.77 to 1.05	0.24
	>0.24 ml/min per 35 L	1.08	0.83 to 1.41	
Cardiac disease[g]	Absent	0.71	0.47 to 1.07	0.15
	Present	0.98	0.85 to 1.13	
Dialysis flux[g]	High	0.94	0.76 to 1.16	0.99
	Low	0.94	0.79 to 1.11	
Unit using Renalin for reprocessing[g]	Non-Renalin	0.95	0.80 to 1.13	0.88
	Renalin	0.93	0.75 to 1.14	
Randomized dose arm[g]	Standard dose	0.88	0.73 to 1.06	0.37
	High dose	1.00	0.82 to 1.20	

[a] ACM, all-cause mortality; RR, relative risk; CI, confidence interval.
[b] RR of ACM in high-flux arm *versus* low-flux arm.
[c] *P* values for interactions test the null hypothesis that the effect of the flux intervention was equal in the two designated subgroups. The *P* values are two-sided and are not adjusted for multiple comparisons. The Bonferroni critical value for seven tests is 0.0071.
[d] The first seven factors in this table are baseline factors that were prespecified in the study protocol for investigation of interactions with the flux and dose interventions.
[e] Subgroups for continuous variables were defined according to the mean value at baseline.
[f] ICED score, index of coexistent disease score ((20)), computed with diabetes mellitus excluded.
[g] The last seven factors were additional factors determined at baseline that were not prespecified in the study protocol for investigation of interactions.
[h] Urea distribution volume as determined by kinetic modeling.

dialysis) were observed only for the albumin main secondary outcome ($P = 0.009$), in addition to the primary outcome of ACM rate ($P = 0.005$).

Specifically, for patients with >3.7 yr of dialysis before the study, high-flux assignment was associated with a lower risk of the main secondary composite outcome of first 15% albumin level decrease or ACM (RR, 0.74; 95% CI, 0.60 to 0.91; $P = 0.005$) but had only marginal to nonsignificant effects on the other three main secondary outcomes (first cardiac hospitalization or ACM, first infectious hospitalization or ACM, and non-vascular access-related hospitalization) (Table 5). In addition, in the subgroup with >3.7 yr of dialysis, high-flux assignment was associated with a 37% risk reduction for cardiac deaths (RR, 0.63; 95% CI, 0.43 to 0.92; $P = 0.016$). There was, however, no significant interaction between flux assignment and prestudy years of dialysis ($P = 0.11$) with respect to cardiac death, because the RR with assignment to high-flux dialysis, compared with low-flux dialysis, were <1.0 for both the long-duration group and the short-duration group.

In contrast, high-flux dialysis did not significantly affect any of the outcome measures listed in Table 5 for patients on dialysis for ≤3.7 yr. It should be noted that for none of the nine listed outcomes was high-flux assignment associated with statistically significant increases in the RR for the entire cohort or for either of the dialysis duration subgroups.

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Table 5. Comparison of effects of high-flux dialysis on clinical outcomes between two subgroups defined according to prestudy years on dialysis

Outcome	No. of Events/Rate (no. of events/100 patient-yr)[a]	All Patients			≤3.7 yr on Dialysis before Study			>3.7 yr on Dialysis before Study			*P* for Interaction[b]
		RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	
ACM[c]	871/16.6	0.92	0.81 to 1.05	0.23	1.05	0.89 to 1.24	0.56	0.68	0.53 to 0.86	0.001	0.005
First cardiac hospitalization or ACM[d,e]	1079/28.5	0.90	0.80 to 1.01	0.078	0.94	0.81 to 1.09	0.40	0.83	0.68 to 1.03	0.09	0.36
First infectious hospitalization or ACM[d,f]	1104/29.9	0.91	0.81 to 1.03	0.13	0.98	0.85 to 1.13	0.78	0.83	0.68 to 1.01	0.06	0.18
First albumin event or ACM[d,g]	1011/24.5	0.92	0.82 to 1.05	0.22	1.05	0.90 to 1.22	0.56	0.74	0.60 to 0.91	0.005	0.009
All non-access hospitalizations[d]	6087/125	1.00	0.90 to 1.10	0.93	1.05	0.93 to 1.18	0.46	0.92	0.77 to 1.10	0.37	0.25
Cardiac death[h,i]	343/6.6	0.80	0.65 to 0.99	0.042	0.91	0.70 to 1.18	0.50	0.63	0.43 to 0.92	0.016	0.11
First cardiac hospitalization or cardiac death[h,i,j,k]	835/22.0	0.87	0.76 to 1.00	0.045	0.89	0.76 to 1.05	0.17	0.82	0.65 to 1.05	0.11	0.58
Infectious death[h]	201/3.8	0.85	0.64 to 1.13	0.26	0.93	0.66 to 1.31	0.67	0.78	0.48 to 1.26	0.31	0.56
First infectious hospitalization or infectious death[h,l]	802/21.7	0.92	0.80 to 1.06	0.26	0.96	0.81 to 1.14	0.65	0.88	0.69 to 1.11	0.28	0.54

[a] Rate is the number of events per 100 patient-yr of follow-up monitoring.
[b] Difference in RR associated with high-flux *versus* low-flux dialysis between patients on dialysis for ≤3.7 yr and those on dialysis for >3.7 yr before randomization.
[c] Primary outcome.
[d] Main secondary outcomes.
[e] Includes 735 cardiac hospitalizations and 344 deaths.
[f] Includes 783 infectious hospitalizations and 321 deaths.
[g] Includes 494 declining albumin events and 517 deaths.
[h] Additional secondary outcomes.
[i] Cardiac deaths include those attributable to myocardial infarction, congestive heart failure, arrhythmia, or other heart diseases.
[j] Cardiac hospitalizations include those attributable to angina, myocardial infarction, congestive heart failure, arrhythmia, or other heart diseases.
[k] Includes 735 cardiac hospitalizations and 100 cardiac deaths.
[l] Includes 783 infectious hospitalizations and 19 infectious deaths.

Causes of Death in the Low-Flux and High-Flux Arms

The causes of death in the low-flux and high-flux arms are presented in Table 6. High-flux dialysis was associated with lower mortality rates for various cardiac causes. Mortality rates for malignancies and gastrointestinal disorders were higher in the high-flux arm, however. For patients with >3.7 yr of dialysis before the study, the major differences between the flux arms were observed with respect to cardiac (0.053 cardiac deaths/patient-yr with high-flux dialysis *versus* 0.076 deaths/patient-yr with low-flux dialysis) and cerebrovascular (0.008 events/patient-yr with high-flux dialysis *versus* 0.019 events/patient-yr with low-flux dialysis) causes.

Different Statistical Analyses of Interactions between Dialysis Duration and Flux

Alternative analyses were performed to examine the robustness of the interaction between the flux intervention and years of dialysis. When prestudy years of dialysis were analyzed as a categorical variable separated according to quintiles, assignment to the high-flux arm was associated with a 32% reduction in the risk of ACM, compared with the low-flux arm (RR, 0.68; 95% CI, 0.50 to 0.92), in the subgroup with the longest duration of dialysis (>6.09 yr). The overall comparison of RR of ACM across the quintiles, however, demonstrated only marginal significance ($P = 0.055$) (Figure 2). When the prestudy dialysis time was treated as a continuous variable instead of being categorized according to quintiles, the decrease in the

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Table 6. Causes of death in the low-flux and high-flux arms

Cause	Low Flux		High Flux	
	No. of Events	No. per 100 patient-yr	No. of Events	No. per 100 patient-yr
Ischemic heart disease[a]	109	4.21	102	3.85
Congestive heart failure[a]	22	0.85	14	0.53
Arrhythmia[a]	35	1.35	24	0.91
Other heart diseases[a]	21	0.81	16	0.60
Cerebrovascular	37	1.43	28	1.06
Peripheral vascular	29	1.12	34	1.28
Respiratory	23	0.89	26	0.98
Malignancy	20	0.77	32	1.21
Gastrointestinal (excluding hepatobiliary)	12	0.46	25	0.94
Non-vascular access infection	32	1.24	29	1.09
Vascular access	26	1.00	21	0.79
Others	64	2.47	59	2.23
Unknown	12	0.46	19	0.72
All	442	17.08	429	16.20

[a] These four entities collectively constitute the category of "cardiac deaths." There were 187 total cardiac deaths in the low-flux arm and 156 total cardiac deaths in the high-flux arm.

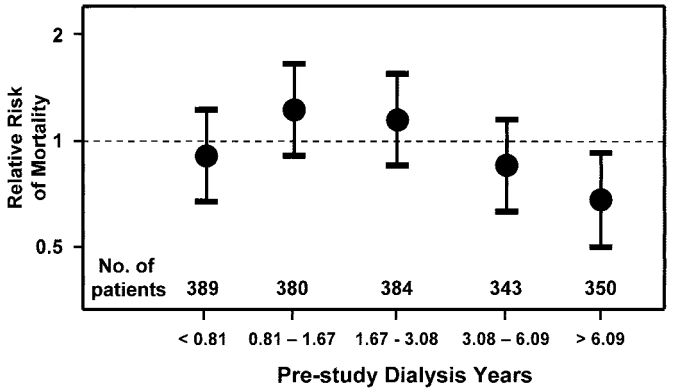

Figure 2. Interactions between the effects of flux interventions on all-cause mortality (ACM) and prestudy years on dialysis, categorized by quintiles. The randomized cohort was separated into quintiles according to the number of prestudy years on dialysis. The number of dialysis years and the corresponding number of patients in each quintile are indicated along the horizontal axis. Each data point represents the mean ± SD of the relative risk (RR) of ACM associated with the quintile. Randomization to high-flux dialysis was associated with a lower risk of ACM (RR, 0.68; 95% confidence interval, 0.50 to 0.92) than was low-flux dialysis in the quintiles with >6.09 yr on dialysis. The *P* value for the overall comparison of RR across the quintiles was 0.055.

RR of ACM associated with high-flux assignment was 3.1% (95% CI, 0.1 to 6.0%; $P = 0.040$) for each 1-yr increase in the duration of dialysis.

In contrast to the increased risk reduction for the high-flux intervention with more years of dialysis before the study, there was no evidence of a similar risk reduction for high-flux dialysis, compared with low-flux dialysis, with additional years of dialysis after randomization. In fact, irrespective of the number of years of dialysis before the study, the RR for the high-flux *versus* low-flux dialysis comparison tended to increase, rather than decrease, with time during the follow-up period (Table 7). Overall, the RR for the high-flux *versus* low-flux dialysis comparison increased by 8.9% (95% CI, 0.2 to 18.7%) each year after randomization ($P = 0.055$). Consequently, the interaction between the flux intervention and the total years of dialysis (defined as the sum of the years of dialysis before the study and additional years of dialysis accrued during the follow-up period) was weaker than the interaction between flux and the years of dialysis before the study. When the total years of dialysis were treated as a continuous variable, the RR for the high-flux arm, compared with the low-flux arm, decreased by only 1.9% (95% CI, 0.9 to 4.6%; $P = 0.18$) for each 1-yr increase in dialysis duration. Furthermore, there were no statistically significant ($P > 0.05$) interactions between the total years of dialysis and the flux interventions for any of the nine outcomes listed in Table 5 (data not shown).

Discussion

Interactions between Flux Interventions and Years on Dialysis

In the entire cohort in the HEMO Study, assignment to the high-flux arm had no significant effect on the ACM rate or any of the four main secondary outcomes (2). The rate of cardiac deaths and the rate of the composite of the first cardiac hospitalization or cardiac death were, however, 20 and 13% lower, respectively, in the high-flux arm, compared with the low-flux arm (Table 5). High-flux dialysis did not have differential effects on subgroups defined according to six of the seven prespecified covariates (Table 4). For example, whereas diabetic patients exhibited a higher overall mortality rate than did nondiabetic patients, there was no difference between the two

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Table 7. RR of ACM for high-flux *versus* low-flux arms, according to prestudy and follow-up years of dialysis

Years of Dialysis before Study	Years of Dialysis in Follow-up Period		
	0 to 1.5	1.5 to 3.0	>3.0
0 to 2.0	1.18 (0.86 to 1.62) (n = 156)[a]	0.79 (0.55 to 1.14) (n = 116)	1.20 (0.83 to 1.73) (n = 116)
2.0 to 4.0	1.00 (0.64 to 1.57) (n = 78)	1.18 (0.70 to 2.01) (n = 55)	1.36 (0.85 to 2.18) (n = 70)
>4.0	0.57 (0.39 to 0.83) (n = 113)	0.67 (0.43 to 1.03) (n = 84)	0.86 (0.55 to 1.32) (n = 83)

[a] Values in parentheses are 95% CI and the numbers of deaths (n).

subgroups in their responses to high-flux dialysis. The effects of high-flux dialysis, however, seemed to vary depending on the duration of dialysis before the study.

Assuming that the interaction between dialysis years and flux was real, we first considered possible mechanisms. The case mixture of the subgroup with >3.7 yr of dialysis before the study was substantially different from that of the subgroup with ≤3.7 yr of dialysis (Table 1). The long-duration group was younger, was more likely to be male and black, was less likely to be diabetic, and exhibited a lower postdialysis body weight. Age, gender, race, diabetic status, and body weight were not noted to interact with the flux interventions, however (Table 4). Therefore, these factors could not individually explain the potential differences in the responses to high-flux dialysis between the long-duration and short-duration groups, although it is conceivable that a combination of these factors and/or other factors could account for the differences.

Another potential explanation is that patients who had been on long-term dialysis had accumulated more toxic middle molecules and lacked the residual kidney function to remove them; therefore, these patients would benefit more from the removal of middle molecules with high-flux dialysis during the follow-up period than would patients on short-term dialysis. As expected, there were fourfold more patients in the long-duration group who were anuric, compared with the short-duration group. Furthermore, patients on long-term dialysis who had been using low-flux dialyzers before the study demonstrated a 41% decrease in ACM rate when randomized to the high-flux arm, compared with the low-flux arm, which is consistent with the idea that more toxic middle molecules had accumulated in this subpopulation. Patients with lower residual kidney function, however, responded to high-flux dialysis similarly to those with greater residual kidney function (Table 4), and anuric patients responded to high-flux dialysis similarly to those without anuria. Therefore, these observations did not seem to explain the flux-dialysis year interaction

We next considered the extent to which the data from the HEMO Study supported the hypothesis that the interaction between flux and years of dialysis on ACM is a real phenomenon, rather than being a spurious subgroup result. On the basis of the initially specified dichotomization according to the mean value (3.7 yr), the P value of 0.005 for the interaction between flux and years of dialysis was lower than the Bonferroni critical value of 0.0071 that is appropriate for the evaluation of seven prespecified factors. Results of further analyses, however, weakened the support for this hypothesis. First, the dependence of the flux effect on prestudy years of dialysis was somewhat weaker and no longer met the Bonferroni threshold when years of dialysis were expressed as a continuous variable (P = 0.040) or subdivided into five groups (P = 0.055). Second, if the relationship between flux and years of dialysis before the study represented a true biologic effect associated with increased years of dialysis, then the risk reduction for the high-flux *versus* low-flux dialysis comparison might be expected to have increased as the follow-up period progressed, with the accrual of additional years of dialysis after randomization. However, such an effect was not observed; in fact, the RR for the high-flux *versus* low-flux interventions tended to increase with follow-up times, irrespective of the years of dialysis before the study (Table 7). In the subgroup with >4 yr of dialysis before the study, the attenuation of the RR toward 1 from an initial RR of 0.57 might in part reflect a survivorship bias; *i.e.*, as follow-up monitoring proceeded, it is possible that a true benefit of high-flux *versus* low-flux dialysis led to the survival of a greater proportion of sicker patients in the high-flux arm to the current time point, thus creating a bias against the high-flux arm, in comparison with the low-flux arm, later in the follow-up period. This explanation does not seem likely for the subgroups with <4 yr of dialysis before the study, for which the mortality risks were similar between the flux arms early in the follow-up period. There are no obvious biologic explanations for why the years during follow-up monitoring should differ from the prestudy years in their influence on the clinical effects of high-flux dialysis. Therefore, we interpret the cumulative evidence as being interesting and worthy of further investigation but insufficient to allow us to definitively conclude at this time that the effect of flux depends on years of dialysis.

Effects of High-Flux Dialysis and Causes of Death

In the entire cohort, the risk reductions associated with the high-flux arm, compared with the low-flux arm, ranged from 0 to 20% for the nine outcomes listed in Table 5. The risk reductions reached statistical significance (P < 0.05, without adjustment for multiple analyses) for two outcomes involving cardiac death. Specifically, high-flux dialysis was associated

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with a 20% decrease in cardiac deaths and a 13% decrease in the composite of first cardiac hospitalization or cardiac death. Consistent with the relationship between flux assignment and ACM rates, the trends favoring high-flux dialysis were generally larger in the subgroup with >3.7 yr of dialysis before the study than in the entire cohort, with risk reductions for high-flux dialysis ranging from 8 to 37% for the same nine outcomes. The lower rates of cardiovascular death associated with the high-flux arm in the entire cohort were, however, counterbalanced by increases in the rates of death attributable to certain other causes. Malignancies and gastrointestinal disorders (excluding hepatobiliary diseases) were particularly noteworthy because of the magnitude of the relative increases in event rates (57 and 104%, respectively) associated with high-flux dialysis, despite the rather modest absolute event rates. Of interest is the retrospective study by Koda *et al.* (8), in which high-flux dialysis was associated with higher rates of death resulting from malignancies, compared with low-flux dialysis, although the event rates were also low in that study.

Several retrospective observational studies reported statistically significant decreases in mortality rates associated with high-flux dialysis, compared with low-flux dialysis (8–11). The effect sizes (19 to 76%) were substantially greater than the statistically insignificant 8% decrease observed in the HEMO Study. In an observational study from the Lombardy registry involving 6444 patients, Locatelli *et al.* (22) observed a statistically insignificant 10% increase in mortality rates associated with hemodialysis, compared with hemofiltration or hemodiafiltration. Although the magnitude of the difference in ACM rates in that study agreed closely with that in the HEMO Study (8%), the extracorporeal modalities used in the two studies were different. In addition, clearances of β_2M were not reported in that study, to permit assessment of the separation of middle-molecule removal results between the two arms.

Effects of Membranes on Cardiac and Infectious Outcomes

In a retrospective study by Hornberger *et al.* (9), although ACM and infectious hospitalization rates were lower for patients using high-flux *versus* low-flux membranes, there was no difference in cardiovascular hospitalization rates. In addition to a 38% decrease in the ACM rate, Koda *et al.* (8) observed that high-flux dialysis was associated with 26 and 29% decreases in cardiac and infectious mortality rates, respectively, compared with low-flux dialysis. Finally, Bloembergen *et al.* (23) reported lower infectious and cardiac mortality rates for patients treated with either modified cellulose or synthetic hemodialysis (both low-flux and high-flux) membranes, compared with patients treated with unsubstituted (low-flux) cellulosic membranes. Comparisons with our study are difficult, because membranes were classified according to materials rather than flux in the earlier study; in addition, unsubstituted cellulosic membranes were excluded from the HEMO Study. Nevertheless, high-flux dialysis was associated with a decrease in the RR of cardiac death in this study (Table 5). One possible explanation is that the enhanced removal of certain middle molecules, such as advanced glycation end products and lipase inhibitors, with high-flux dialysis decreases atherogenesis. In contrast, randomization to the high-flux arm in the HEMO Study was not associated with an improvement in infectious outcomes. Several proteins that inhibit granulocyte functions *in vitro* were previously isolated from the serum of patients with renal failure (24,25). Because those proteins are substantially larger than β_2M and therefore might not have been removed by the high-flux membranes used in the HEMO Study, the negative results with respect to infectious outcomes neither substantiate nor refute the clinical significance of these proteins.

Effects of Membranes on Serum Albumin Levels

In this study, randomization to high-flux dialysis had no significant effect on the main secondary composite outcome of serum albumin level decrease or ACM (RR, 0.92; $P = 0.22$). For patients with >3.7 yr of dialysis before the study, however, there was a 26% decrease ($P = 0.005$) in the risk of this outcome. Serum albumin levels represent one of the strongest predictors of clinical outcomes among patients undergoing maintenance hemodialysis (26). Inasmuch as serum albumin levels partially reflect nutrition, the effect of dialysis membranes on protein intake is of interest. Dialysis using the high-flux AN69 membrane has been associated with higher protein catabolic rates, compared with a low-flux cellulose acetate membrane (27). In contrast, a more recent study noted that switching from low-flux to high-flux polysulfone dialyzers did not increase the protein catabolic rate, although a significant increase in serum albumin levels was observed (28). This latter observation is in general agreement with the decrease in albumin composite events in our study. If the increase in serum albumin levels was indeed the result of improved dietary intake, then a potential explanation could have involved the removal of plasma substances that inhibit appetite, such as the putative factor in uremic plasma identified by Anderstam *et al.* (29) (1 to 5 kD), leptin (16 kD) (30), and other peptides (31). However, high-flux dialysis could also remove more plasma amino acids (32) and proteins (12,13) than low-flux dialysis, which would result in lower serum albumin levels. The loss of amino acids into the dialysate was not examined in the HEMO Study. However, the loss of albumin through the dialyzers was observed to be quite modest for a subset of HEMO Study patients examined (33). The average loss among six patients for whom albumin was detectable in the dialysate was only 0.5 g/session.

Hypoalbuminemia could also result from the suppression of hepatic albumin synthesis as a result of inflammation (34). A potential stimulus of systemic inflammatory responses during high-flux dialysis is the back-transfer of cytokine-inducing substances from contaminated dialysate through the dialyzer membrane. Despite the greater potential for albumin leakage into the dialysate and back-transfer of cytokine-inducing substances, randomization to high-flux dialysis was associated with a lower, rather than a higher, incidence of the decreased serum albumin level composite outcome in the HEMO Study (Table 5). The analysis of the data on C-reactive protein from the HEMO Study will be reported separately.

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Enhancement of β_2M Clearance

The HEMO Study was performed using intermittent hemodialysis in a primarily diffusive mode, on a thrice-weekly basis. The mean β_2M clearance, even in the high-flux arm, was rather modest (33.8 ml/min). This was attributable in part to certain reprocessing methods (*e.g.*, Renalin without bleach), which markedly decreased the β_2M clearance of certain dialyzers (*e.g.*, CT190). Other extracorporeal techniques, such as the use of certain dialyzers and reprocessing methods, daily or nocturnal hemodialysis, hemodiafiltration, or sorbent technology, could provide substantially greater removal of β_2M. In view of the positive trends in the overall results and the beneficial effects of high-flux dialysis in certain outcome and subgroup analyses (Table 5) in the HEMO Study, further studies that involve greater β_2M clearances and specific targeting of cardiac outcomes may produce more definitive results.

Conclusion

On the basis of the comparison between the two flux arms, with a RR of 0.92 (95% CI, 0.81 to 1.05; $P = 0.23$), the primary conclusion of the HEMO Study is that high-flux dialysis does not lead to a substantial reduction in mortality rates, compared with low-flux dialysis (2). The lower confidence limit of 0.81 seems to exclude a risk reduction of >19% for high-flux dialysis, as has been reported in some observational studies. The 8% risk reduction for high-flux dialysis observed in the HEMO Study is, however, consistent with the 5% risk reduction recently reported by the United States Renal Data System (35). Lower risks were also observed in the high-flux arm, compared with the low-flux arm, for most of the secondary outcomes considered in this report, including cardiac death, for which a 20% risk reduction was observed. None of these effects reached the criterion for statistical significance after adjustment for the multiple comparisons performed. The overall pattern, however, is consistent with the possibility of a benefit of high-flux dialysis that was too small to be detected, given the power of the study. For example, detection of an 8% reduction in risk for high-flux dialysis with 80% power would have required randomization of approximately 10,000 patients, instead of 1846 patients, under the conditions of the HEMO Study. This study also does not exclude the possibility that greater benefits could be accrued from other modalities that are associated with higher clearances of β_2M. The support of the HEMO Study data for a benefit of high-flux dialysis is strongest for patients with several years of prior dialysis. The strength of the relationship between the effect of flux and years of dialysis, however, varied in different analyses. Therefore, the suggestion of a greater benefit of high-flux dialysis for patients with more prior years of dialysis will require confirmation in another large randomized trial in which groups of patients with different durations of prior dialysis are compared.

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