

Association of Achieved Dialysis Dose with Mortality in the Hemodialysis Study: An Example of “Dose-Targeting Bias”

Tom Greene,* John Daugirdas,[†] Thomas Depner,[‡] Michael Allon,[§] Gerald Beck,* Cameron Chumlea,^{||} James Delmez,[¶] Frank Gotch,** John W. Kusek,^{††} Nathan Levin,^{‡‡} William Owen,^{§§} Gerald Schulman,^{|||} Robert Star,^{††} Robert Toto,^{¶¶} and Garabed Eknoyan;*** for the Hemodialysis Study Group

*Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, Ohio; [†]University of Illinois, School of Medicine, Chicago, Illinois; [‡]Division of Nephrology, University of California Davis, Sacramento, California; [§]University of Alabama at Birmingham, Birmingham, Alabama; ^{||}Department of Community Health, Wright State University, Boonshoft School of Medicine, Dayton, Ohio; [¶]Renal Division, Washington University School of Medicine, St. Louis, Missouri; **University of California, School of Medicine, San Francisco, California; ^{††}National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland; ^{‡‡}Renal Research Institute, Beth Israel Medical Center, New York, New York; ^{§§}University of Tennessee Health Science Center, Memphis, Tennessee; ^{|||}Vanderbilt University Medical Center, Nashville, Tennessee; ^{¶¶}University of Texas Southwestern Medical Center, Dallas, Texas; ***Baylor College of Medicine, Houston, Texas

In the intention-to-treat analysis of the Hemodialysis Study, all-cause mortality did not differ significantly between the high versus standard hemodialysis dose groups. The association of mortality with delivered dose within each of the two randomized treatment groups was examined, and implications for observational studies were considered. Time-dependent Cox regression was used to relate the relative risk (RR) for mortality to the running mean of the achieved equilibrated Kt/V (eKt/V) over the preceding 4 mo. eKt/V was categorized by quintiles within each dose group. Analyses were controlled for case-mix factors and baseline anthropometric volume. Within each randomized dose group, mortality was elevated markedly when achieved eKt/V was in the lowest quintile (RR, 1.93; 95% confidence interval [CI], 1.40 to 2.66; $P < 0.0001$ in the standard-dose group; RR, 2.04; 95% CI, 1.50 to 2.76; $P < 0.0001$ in the high-dose group; RR relative to the middle quintiles). The mortality rate in the lowest eKt/V quintile of the high-dose group was higher than in the full standard-dose group (RR, 1.59; 95% CI, 1.29 to 1.96; $P < 0.0001$). Each 0.1 eKt/V unit below the group median was associated with a 58% higher mortality in the standard-dose group ($P < 0.001$) and a 37% higher mortality in the high-dose group ($P < 0.001$). The magnitude of these dose-mortality effects was seven- to 12-fold higher than the upper limit of the 95% CI from the intention-to-treat analysis. The effects were attenuated in lagged analyses but did not disappear. When dialysis dose is targeted closely, as under the controlled conditions of the Hemodialysis Study, patients with the lowest achieved dose relative to their target dose experience markedly increased mortality, to a degree that is not compatible with a biologic effect of dose. The possibility of similar (albeit smaller) biases should be considered when analyzing observational data sets relating mortality to achieved dose of dialysis.

J Am Soc Nephrol 16: ???–???, 2005. doi: 10.1681/ASN.2005030321

There has been recent interest in reconciling findings from observational studies and randomized clinical trials (1–8). The field of nephrology relies heavily on observational studies, most notably from the United States Renal Data System (USRDS) and large providers of treatment for patients with ESRD (9,10). In particular, by the early 1990s, several observational studies had demonstrated an inverse re-

lationship between mortality and dialysis dose (11–17). In the United States, these findings led to practice guidelines that recommended a minimum single pool Kt/V (spKt/V) of 1.2, corresponding to a urea reduction ratio (URR) of approximately 65% (18).

By the mid-1990s, technological advances led to the feasibility of substantially higher dialysis doses, and a randomized trial, the Hemodialysis (HEMO) Study, was performed to compare outcomes between patients who were assigned to a high-dose group with target spKt/V approximately 1.65 and a standard-dose group with target spKt/V approximately 1.25. Completed in 2001, the HEMO Study found no significant differences in mortality or hospitalization between the dose groups (19).

Received March 25, 2005. Accepted August 11, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Tom Greene, Cleveland Clinic Foundation, Department of Biostatistics and Epidemiology, Wb-4, 9500 Euclid Avenue, Cleveland, OH 44195. Phone: 216-444-9933; Fax: 216-445-2781; E-mail: tgroene@bio.ri.ccf.org

In contrast to the HEMO Study, observational studies continue to suggest that reductions in mortality with increased hemodialysis dose extend to dose levels similar to or higher than the target dose in the high-dose group of the trial (20–24). Because the observational studies had larger sample sizes than the HEMO Study, it is possible that the observational findings may reflect a true dose effect that was too small to be detected by the randomized trial. Alternatively, it is possible that in the observational setting, relationships between dialysis dose and outcome may be subject to bias as a result of confounding from factors linked to both dose and outcome.

Because of the controlled conditions of the HEMO Study, delivered equilibrated Kt/V (eKt/V) values were narrowly distributed within each dose group, making it unlikely that different levels of delivered eKt/V within a dose group could produce detectable biologic effects on mortality. Thus, any relationships of mortality with delivered dose within the individual dose groups more likely are due to other factors, perhaps related to the patient's clinical status, that affect both dialysis dose and mortality. The goal of this study was to take advantage of the controlled setting of the HEMO Study to determine whether factors related to the patient's clinical condition did indeed affect delivered dose and, if so, to consider the implications for observational studies.

Materials and Methods

Study Design

The HEMO Study was a randomized, clinical trial of the effects of dialysis dose and membrane flux (19,25–27) on survival and other outcomes. Using a 2×2 factorial design, qualifying patients were randomized with equal allocation to either a target eKt/V of 1.45 or a target eKt/V of 1.05 and to either high-flux or low-flux membranes. Entry criteria included a three-treatment-per-week dialysis schedule, age 18 to 80 yr, residual renal clearance <1.5 ml/min per 35 L of urea volume, and anticipated ability to achieve a target eKt/V of 1.45 during a 4.5-h dialysis. A total of 1846 patients were randomized in 72 dialysis units affiliated with 15 clinical centers in the United States. The mean follow-up period for mortality was 2.84 yr.

Implementation of Dose Intervention

During the conduct of the trial, eKt/V was computed using the Daugirdas-Schneditz rate equation, $eKt/V = spKt/V - 0.6 K/V + 0.03$ (27,28), where spKt/V was determined from the pre- and postdialysis blood urea nitrogen (BUN) using the two-BUN method (29). Conceptually, eKt/V can be regarded as the ratio of the total treatment clearance of urea, Kt, to the kinetically modeled volume of urea distribution. The kinetic modeling methods are presented elsewhere (27,29–31).

The dose intervention was monitored by monthly kinetic modeling and administered with centrally generated dialysis prescription reports. The central prescription reports provided choices of dialyzer model, blood flow, dialysate flow, and treatment time that resulted in a targeted eKt/V of 1.05 or 1.45, depending on the patient's dose group and running mean kinetic volume (Vm). The running mean Vm was the unweighted average of the kinetic volumes over the last four to six modeled dialyses, with the most extreme value excluded when the coefficient of variation of the kinetic volumes exceeded 10%. The central prescription reports were updated following designated changes in Vm.

When followed, the prescription algorithm ensured that the long-

term mean achieved eKt/V closely approximated the patient's target eKt/V. However, variations in achieved eKt/V could occur as a result of fluctuations in Vm or of failure of the clinical sites to use the central prescriptions. The reasons for these failures included an unwillingness of the patient to remain in the dialysis clinic for the required time, inadequate access blood flow, or a desire by the patient or the patient's physician for a different dose than the study target. Causes of variations in Vm include gain or loss of muscle mass (*i.e.*, total body water) or extracellular fluid and technical problems with the delivery of dialysis, including access recirculation and inaccurate blood pump calibration.

Recalculation of eKt/V

On the basis of data obtained during the trial, the original rate equation was modified to $eKt/V = spKt/V - 0.40 K/V (+ 0.01$ for patients in the high dose group) for reporting the trial results (31). The modified equation gives eKt/V values approximately 0.06 Kt/V units higher than the original rate equation. However, for maintaining consistency in the protocol, the original rate equation was retained to implement the dose intervention throughout the trial. The modification to the formula for eKt/V did not substantially affect the relative values within each dose group in this analysis.

Measurements

Baseline evaluation included the five case-mix factors: Age, gender, race (black *versus* nonblack), diabetic status, and years of dialysis before the trial. An anthropometric estimate of urea volume was obtained using the Watson formula (Vant) (32). Comorbidity was summarized using the Karnofsky index (33), the overall score from the Index of Coexisting Disease (ICED) (34,35), and eight subindices from the ICED evaluating specific domains: Congestive heart failure, arrhythmia, ischemia and other cardiac complications, cerebral and peripheral vascular disease, respiratory disease, nervous system disorders, gastrointestinal disease and hepatitis, and malignancy. Serum creatinine was obtained from local biochemistry measurements.

Kinetic modeling sessions included central measurements of pre- and postdialysis BUN and predialysis serum albumin by nephelometry (Spectra East, Rockleigh, NJ). Access type, occurrence of access revisions during the previous month, hypotensive episodes, and pre- and postdialysis weight and BP were ascertained from the dialysis clinic's flow sheets. Hospitalizations were identified by chart review and patient interview and cross-checked with Medicare records (36).

Data Analysis

All survival analyses were stratified by the 15 clinical centers and conducted with follow-up time censored at transplantation or 4 mo after transfer of patients to nonparticipating dialysis units. Because of its greater familiarity, we use the expression "relative risk" (RR) when referring to hazard ratios in Cox regression analyses.

Predictors of Low eKt/V. Generalized estimating equations for binomial responses with robust SE (37) were used to relate baseline and follow-up factors to the probability that delivered eKt/V fell into the lowest quintile (defined below) for the patient's assigned dose group at each modeled dialysis. Potential predictors of low eKt/V were evaluated individually within each dose group, controlling for baseline Vant, the five case-mix factors, and clinical center.

Association of Mortality with Delivered eKt/V at Entry. Cox regression (38) was used to relate mortality risk to baseline eKt/V, adjusting for Vant and the five case-mix factors. RR were estimated separately in the first year and after 1 yr of follow-up. Baseline eKt/V was defined as the average delivered eKt/V for two baseline kinetic

modeling sessions performed while the patient remained on his or her prestudy dialysis prescription.

Association of Mortality with Delivered eKt/V during Follow-Up. Time-dependent Cox regression was used to relate mortality risk at each follow-up time to the immediately preceding running mean eKt/V. A patient's running mean eKt/V was computed as the unweighted average of the eKt/V values over the preceding 4-mo period, with the exception of the first 4 mo after randomization, when one to three eKt/V values were averaged depending on the number of previous follow-up kinetic modeling sessions. Twenty patients with no follow-up kinetic modeling sessions were excluded. We refer to the running mean eKt/V as the 4-mo running mean, recognizing that fewer measurements were averaged in the first 3 mo.

Both quintile models and segmented regression models were used. For quintile models, the five quintiles of the 4-mo running mean eKt/V values throughout the follow-up period were first obtained for each dose group. At each follow-up time, the most recent 4-mo running mean eKt/V value then was categorized into one of the five quintiles corresponding to the patient's assigned dose group. In segmented regression models, separate slopes relating log RR to achieved eKt/V were estimated below and above the median eKt/V level within each dose group.

Covariate Adjustment. We considered three levels of covariate adjustment: (1) Adjustment for baseline Vant and the five case-mix factors; (2) adjustment for Vant and the case-mix factors plus baseline Karnofsky score and the eight comorbidity indices from the ICED; and (3) adjustment for the above plus baseline levels of predialysis serum albumin, serum creatinine, systolic BP, and equilibrated normalized protein catabolic rate.

Interactions. The basic models were expanded to include interaction terms to evaluate the association of mortality with eKt/V separately for selected patient subgroups. Models with time-dependent interaction terms were used to evaluate the association of mortality with eKt/V separately when different types of access were used (venous catheter, graft, or fistula) and for time periods with and without access issues, defined as the use of a venous catheter or an access procedure at any time in the preceding 4 mo.

Lagged Analyses. The analyses relating mortality risk to the running mean eKt/V over the preceding 4 mo may be sensitive to reverse causality resulting from accentuated effects of the patient's condition on delivered eKt/V in the period immediately preceding death. Thus, the segmented regression analyses were repeated with time lags ranging from 1 to 12 mo between the evaluation of the mortality risk and the 4-mo running mean eKt/V.

In a related analysis, mean eKt/V during the first 4 mo of follow-up were related to mortality during the following year (months 4 to 16). This analysis was repeated for successive periods throughout the first 3 yr, in each case relating mortality in a 1-yr interval to the immediately preceding the 4-mo running mean eKt/V.

Results

Baseline Characteristics

Baseline characteristics and treatment parameters have been described previously (19). Briefly, 56.2% were female, 62.6% were black, 44.6% had diabetes, 80.1% had a history of cardiac disease, mean (SD) age was 57.6 yr (14.0 yr), mean years of dialysis was 3.7 (4.4), and mean anthropometric volume was 34.9 L (6.1 L). At baseline, mean URR, eKt/V (revised HEMO Study formula), treatment time, and blood flow were 73% (5%), 1.43 Kt/V units (0.21 Kt/V units), 214 min (25 min), and 396 ml/min (54 ml/min), respectively.

Follow-Up Measures of Dose

A total of 62,264 kinetic modeling sessions were performed during follow-up. eKt/V or Vm could not be calculated in 4.9% of sessions as a result of treatment interruptions longer than 15 min (2.5% of sessions) or extreme BUN measurements (2.4% of sessions). The analyses of this report are restricted to the first modeling session within each follow-up month. This resulted in excluding an additional 6.4% of sessions. After all exclusions, the data set included 54,841 kinetic modeling sessions conducted in 1826 of the 1846 randomized patients.

During follow-up, the means (SD) of the patient-averaged values of URR, eKt/V (revised HEMO Study formula), treatment time, and blood flow were 66.3% (2.6%), 1.16 Kt/V units (0.09 Kt/V units), 190 min (23 min), and 324 ml/min (63 ml/min), respectively, in the standard-dose group, and 75.2% (2.6%), 1.53 Kt/V units (0.10 Kt/V units), 219 min (23 min), and 410 ml/min (50 ml/min) in the high-dose group.

Running Mean eKt/V Quintiles

Table 1 summarizes treatment parameters for modeling sessions within the 4-mo running mean eKt/V quintiles in the two dose groups. Prescribed eKt/V (defined by the dialysis prescription Kt taken from the dialysis run-sheet and the running mean Vm just before the current session) was similar to the eKt/V target in eight of the 10 quintiles, excepting the top quintile in the standard-dose group and the bottom quintile in the high-dose group. The prescribed eKt/V was at least 10% lower than the high goal target of 1.45 for 23% of modeling sessions in the bottom quintile of the high-dose group. Much of the variation in delivered eKt/V was related to changes in Vm over time; the mean change in Vm from baseline was 16.0% higher in the first compared with the fifth quintile of the standard-dose group (11.6 *versus* -4.4%) and 20.2% higher in the first compared with the fifth quintile of the high-dose group (15.1 *versus* -5.1%).

Predictors of Lower eKt/V

Among the case-mix factors, black race, and greater baseline anthropometric volume were associated with greater odds that delivered eKt/V would fall into the lowest quintiles in both dose groups (Table 2). After controlling for the case-mix factors and baseline anthropometric volume, use of venous catheters and several indices of comorbidity, including lower baseline Karnofsky score, higher baseline ICED score, higher hospitalization rates, and declining serum albumin, each were associated with increased odds of a lowest quintile eKt/V in one or both dose groups.

Association of Mortality with Achieved eKt/V at Baseline

As shown in Table 3, in the first year of follow-up, the relative risk of mortality was 1.71 (95% CI, 1.10 to 2.67) for patients with the lowest baseline eKt/V quintile (eKt/V < 1.24) compared with patients in the middle quintile (eKt/V of 1.35 to 1.45). There was no significant association of baseline eKt/V with mortality after 1 yr.

Association of Mortality with Achieved eKt/V during Follow-Up

Figure 1 shows the relationship of mortality risk during follow-up with the mean eKt/V during the preceding 4 mo.

Table 1. Means of selected treatment characteristics by 4-mo running mean eKt/V quintile^a

Achieved eKt/V Quintile Range (Revised Formula)	URR (%)	Achieved eKt/V (Standard Formula)	Prescribed eKt/V (Standard Formula)	% with Prescribed eKt/V at Least 10% Below Target	Treatment Time (Min)	Blood Flow (ml/min)	V _m (L)	Change in V _m from Baseline
Standard-dose group								
<1.08	63%	0.97	1.04	1.5%	188	328	36.1	+11.6
1.08 to 1.12	65%	1.04	1.06	0.2%	188	325	33.0	+4.2
1.12 to 1.16	66%	1.07	1.07	0.1%	187	326	31.7	+1.0
1.16 to 1.22	67%	1.11	1.08	0.1%	188	326	30.5	-1.5
>1.22	71%	1.25	1.18	0.1%	196	341	29.0	-4.4
High-dose group								
<1.43	71%	1.26	1.35	23.3%	219	413	37.1	+15.1
1.43 to 1.51	74%	1.39	1.42	5.0%	219	417	32.9	+5.4
1.51 to 1.57	76%	1.45	1.45	1.9%	218	416	31.1	+1.7
1.57 to 1.65	77%	1.51	1.47	0.9%	219	417	29.9	-1.1
>1.65	79%	1.61	1.50	0.3%	220	413	27.9	-5.1

^aShown are the mean values of the indicated parameters stratified by quintiles of the 4-mo running mean eKt/V updated at each kinetic modeling session. The analysis is based on 54,841 follow-up kinetic modeling sessions. eKt/V, equilibrated Kt/V; URR, urea reduction ratio; V_m, mean kinetic volume.

The adjusted RR of mortality is significantly elevated in the lower eKt/V quintiles within both dose groups, resulting in an irregular dose-mortality relationship. The adjusted mortality risk was greater in the lowest eKt/V quintile of the high-dose group than in the entire standard-dose group (RR, 1.59; 95% CI, 1.29 to 1.96; $P < 0.0001$), even though the mean achieved eKt/V level in the lowest-quintile high-dose group was higher than the mean eKt/V in the standard-dose group (data not shown). Compared with the middle quintile of the high-dose group, the adjusted relative mortality risk of lowest high-dose quintile was 2.04 (95% CI, 1.50 to 2.74).

As shown in the top row of Table 4, in the standard-dose group, a 0.10 lower mean eKt/V was associated with a 58% (95% CI, 33% to 89%; $P < 0.00001$) increased mortality risk for eKt/V values less than the group median of 1.14. Similarly, in the high-dose group, a 0.10 lower eKt/V was associated with a 37% (95% CI, 25% to 50%; $P < 0.00001$) increased mortality risk for eKt/V values <1.54. The elevated adjusted RR for mortality at the lower eKt/V values within each dose group were seen consistently irrespective of whether baseline anthropometric volume or indicators of baseline comorbidity were included as covariates (data not shown).

As indicated by the interaction P values in Table 4, the increase in mortality risk at lower achieved eKt/V was larger for women than men among patients who were randomized to the high goal. The increase in mortality at lower eKt/V levels was similar between larger and smaller patients in both dose groups and also did not differ significantly between different types of access. Among patients who were randomized to the standard dose, the increase in mortality at lower eKt/V levels was larger among patients without recent access procedures or hospitalizations.

Association of Mortality with Lagged eKt/V

Figure 2A relates mortality at each follow-up time point to the running mean eKt/V lagged by varying numbers of months. In the standard-dose group (□), the RR per 0.10 reduction in eKt/V attenuated by approximately half for lag periods of 6 mo or greater. In the high-dose group (■), the strength of the association of mortality with reduced eKt/V largely persisted and remained statistically significant (with $P < 0.001$) with lags up to 12 mo.

Consistent with the lagged analyses in Figure 2A, Figure 2B shows that the RR relating mortality during a given 1-yr period to the previous 4-mo running mean eKt/V tend to be moderately reduced compared with the time-dependent analysis in Figure 1. The variability in these RR over the successive assessment periods is increased as a result of the limited number of deaths occurring within any 1-yr interval and the use of different intervals for V_m in each analysis. However, the average RR remains >1, particularly in the high-dose group.

Discussion

The analyses of mortality in this report are *as-treated* analyses, in which the outcome is related to the treatment actually received. It is widely recognized that *as-treated* analyses are subject to bias because patients who are at increased risk for poor outcomes are often also at increased risk for poor compliance or inability to attain intervention targets (39–42). To avoid such biases, primary conclusions from randomized trials are based on intention-to-treat analyses that compare patients according to their randomized assignment.

The HEMO Study provides a clear example in which *as-treated* analyses are contradicted by the intention-to-treat results. In the intention-to-treat analysis, the RR for mortality for the high- versus standard-dose group was 0.96 (95% CI, 0.84 to

Table 2. Predictors of occurrence of eKt/V within lowest quintile for patient's assigned dose group^a

Analysis	Factor	Standard-Dose Group			High-Dose Group		
		OR	95% CI	P	OR	95% CI	P
Multivariate analysis of case mix factors ^b	Age (per 10 yr)	1.01	(0.98 to 1.05)	0.40	1.03	(0.98 to 1.08)	0.27
	Diabetic	1.09	(1.00 to 1.20)	0.06	0.99	(0.87 to 1.14)	0.93
	Black race	1.25	(1.11 to 1.40)	0.0002	1.30	(1.11 to 1.52)	0.001
	Female	0.99	(0.87 to 1.12)	0.84	1.01	(0.83 to 1.22)	0.92
	Years on dialysis	1.00	(0.99 to 1.01)	0.44	1.00	(0.98 to 1.02)	0.95
	Baseline Vant (per 5 L)	1.12	(1.06 to 1.18)	<0.0001	1.21	(1.12 to 1.32)	<0.0001
Baseline comorbidity, controlling for case mix ^c	Baseline ICED (per 1 unit)	1.08	(1.02 to 1.14)	0.005	1.05	(0.97 to 1.14)	0.22
	Baseline Karnofsky (per 10%)	0.95	(0.93 to 0.98)	0.0004	0.94	(0.90 to 0.98)	0.004
	Baseline albumin (per 0.5 g/dl)	0.79	(0.60 to 1.02)	0.07	0.78	(0.53 to 1.15)	0.22
	Baseline systolic BP	1.00	(0.99 to 1.02)	0.95	0.98	(0.97 to 1.00)	0.02
Follow-up factors, controlling for case-mix factors ^d	Increase in albumin (per 0.5 g/dl)	0.71	(0.41 to 1.23)	0.22	0.78	(0.39 to 1.58)	0.50
	Decrease in albumin (per 0.5 g/dl)	1.65	(1.15 to 2.38)	0.007	2.35	(1.54 to 3.60)	<0.0001
	Increase in weight (per 5 kg)	1.06	(1.00 to 1.13)	0.04	1.03	(0.94 to 1.13)	0.49
	Decrease in weight (per 5 kg)	1.00	(0.94 to 1.06)	0.88	0.92	(0.85 to 1.00)	0.04
	Graft (<i>versus</i> fistula)	0.84	(0.76 to 0.92)	0.0002	0.64	(0.56 to 0.74)	<0.0001
	Catheter (<i>versus</i> fistula)	1.25	(1.05 to 1.48)	0.01	2.31	(1.91 to 2.80)	<0.0001
	Access hospitalization rate (past 4 mo)	1.09	(1.05 to 1.12)	<0.0001	1.15	(1.12 to 1.18)	<0.0001
	Nonaccess hospitalization rate (past 4 mo)	1.02	(1.00 to 1.03)	0.03	1.02	(1.00 to 1.04)	0.02

^aOR, odds ratio; ICED, Index of Coexisting Disease; Vant, anthropometric estimate of urea volume.

^bModel also controlled for flux group and clinical center.

^cEach indicated factor was analyzed separately, controlling for the case-mix variables in the first panel plus flux group and clinical center.

^dEach indicated factor was analyzed separately, controlling for the case-mix variables in the first panel plus flux group and clinical center. Models for change in serum albumin also controlled for baseline albumin. Follow-up albumin and weight values lagged by 1 mo before calculation of change from baseline to avoid coupling as a result of hemodilution effects on weight and solute concentrations. Segmented regression was used to separately estimate effects of increases and decreases in serum albumin and weight.

Table 3. Association of mortality with baseline eKt/V^a

Baseline eKt/V Quintile	Year 1 of Follow-Up		After Year 1 of Follow-Up	
	RR	95% CI	RR	95% CI
<1.24	1.71 ^b	(1.10 to 2.67)	0.82	(0.62 to 1.07)
1.24 to 1.35	1.17	(0.74 to 1.86)	0.88	(0.68 to 1.14)
1.35 to 1.45	1.00 (reference)	—	1.00 (reference)	—
1.45 to 1.58	1.22	(0.79 to 1.90)	0.95	(0.73 to 1.22)
>1.58	1.32	(0.85 to 2.04)	1.10	(0.86 to 1.42)

^aShown are relative risks (RR) for mortality for patients within designated baseline eKt/V quintiles *versus* the middle quintile (baseline eKt/V, 1.35 to 1.45). RR were estimated separately for the first 1 yr of follow-up and after 1 yr and adjusted for the following baseline factors: Age, diabetic status, race, gender, years of dialysis, anthropometric V, and randomized flux group. Analyses were stratified by clinical center.

^bP < 0.05.

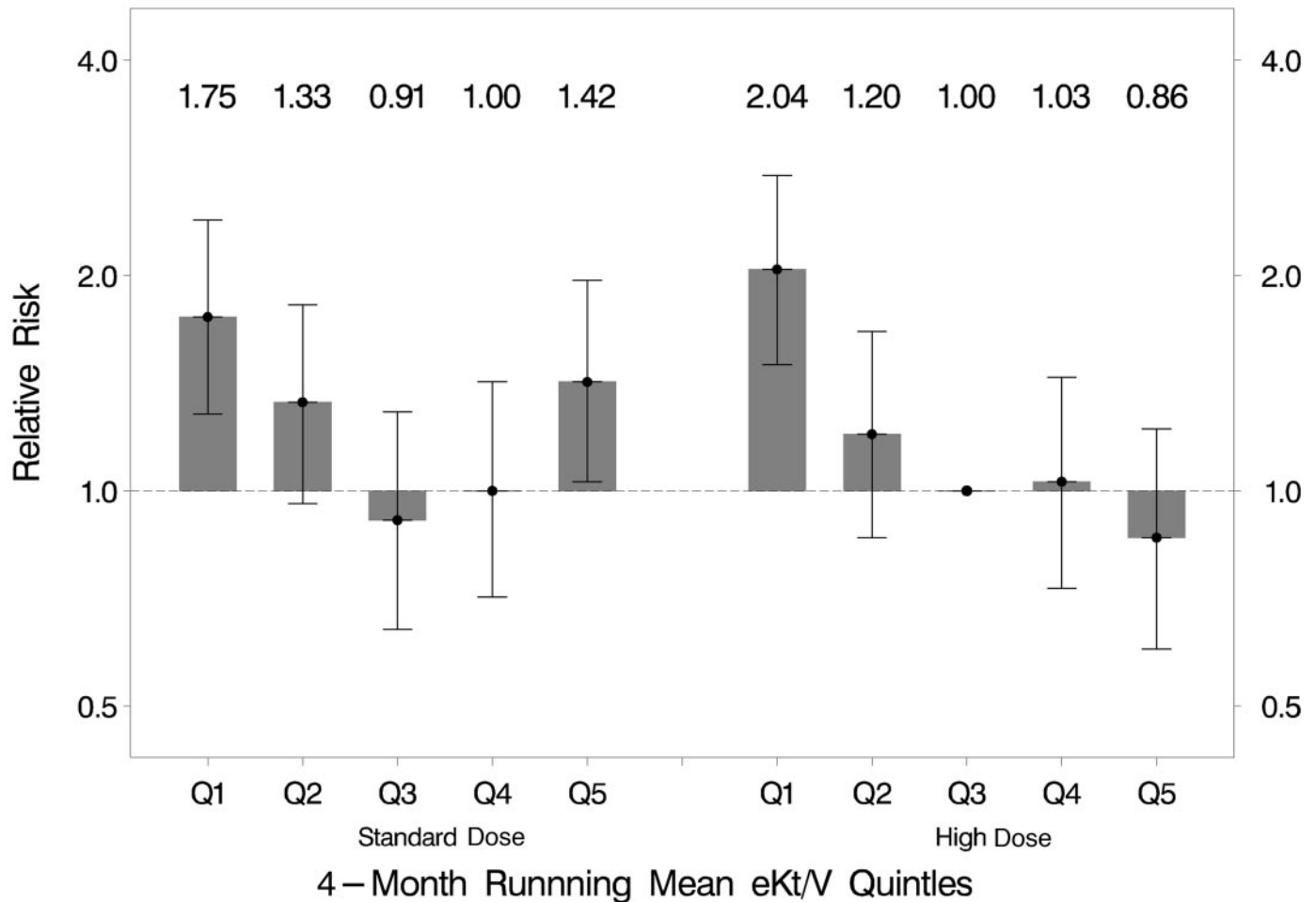


Figure 1. Association of mortality with the most recent 4-mo mean equilibrated Kt/V (eKt/V). Shown are the relative risks (RR; and 95% confidence intervals [CI]) of mortality within each of the five quintiles of the 4-mo average eKt/V values of the standard-dose group and the first, second, fourth, and fifth quintiles of the high-dose group, with the middle quintile of the high-dose group as the reference. Numerical values of the RR are provided on the top of the plot. The RR were computed by time-dependent Cox regression with stratification by clinical center and adjustment for age, gender, race, diabetic status, years of dialysis before the trial, and anthropometric volume.

1.10), or, conversely, the RR for the standard- versus high-dose group was 1.04 (95% CI, 0.91 to 1.19). The mean difference in achieved eKt/V between the two dose groups was 0.37 Kt/V units, so the intention-to-treat effect represents an average risk increase of 4% per 0.37 decrease in eKt/V, or, equivalently, a 1.1% average increase in risk per 0.10 reduction in eKt/V. The upper limit of the 95% CI for standard- versus high-dose RR similarly represents a maximum risk increase of 4.7% per 0.10 reduction of eKt/V. By contrast, in the as-treated analysis, each 0.10 reduction in achieved eKt/V below the group median was associated with risk increases of 58% in the standard-dose group and 37% in the high-dose group, far exceeding the intention-to-treat upper confidence bound. Furthermore, patients in the lowest achieved eKt/V quintile of the high-dose group experienced a 59% greater risk for mortality than did patients in the standard-dose group, despite their higher achieved eKt/V. Thus, the elevated risk for patients with comparatively low eKt/V levels in each dose group must reflect extraneous factors

that are associated with both increased mortality and lower eKt/V.

What these factors are is not entirely clear, and somewhat different factors may be operating in the two dose groups. Whereas almost all patients who were assigned to the HEMO standard-dose group were able to attain the 1.05 target, the mean prescribed eKt/V was at least 10% less than the high-dose target for 23% of the sessions in the lowest eKt/V quintile in the high-dose arm, indicating that a substantial number of patients in that group were unable or unwilling to achieve the target dose (Table 1). Larger anthropometric volume, increases in V_m over time, and markers of comorbidity including hospitalizations and declining serum albumin were associated with lower values of eKt/V in both dose groups (Tables 1 and 2). Black race was also associated with a greater propensity for lower eKt/V, possibly because black individuals have a higher average muscle mass and total body water and hence a higher V_m than white individuals of a similar height and weight (43).

Table 4. Association of mortality with previous 4-mo mean eKt/V by patient and treatment characteristics^a

Subgroup or Treatment Characteristic	RR per 0.10 Decrease in Mean eKt/V for eKt/V < 1.14 in Standard-Dose Group			RR per 0.10 Decrease in Mean eKt/V for eKt/V < 1.54 in High-Dose Group		
	RR	95% CI	Interaction <i>P</i>	RR	95% CI	Interaction <i>P</i>
All patients	1.58	1.33 to 1.89	—	1.37	1.25 to 1.50	—
Male	1.44	1.08 to 1.94	0.40	1.20	1.04 to 1.39	0.02
Female	1.69	1.36 to 2.08		1.50	1.34 to 1.68	
Vant < 35 L	1.56	1.23 to 1.98	0.89	1.36	1.21 to 1.53	0.91
Vant > 35 L	1.60	1.24 to 1.06		1.38	1.20 to 1.58	
No access issues	1.86	1.47 to 2.36	0.02	1.41	1.25 to 1.59	0.20
≥1 access issue ^b	1.20	0.92 to 1.56		1.26	1.10 to 1.45	
Fistula	1.68	1.16 to 2.42	0.17	1.15	0.93 to 1.42	0.10
Graft	1.62	1.26 to 2.07		1.44	1.27 to 1.64	
Venous catheter	1.03	0.67 to 1.59		1.18	0.96 to 1.44	

^aAll RR adjusted for case-mix factors and anthropometric V. The analyses were stratified by clinical center.

^bIndicates at least one of the following in the previous 4 mo: (1) An access-related hospitalization, (2) an access modification or change in the type of access, or (3) use of a venous catheter.

It is well known that mortality is increased in patients who receive dialysis with venous catheters (44,45). Catheters can limit blood flow or cause recirculation that prevents delivery of an adequate eKt/V. It is conceivable that the type of vascular access may have influenced the relationship between eKt/V and mortality in the HEMO Study. However, although use of catheters was a strong predictor of a lowest quintile eKt/V in both dose groups (Table 2), the low eKt/V–mortality association strengthened, rather than weakened, after periods without any recorded access modifications or use of catheters. Other sensitivity analyses (not reported here) indicated that this result persists when we also exclude periods in which a dialysis interruption, shortfall in treatment time, or change in blood or dialysate flow was recorded for one or more modeled dialyses. Thus, access-related issues and other technical factors that influence V_m do not, by themselves, seem to explain the large bias in the as-treated analysis.

The most recent large-scale studies from the USRDS and Dialysis Outcomes and Practice Patterns Study (23,46) have reported estimated dose effects that are close to or greater than the 95% upper confidence bound of 4.7% per 0.10 reduction in eKt/V. Thus, the biases observed in the HEMO Study as-treated analyses are larger than the effects of dose on mortality reported in recent observational studies. This indicates that the magnitudes of the bias estimates from the HEMO trial do not generalize directly to observational data sets. However, this also raises the question of whether estimated dose effects in observational studies may be biased upward, albeit to a lesser extent than in the HEMO as-treated analyses. At least three factors may have led to different results between the HEMO Study as-treated analyses and observational studies: (1) The analytic methods, (2) the controlled conditions of the HEMO trial, and (3) the patients included in the studies.

Regarding analytic methods, the consistency of the HEMO as-treated results when adjusted for a wide range of baseline covari-

ates suggests that the differences are unlikely to be explained by differences in covariate adjustment strategies. However, the results of the as-treated analyses, which related mortality to the mean eKt/V over the immediately preceding 4-mo, may have been especially sensitive to the effects of deteriorating conditions immediately preceding death. By contrast, most observational studies have related mortality over a 1- to 1.5-yr follow-up period to measured dose at the start of the study, resulting in an average lag time of 0.5 to 0.75 yr. In fact, some attenuation was observed in the RR for lower eKt/V when a lag time was introduced in the HEMO as-treated analyses (Figure 2, A and B). However, even with a lag of 1 yr, the RR associated with lower eKt/V remained >1, particularly in the high-dose group, whose conditions more closely reflect current treatment practice.

When dialysis dose is targeted precisely, as in the HEMO Study, variations in V_m and comorbidities may lead to prescription shortfalls accounting for a greater proportion of the variation in delivered dose than in the observational setting, where prescribed dose may depend on variations in practice patterns and other factors. Thus, the confounding effects in the HEMO Study as-treated analyses are likely to have been increased as a result of the controlled conditions of the trial. The strong relationship between baseline eKt/V and mortality in the first year after randomization suggests also that because HEMO patients were selected on the basis of their ability to achieve the high-dose target, a lower delivered eKt/V at baseline was a surrogate for risk factors associated with mortality risk.

Although their effects should be reduced, the confounding relationships involving eKt/V and comorbid conditions associated with dose-target shortfalls seem likely to occur also in the observational setting. The strategy of targeting a URR of at least 75% (corresponding roughly to the HEMO Study high-dose target) is consistent with the practice in many dialysis units at the present time. If such a dose-targeting bias does

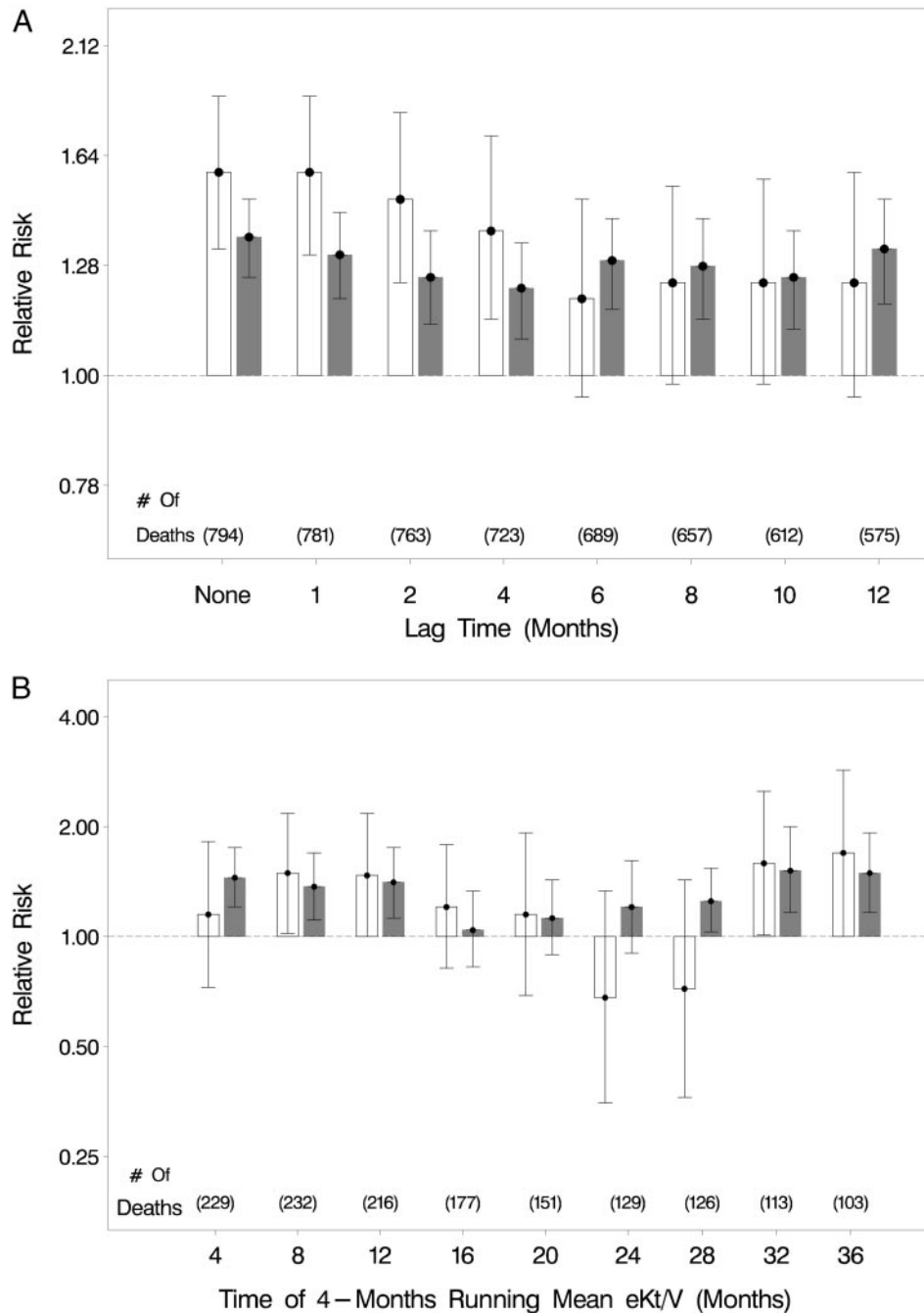


Figure 2. Panel A displays the results of time-dependent Cox regression analyses relating mortality at each follow-up time point to the running mean eKt/V lagged by the indicated numbers of months. Panel B displays results of standard Cox regressions relating mortality during the designated 1-yr intervals to the running mean eKt/V during the preceding 4 mo. Both panels present RR per 0.10 reduction in eKt/V below the median values in standard dose group (□) and the high dose group (■), with stratification by clinical center and adjustment for age, gender, race, diabetic status, years of dialysis prior to the trial, and anthropometric volume. The scales of the vertical axes differ between the panels due to a greater variability of the RR in B compared to A, which resulted, in part, from the smaller number of events in the 1-yr assessment periods of B.

exist, then regardless of how much the average dose is increased, patients who receive lower amounts of dialysis may always seem to do worse. One explanation for a report that dose thresholds seemed to increase steadily in successive analyses of a national database between 1994 and 1997 (24) is that increasing *de facto* dose targets over this period may have

shifted the dose-targeting bias to higher dose levels. Conceivably, a dose-targeting bias, if unrecognized, might lead to a never-ending cycle of recommendations for ever higher dialysis doses.

The randomized comparisons of the HEMO trial suggested a stronger effect of dose in women than in men (46), a phenom-

enon also reported from recent observational analyses of achieved dose from the USRDS and international data (47). However, the possibility of a larger dose-targeting bias in women than in men, suggested in Table 4 of this study, indicates the need for continuing caution when interpreting this subgroup result.

The discrepancy of the as-treated analysis with the intention-to-treat analysis in the HEMO trial is in some respects analogous to a similar discrepancy in a previous randomized trial of the effect of normalizing hematocrit level with administration of erythropoietin in hemodialysis patients with congestive heart failure or ischemic heart disease (48). In that study, higher achieved hematocrit levels were associated with lower mortality within the individual treatment arms. However, the intention-to-treat analysis found no significant difference in mortality between the randomized groups.

In summary, the dose-targeting bias that was revealed under the controlled conditions of the HEMO Study emphasizes that caution is necessary when interpreting nonrandomized relationships between dialysis dose and outcome. However, we caution against sweeping generalizations of the implications of these findings for observational research. The large majority of clinical questions will continue to be addressed by observational studies as a result of the limited number of randomized trials that can be conducted. Continued advances in statistical methods and increased ability to identify sources of confounding will lead to continuing improvements in the quality of observational inference.

References

- Concato J, Shah Nirav, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 342: 1887–1892, 2000
- Benson K, Hartz AJ: A comparison of observational studies and randomized, controlled trials: Special Articles. *N Engl J Med* 342: 1878–1886, 2000
- Pocock SJ, Elbourne DR: Randomized trials or observational tribulations? *N Engl J Med* 342: 1907–1909, 2000
- Prentice RL: Methodologic challenges in chronic disease population research. *Biostatistics* 2: 365–381, 2001
- Dunn D: The dangers of inferring treatment effects from observational data: A case study in HIV infection. *Control Clin Trials* 23: 106–110, 2002
- Lane C: Postmenopausal hormone replacement therapy: How could we have been so wrong? *Ann Intern Med* 137: 290, 2002
- Grodstein F, Clarkson TB, Manson JE: Understanding the divergent data on postmenopausal hormone therapy: Sounding board. *N Engl J Med* 348: 645–650, 2003
- Machens K, Schmidt-Gollwitzer K: Issues to debate on the Women's Health Initiative (WHI) study. Hormone replacement therapy: An epidemiological dilemma? *Hum Reprod* 18: 1992–1999, 2003
- Whitman W: *US Renal Data System, USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2004
- Lowrie EG, Huang WH, Lew NL, Liu Y: The relative contribution of measured variables to death risk among hemodialysis patients. In: *Death on Hemodialysis: Preventable or Inevitable?* edited by Hingham MA, Friedman E, Dordrecht, Kluwer Academic Publishers, 1994, pp 121–141
- Lowrie E, Lew N, Liu Y: The effect of difference in urea reduction ration (URR) on death risk in hemodialysis patients: A preliminary analysis. Memorandum to Medical Directors, 1991
- Hakim RM, Depner TA, Parker TF: Adequacy of hemodialysis. *Am J Kidney Dis* 20: 107–123, 1992
- Owen W, Lew N, Liu Y, Lowrie E, Lazarus M: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329: 1001–1006, 1993
- Hakim RM, Breyer J, Ismail N, Schulman G: Effects of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 23: 661–669, 1994
- Parker 3rd TF, Husni L, Huang W, Lew N, Lowrie EG; Dallas Nephrology Associates: Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. *Am J Kidney Dis* 23: 670–680, 1994
- Collins AJ, Ma JZ, Umen A, Keshaviah P: Urea index and other predictors of hemodialysis patient survival. *Am J Kidney Dis* 23: 272–282, 1994
- Lowrie EG: Chronic dialysis treatment: Clinical outcome and related processes of care. *Am J Kidney Dis* 24: 255–266, 1994
- Hemodialysis Adequacy Work Group: NKF-DOQI practice guidelines for hemodialysis adequacy. *Am J Kidney Dis* 30[Suppl 2]: S15–S66, 1997
- Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 19: 347: 2010–2019, 2002
- Held PJ, Port FK, Wolfe RA, Stannard DC, Carroll CE, Daugirdas JT, Bloembergen WE, Greer JW, Hakim RM: The dose of hemodialysis and patient mortality. *Kidney Int* 50: 550–556, 1996
- Li Z, Lew NL, J Lazarus M, Lowrie EG: Comparing the urea reduction ratio and the urea product as outcome-based measures of hemodialysis dose. *Am J Kidney Dis* 35: 598–605, 2000
- Wolfe RA, Ashby VB, Daugirdas JT, Agodoa LYC, Jones CA, Port FK: Body size, dose of hemodialysis and mortality. *Am J Kidney Dis* 35: 80–88, 2000
- Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA: Dialysis dose and body mass index are strongly associated with survival in hemodialysis in patients. *J Am Soc Nephrol* 13: 1061–1066, 2002
- Szczzech LA, Lowrie EG, Li Z, Lew NL, Lazarus JM, Owen WF Jr: Changing hemodialysis thresholds for optimal survival. *Kidney Int* 59: 738–745, 2001
- Greene T, Beck GJ, Gassman JJ, Gotch FA, Kusek JW, Levey AS, Levin NW, Schulman G, Eknoyan G: Design and statistical issues of the hemodialysis (HEMO) study. *Control Clin Trials* 21: 502–525, 2000
- Eknoyan G, Levey AS, Beck GJ, Agodoa LY, Daugirdas JT, Kusek JW, Levin NW, Schulman G: The Hemodialysis

- (HEMO) Study: Rationale for selection of interventions. *Semin Dial* 9: 24–33, 1996
27. Daugirdas JT, Depner TA, Gotch FA, Greene T, Keshaviah P, Levin NW, Schulman G. Comparison of methods to predict equilibrated Kt/V in the HEMO Pilot Study. *Kidney Int* 52: 1395–1405, 1997
 28. Daugirdas JT, Schneditz D: Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two pool urea kinetic analysis. *ASAIO J* 41: M719–M724, 1995
 29. Depner TA: *Prescribing Hemodialysis: A Guide to Urea Modeling*, Dordrecht, the Netherlands, Kluwer Academic, 1991
 30. Daugirdas JT, Greene T, Depner TA, Gotch FA, Star RA; the Hemodialysis (HEMO) Study Group: Relation between apparent (single-pool) and true (double-pool) urea distribution volume in the HEMO Study. *Kidney Int* 56: 1928–1933, 1999
 31. Daugirdas JT, Greene T, Depner TA, Leypoldt J, Gotch F, Schulman G, Star R; for the HEMO Study Group: Factors affecting postdialysis rebound in serum urea concentration, including the rate of dialysis: Results from the HEMO Study. *J Am Soc Nephrol* 15: 194–203, 2004
 32. Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements: *Am J Clin Nutr* 33: 27–39, 1980
 33. McClellan WM, Anson C, Birkeli K, Tuttle E: Functional status and quality of life: Predictor of early mortality among patients entering treatment for end-stage renal disease. *J Clin Epidemiol* 44: 83–89, 1991
 34. Greenfield S, Nelson E: Recent developments and future issues in the use of health status assessment measures in clinical settings. *Med Care* 30: 23–41, 1992
 35. Miskulin DC, Athienites NV, Yan G, Martin AA, Ornt DB, Kusek JW, Meyer KB, Levey AS; Hemodialysis (HEMO) Study Group: Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. *Kidney Int* 60: 1498–1510, 2001
 36. Beck G, Weiss B, Collins A, Gassman J, Levey A, Ornt D, Radeva M, Yan G; the HEMO Study Group: Comparison of hospitalization identified in a multi-center clinical trial with an external national database. *Control Clin Trials* 24: 133S, 2003
 37. Diggle P, Liang K, Zeger S: *Analysis of Longitudinal Data*, London, Chapman & Hall, 1994
 38. Therneau TM, Grambsch PM: *Modeling Survival Data: Extending the Cox Model*, New York, Springer, 2000
 39. Piantadosi S: *Clinical Trials: A Methodologic Perspective. Section 11.3: Treatment Non-Adherence*, New York, Wiley, 1997 pp 276–281
 40. Peduzzi P, Wittes J, Holford T: Intent-to-treat analysis and the problem of crossovers. An example from the Veterans Administration coronary bypass surgery study. *J Thorac Cardiovasc Surg* 101: 481–487, 1991
 41. Peduzzi P, Wittes J, Detre K, Holford T: Analysis as-randomized and the problem of non-adherence: An example from the Veterans Affairs Randomized Trial of Coronary Artery Bypass Surgery. *Stat Med* 12: 1185–1195, 1993
 42. Frangakis C, Rubin D: Addressing complications of intention-to-treat analysis in the combined presence of all-or-none treatment-noncompliance and subsequent missing outcomes. *Biometrika* 86: 365–379, 1999
 43. Chumlea WC, Guo SS, Zeller CM, Reo NV, Baumgartner RN, Garry P, Wang J, Pierson RN, Heymsfield SB: Total body water reference values and prediction equations for adults. *Kidney Int* 59: 2250–2258, 2001
 44. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK: Type of vascular access and mortality in US hemodialysis patients. *Kidney Int* 60: 1443–1451, 2001
 45. Xue JL, Dahl D, Ebben JP, Collins AJ: The association of initial hemodialysis access type with mortality outcomes in elderly Medicare ESRD patients. *Am J Kidney Dis* 42: 1013–1019, 2003
 46. Depner T, Daugirdas J, Greene T, Allon M, Beck G, Chumlea C, Delmez J, Gotch F, Kusek J, Levin N, Macon E, Milford E, Owen W, Star R, Toto R, Eknoyan G for the HEMO Study Group: Dialysis dose and effect of gender and body size on outcome in the HEMO Study. *Kidney Int* 65: 1386–1394, 2004
 47. Port FK, Wolfe RA, Hulbert-Shearon TE, McCullough KP, Ashby VB, Held PJ: High dialysis dose is associated with lower mortality among women but not among men. *Am J Kidney Dis* 43: 1014–1023, 2004
 48. Besarab A, Bolton W, Browne J, Egrie J, Nissenson A, Okamoto D, Schwab S, Goodkin D: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998