
Design Paper

Design and Statistical Issues of the Hemodialysis (HEMO) Study

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ABSTRACT: The Hemodialysis Study is a multicenter clinical trial of hemodialysis prescriptions for patients with end stage renal disease. Participants from over 65 dialysis facilities associated with 15 clinical centers in the United States are randomized in a 2×2 factorial design to dialysis prescriptions targeted to a standard dose (equilibrated $Kt/V = 1.05$) or a high dose (equilibrated $Kt/V = 1.45$), and to either low or high flux membranes. The primary outcome variable is mortality; major secondary outcomes are defined based on hospitalizations due to cardiovascular or infectious complications, and on the decline of serum albumin. The Outcome Committee, consisting of study investigators, uses a blinded review system to classify causes of death and hospitalizations related to the major secondary outcomes. The dialysis dose intervention is directed by the Data Coordinating Center using urea kinetic modeling programs that analyze results from dialysis treatments to monitor adherence to the study targets, adjust suggested dialysis prescriptions, and assist in trouble-shooting problems with the delivery of dialysis. The study design has adequate power to detect reductions in mortality rate equal to 25% of

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Received November 22, 1999; accepted February 10, 2000.

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the projected baseline mortality rate for both of the interventions. *Control Clin Trials* 2000;21:502–525 © Elsevier Science Inc. 2000

KEY WORDS: *Dialysis, renal failure, end stage renal disease, urea kinetic modeling, clinical trial*

INTRODUCTION

End stage renal disease (ESRD) is a chronic condition in which kidney function is impaired to the extent that the patient's survival requires removal of toxins from the blood by dialysis therapy or kidney transplantation. ESRD is a rapidly growing health-care problem in the United States, with approximately 304,000 prevalent and 79,000 incident patients in 1997 [1]. The prevalence and incidence rates are both increasing by approximately 5% per year. The estimated direct monetary cost of treating ESRD exceeded \$15.6 billion in 1997, and is increasing [2].

Due in part to a limited availability of kidneys for transplantation, hemodialysis (HD) is the primary method of treatment and is currently used for approximately 61% of U.S. ESRD patients. HD removes toxins from the body by extracorporeal circulation of the blood through a semipermeable membrane, referred to as a dialyzer. The toxins are removed primarily by diffusion across the membrane to a dialysate solution which is circulated on the opposite side of the membrane. A surgically constructed vascular access connects the extracorporeal circuit to the patient's vascular system. Treatments are almost always performed three times per week in specially equipped dialysis facilities for 3–4 hours per treatment.

In spite of numerous therapeutic advances since dialysis therapy became widespread in the 1960s, mortality and hospitalization rates of dialysis patients remain high. In the U.S., median survival of dialysis patients is less than 4 years, and life expectancy is one-third to one-fifth of that of the general population at any given age [3]. Dialysis patients average approximately 1.4 hospital admissions per year for an average of 11 hospital days per patient. Reported mortality rates of dialysis patients are higher in the United States than in most other developed countries [4]. It is not clear to what extent this is due to a greater tendency in the United States to provide dialysis to patients with higher comorbidity, or to differences in the general medical care of dialysis patients between the United States and other countries. In any case, the past two decades have seen consistent increases in the mean age and the prevalence of comorbid conditions in the U.S. dialysis population [5].

In response to the increasing prevalence of ESRD and the poor outcome of dialysis patients, the National Institute of Digestive and Kidney Disease (NIDDK) of the National Institutes of Health (NIH) funded the Hemodialysis (HEMO) Study to determine if the mortality and morbidity of HD patients can be reduced by modifying the dose of dialysis and the type of membrane used for the removal of toxins from the blood. This paper summarizes the design and conduct of the HEMO Study. Particular attention is given to the approaches taken to confront methodological obstacles to achieving the objectives of the study.

BACKGROUND AND RATIONALE OF THE INTERVENTIONS

The HEMO Study is designed to test two interventions: the dialysis dose (or Kt/V) intervention and the membrane flux intervention. The rationale for investigating these two interventions are described below. See [6] for additional details.

Dialysis Dose Intervention

The NIH-funded National Cooperative Dialysis Study (NCDS), completed in 1981, was the only major clinical trial prior to the HEMO Study to examine prospectively the effect of dialysis dose on patient outcome. The NCDS used the concentration of urea in the blood (BUN) as a measure of the dose of dialysis, with lower average BUNs indicating a higher dialysis dose. Urea is a low molecular weight solute, resulting from the catabolism of protein, whose concentration is widely used as a surrogate for the level of toxins in the blood. The NCDS showed that patients randomized to a low time-averaged BUN target had fewer comorbid events than patients randomized to a higher time-averaged BUN target [7–9].

After the NCDS, researchers observed that the interpretation of the average BUN is confounded by variations in diet, as a low average BUN may indicate either a high dialysis dose or a low protein intake in poorly nourished patients [10]. Due to this limitation, the dimensionless quantity $spKt/V$, which assesses dialysis dose independently of protein intake, is now widely used instead of the average BUN. In the expression $spKt/V$, K represents the dialyzer clearance, which is the rate of urea removal expressed as the volume of body water cleared of urea per unit time, t represents the total time of the dialysis treatment, and V represents the total volume of body water in which the urea is distributed. The prefix *sp* refers to the formulation of Kt/V using a one-compartment kinetic model assuming a uniform distribution of urea throughout a “single pool” of body water. Under the one compartment model, $spKt/V$ can be calculated from readily available measurements, and is primarily determined from the reduction in the BUN from the beginning to the end of dialysis [11]. Post-hoc correlational analyses of the NCDS found an increased rate of adverse events when $spKt/V$ was below 0.8, which led to a general recommendation that $spKt/V$ should be at least 1.0 [10].

During the 1980s and 1990s, technological improvements provided the possibility of high-efficiency dialysis with increased dialyzer clearance K , allowing for levels of $spKt/V$ which substantially exceed 1.0 within 3-5 hours of treatment in most patients. Several observational studies have reported lower mortality rates at levels of $spKt/V$ greater than 1.2 or 1.4 than at 1.0 [12–15]. As a result, clinical practice guidelines now call for dialysis prescriptions to maintain $spKt/V$ at or above 1.2 [16]. However, the observational studies suggesting benefits of $spKt/V$ of 1.2 or higher are subject to confounding by extraneous factors, and a benefit of such high levels of $spKt/V$ has not been established in a randomized clinical trial.

Recently it has been recognized that the BUN increases sharply in the 30-60 minutes after dialysis (postdialysis rebound), reflecting a disequilibrium that develops during dialysis because the concentration of urea in the peripheral

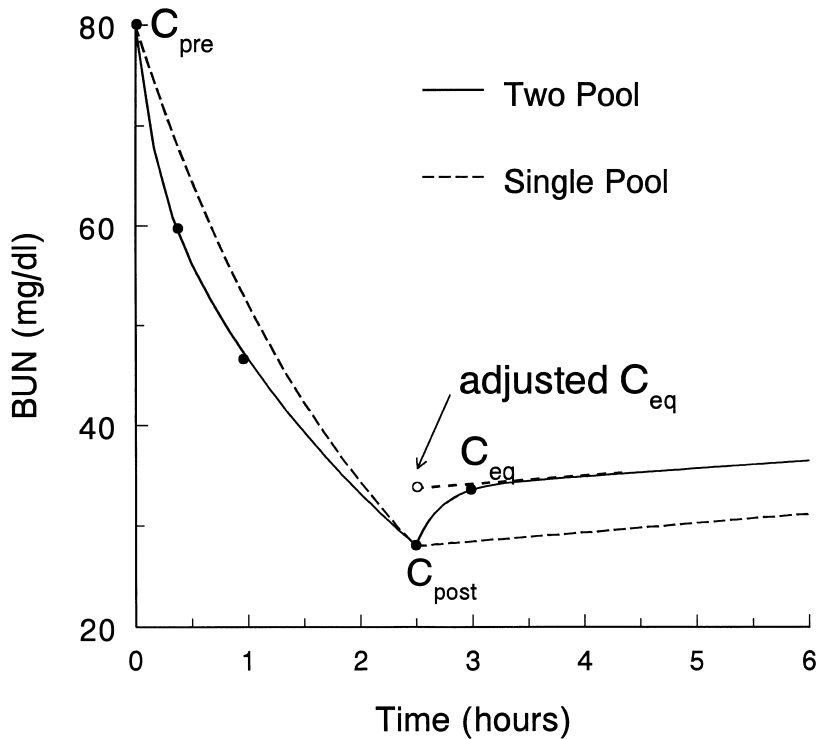


Figure 1 Change in BUN during and after dialysis. Shown are BUN concentration curves during and after a dialysis session based on single-pool (dashed line) and double-pool (solid line) kinetic models. The greater fall in BUN during dialysis and the rebound after dialysis results from urea disequilibrium within the patient. C_{pre} = BUN before dialysis, C_{post} = BUN immediately after dialysis, C_{eq} = BUN 30 minutes after the end of dialysis, adjusted C_{eq} = C_{eq} after subtracting the effect of urea generation for 30 minutes.

blood declines more rapidly than in relatively poorly perfused regions such as skeletal muscle that serve as a reservoir for urea [17–18]. As a result, $spKt/V$ overestimates the “true” dialysis dose when it is based on the change in BUN from the beginning to the immediate end of dialysis (see Figure 1). To avoid a bias due to variations in postdialysis rebound, dialysis dose in the HEMO Study is expressed in terms of equilibrated Kt/V (eKt/V), an alternative formulation of Kt/V based on kinetic models which adjust for the disequilibrium of urea during dialysis [19–20].

The dialysis dose intervention of the HEMO Study randomizes patients to target eKt/V levels of 1.05 (standard Kt/V goal) or 1.45 (high Kt/V goal). Under high-efficiency dialysis, the average eKt/V is approximately 0.2 Kt/V units lower than $spKt/V$, so that these target levels correspond to $spKt/V$ values of approximately 1.25 and 1.65. The $spKt/V$ of 1.25 is consistent with the current recommended standard in the United States of $spKt/V > 1.2$, and is similar to the average levels of $spKt/V$ achieved in the United States [19]. The high Kt/V goal represents the highest dose achievable in a high percentage of patients within 4.5 hours per treatment using currently available technology.

Table 1 HEMO Study Design

Flux Intervention*	Kt/V Intervention	
	Standard Goal (Target eKt/V = 1.05)	High Goal (Target eKt/V = 1.45)
Low flux dialyzers		
High flux dialyzers		

* Dialyzers with a mean β_2 M clearance < 10 mL/min on first use are classified as low flux. A high flux dialyzer must satisfy both of the following: (1) an ultrafiltration coefficient > 14 mL/h/mm Hg, and (2) a mean β_2 M clearance > 20 mL/min at first use or over the lifetime of the dialyzer with a particular reprocessing method.

Flux Intervention

Although all dialysis membranes currently in use are able to remove low molecular weight solutes such as urea, there is a wide variation in the ability of different membranes to remove solutes with larger molecular weights. Conventional low flux cellulosic membranes, frequently used in the past for HD, remove an insignificant fraction of substances with molecular weight over 10,000 daltons. By contrast, the normal kidney excretes and/or catabolizes substances with molecular weights up to 60,000 daltons. A wide variety of so-called high flux membranes are now available which can effectively remove middle-sized molecules of at least the molecular weight of β_2 microglobulin (β_2 M) (11,900 daltons), and some membranes may remove substances of molecular weight up to 60,000 daltons [21].

High flux membranes are in general more expensive than low flux membranes, but their clearance properties appear to approximate more closely those of the normal kidney, leading to the hypothesis that high flux membranes may reduce mortality and morbidity. This hypothesis is supported by reports of favorable effects of high flux membranes on lipid metabolism [22], carpal-tunnel syndrome, and bone cysts [23]. High flux membranes have also been shown to remove polypeptides that accumulate in HD patients [24], and to remove anaphylotoxins [25]. Recently, beneficial effects of high flux membranes on mortality have been suggested in observational studies [26].

The flux intervention in the HEMO Study is defined primarily by the ability of membranes to remove β_2 M, as quantified by the clearance of β_2 M. The β_2 M clearance is calculated using a variable-volume single-pool model based on the change in the concentration of β_2 M from the beginning to the end of dialysis while taking into account the fluid removed from the blood during dialysis.

DESIGN AND OUTCOME VARIABLES

The HEMO Study is based on the 2×2 factorial design shown in Table 1. Randomization is stratified by the 15 participating clinical centers, age group (≤ 55 years, > 55 years), and diabetic status. The 15 clinical centers recruit patients from up to ten dialysis facilities each; as of July 1, 1999, a total of 67 dialysis units had contributed randomized patients to the study. Screening inclusion criteria require that the patient must be 18-80 years of age, on in-center HD for three treatments per week, and have been on dialysis for ≥ 3

Table 2 Exclusion Criteria

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1. Currently in an acute care or chronic care hospital
 2. An interdialytic 24-hour urine collection with a urea clearance > 1.5 mL/min (per 35L urea volume)
 3. Current pregnancy
 4. Scheduled living donor renal transplant within the period of study
 5. Less than 6 months since patient returned to hemodialysis after renal transplantation
 6. Active malignancies requiring current chemotherapy or radiation therapy
 7. Severe congestive heart failure (New York Heart Association Class IV) after maximal therapy
 8. Unstable angina pectoris: new onset angina, recent exacerbation of frequency, duration, or severity of angina pectoris
 9. Symptomatic AIDS according to the CDC classification*
 10. Active systemic infections, such as tuberculosis or systemic fungal infection
 11. Chronic pulmonary disease requiring supplemental oxygen
 12. Cirrhosis with encephalopathy or abnormal PT
 13. Severe malnutrition (serum albumin < 2.60 gm/dL for two of three baseline nephelometry measurements)
 14. Expected geographic unavailability at the clinical center for > 20 dialysis treatments per year
 15. Use of investigational drugs or involvement in other intervention protocols
 16. Unable to follow protocol due to mental incompetence or other reason
 17. Unwillingness to participate in the procedures of the protocol
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* CDC. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *Morbidity and Mortality Weekly Report* 1987;36:1-15S.

months. Patients must also achieve an $eKt/V > 1.3$ within 4.5 hours on two of three consecutive attempts during baseline to be randomized. The exclusion criteria are given in Table 2.

The primary outcome variable in the HEMO Study is all-cause mortality. The following secondary composite outcomes are also given priority in the analysis plan:

- (S1) first cardiovascular hospitalization or death,
- (S2) first infection hospitalization or death, and
- (S3) first declining albumin event or death.

The first declining albumin event is defined as a decline in serum albumin by >15% from the mean of two baseline serum albumin determinations on two consecutive monthly follow-up measurements. The serum albumin composite was identified as a key secondary outcome because low or declining serum albumin levels are strong predictors of mortality in observational studies of dialysis patients [27, 28]. The composite outcomes involving the first cardiovascular or the first infection hospitalization were selected because a high percentage of deaths of dialysis patients are attributed to cardiovascular disease or infection [29-31]. The overall rate of hospital admissions for causes other

than repair or modification of the dialysis vascular access is also designated as a key secondary outcome.

Other secondary objectives of the HEMO Study include the evaluation of the effects of the dialysis dose and flux interventions on rates of death or hospitalization due to specific cardiovascular and cerebrovascular causes and to specific classes of infection. The HEMO Study will also test the effects of the interventions on changes from baseline to follow-up in indices of nutritional status, comorbidity, access-related problems, quality of life, and functional status. The effects of the interventions on nutritional status are of particular interest because nutritional markers have been found to be especially strong predictors of patient outcome in observational studies of dialysis patients [27, 28]. Nutritional variables of interest include biochemical measures such as serum albumin, serum creatinine, and serum bicarbonate and anthropometric measurements [32]. Observational studies have also reported associations between Kt/V and a measure of protein catabolism derived from kinetic modeling, the normalized protein catabolic rate (nPCR) [33]. In the metabolically stable patient, nPCR is considered to reflect protein intake. As with Kt/V, nPCR is computed using urea kinetic modeling from the predialysis and postdialysis BUNs. The interpretation of correlations between Kt/V and nPCR from observational studies is controversial due to the possibility of an artificially induced correlation resulting from the computation of both Kt/V and nPCR from the same BUN measurements [34, 35]. Nonetheless, these findings have contributed to a wide acceptance of the hypothesis that higher Kt/V leads to improved nutritional status, which in turn leads to improved outcome. The HEMO Study will test the effects of Kt/V on measures of nutritional status, including nPCR, by comparing randomized treatment groups to avoid the potential biases of prior observational studies.

DESIGN COMPLICATIONS

Recruitment Method

Due to limitations in the available financial resources, it was recognized that each clinical center would be able to carry out the requirements of the HEMO Study protocol for no more than 60 randomized patients at any one time, giving 900 randomized patients among all 15 centers. Due to the rapidly changing technology of dialysis, it was also felt that to assure the relevance of the study's findings the completion date should be targeted no later than the fall of 2001, 6.5 years after the start of randomization. Under the scenarios considered in the power calculations (later in this paper), these constraints allowed for approximately 3000 patient-years of follow-up, which would provide adequate power to detect treatment effects no smaller than 33% of the projected mortality rates in the standard Kt/V and low flux arms. However, results from observational studies suggested effect sizes smaller than 30%.

To increase the patient-years of follow-up while limiting the number of randomized patients to 60 per center at any one time, a recruit-with-replacement plan was devised in which 900 patients are to be randomized in the first 1.5/2 years of the study. Subsequently, in all but the final year of follow-up, all patients who die, terminate HD due to renal transplantation, switch to another

type of dialysis, or transfer to a nonparticipating dialysis facility are replaced with a newly randomized patient. The projected rate of such deaths or dropouts exceeds 20% per year. The recruit-with-replacement strategy increases the projected patient-years of follow-up to over 5000, providing adequate power to detect effects of approximately 25% while maintaining the restriction that the clinical centers would not be required to follow more than 900 randomized patients at any one time. The recruit-with-replacement strategy is particularly well-suited to the HD setting where recruitment efforts are simplified by easy patient accessibility at scheduled dialysis treatments, and where the rates of mortality and other types of dropout are high. One complication is the expectation that a substantial fraction of replacement patients will be relatively new dialysis patients appearing in participating dialysis facilities after the supply of prevalent patients has been exhausted. Randomization is stratified in random blocks over calendar time to assure approximate balance in randomization at all stages of the study. Years of dialysis is a prespecified covariate in the primary analysis to prevent confounding of the treatment comparisons with variations in the duration of prior dialysis for randomized patients as the study progresses.

Specification of Composite Secondary Outcomes

The designation of the “main” secondary composite outcomes S1, S2, and S3, as previously defined, is intended to further address the limitations in power imposed by the constraints on the total patient-years of follow-up. The cardiovascular composite outcome has a projected event rate approximately 50% greater than that of mortality alone (Patrick Parfrey, personal communication). A similar increase in event rates for the infection and declining albumin composites is expected. Such an increase in event rate would allow detection of effects on the secondary composite outcomes which are 15–20% smaller than the minimum detectable effects on mortality.

Determination of eKt/V

Increasing awareness of the deficiency of spKt/V in quantifying dialysis dose (due to postdialysis urea rebound) appeared in the renal community at approximately the same time that the HEMO Study was designed. Unfortunately, in contrast to spKt/V, which is calculated from urea concentrations at the beginning and end of dialysis, direct calculation of eKt/V requires the measurement of blood urea concentration 30–60 minutes after the end of the dialysis treatment when the rebound is almost complete. It is not feasible to require patients to routinely stay in the dialysis facility for an extended period after dialysis treatments. It was therefore essential to develop a method to monitor eKt/V without requiring blood samples more than a few minutes after the end of dialysis.

To address this difficulty, several newly proposed methods for predicting eKt/V based on measurements of urea concentrations in the blood and/or dialysate during dialysis were investigated in 295 modeled dialysis sessions conducted in 49 patients enrolled in the HEMO Pilot Study during 1994 [20]. Fortunately, a simple approach derived from a regional blood flow urea kinetic

model [36] was found to accurately predict the actual eKt/V based on the equation:

$$eKt/V = spKt/V - 0.6 (K/V) + 0.03,$$

where K/V is the “rate of dialysis,” expressed in hours^{-1} as the ratio of the dialyzer clearance to the volume of body water. Since $spKt/V$ can be readily determined from the predialysis and postdialysis urea concentrations, this rate adjustment formula provides a basis for carrying out monthly monitoring of the Kt/V intervention without requiring delayed blood samples after the end of dialysis. To further validate this estimate of eKt/V , urea concentrations are measured in 30- and 60-minute postdialysis samples obtained at the 4-month and 36-month follow-up visits.

Confounding of Kt/V Intervention with Treatment Time

It has been hypothesized that a longer treatment time improves patient outcome independent of the dialysis dose [37]. Longer treatment times allow a more gradual removal of fluid from the body during dialysis, potentially allowing better control of blood pressure [38], and minimizing errors in the delivery of dialysis. On the other hand, long treatment times inflate the cost of dialysis to the care delivery system and are a burden to patients who must undergo many hours of dialysis treatment each week.

The separation of eKt/V between the Kt/V groups may be achieved either by varying the dialyzer clearance K , the treatment time t , or a combination of both. To prevent confounding between dialysis dose and treatment time, the initial design adopted in the Pilot Study required similar treatment times in both Kt/V arms, with the separation in Kt/V achieved entirely by manipulation of K . However, in evaluating the results of the Pilot Study it was recognized that this design artificially departed from current clinical practice by requiring a low-efficiency dialysis with low K in the standard Kt/V arm. Thus the Pilot Study design had the drawback that a finding of no significant difference between the Kt/V arms would not establish the adequacy of an eKt/V of 1.05 achieved by short-time high-efficiency dialysis, a more realistic condition in clinical practice. The decision was therefore made to confound Kt/V and treatment time in the Full-Scale Study by stipulating that high-efficiency dialysis should be used with as short a treatment time as possible (subject to a minimum time of 2.5 hours) in both Kt/V groups. Thus, although some variation in K between the Kt/V groups is inevitable, the Kt/V intervention will be designed to achieve as much of the separation in Kt/V between the treatment groups as possible by varying treatment time. This design will reduce the clarity of the biological implications of the study if a positive effect for the dialysis dose intervention is obtained, but addresses the more clinically relevant question of whether a high dialysis dose with longer treatment time improves outcome relative to a standard dose with shorter treatment time.

Confounding of Flux Intervention with Biocompatibility

Some low flux membranes are known to induce potentially adverse biological effects associated with activation or release of inflammatory mediators [39].

Such membranes are considered less “biocompatible” than most high flux membranes. This introduces a possible confound between flux and biocompatibility.

Among low flux membranes, the class referred to as unsubstituted cellulosic membranes is regarded as being the least biocompatible, and has been associated with higher mortality in an observational study of chronic HD patients [40]. Although unsubstituted cellulosic membranes were still widely used when the HEMO Full-Scale Study began in 1995, current trends suggest a declining utilization of these dialyzers. These observations raised the concern that if morbidity/mortality is shown to be higher in the low flux arm, it would not be clear whether the difference was due to the lower flux or to the lesser biocompatibility of the membranes. If unsubstituted cellulosic membranes are phased out of clinical practice by the time the study is completed, the implications of a positive effect for the flux intervention would be diminished. The decision was therefore made to exclude unsubstituted cellulosic membranes from the study, with the understanding that this would reduce but not eliminate the confound between flux and biocompatibility.

CONDUCT OF THE STUDY

Data Collection and Organization

Data collected by the 15 clinical centers is written on centrally produced study paper forms and then remotely key-entered by clinical center personnel via the Internet into the central database located on a Sun System at the Data Coordinating Center (DCC). The central database is programmed in Oracle, and includes appropriate quality control mechanisms (see next section).

The staff at a clinical center usually includes a nephrologist principal investigator, one or more co-investigators who may be physicians at the participating dialysis clinics, a full-time study coordinator, a part-time dietitian, and a part-time key entry person. The study coordinators and dietitians are responsible for data collection, patient instruction, and coordination with nonstudy nurses, technicians, and dietitians at each of the dialysis units associated with their center. In most cases blood samples are drawn by dialysis unit technicians according to a standardized protocol under the supervision of the study coordinator. The participating centers, central facilities, and other investigators are listed in the appendix.

Study Timeline

The Pilot Study was conducted in 49 patients during 1994 to assess the feasibility of the study procedures and data collection forms and to investigate alternative strategies for kinetic modeling. Patient randomization for the Full-Scale Study began in May 1995. The recruitment plan called for 900 randomized patients to be accrued in the 18 months from May 1995 to November 1996. In accordance with the recruit-with-replacement strategy, the clinical centers are required to recruit additional patients to maintain a target of 900 concurrently active patients until November 1, 2000. Including both initial and replacement patients, a total of 1517 patients were randomized by July 1, 1999. Regular patient follow-up is scheduled to terminate on November 1, 2001. The protocols

for both the Pilot and Full-Scale studies were approved by an External Advisory Committee and the Institutional Review Boards of the participating clinical centers prior to initiation of enrollment.

Baseline Procedures

Demographic and clinical information is obtained at the time of baseline enrollment for all study participants. During the 2–3 weeks after enrollment, patients are maintained on their usual dialysis prescriptions prior to study entry to allow an assessment of the condition of the patients prior to modification by the study procedures. During this initial phase of baseline, two weekly kinetic urea modeling sessions are conducted to assess baseline dialysis dose and other kinetic parameters. Timed urine collections over 24–46 hours are performed for patients with remaining urine output prior to one of these two kinetic modeling sessions to measure the residual urea clearance of the native kidney (Kru). Patients with $Kru > 1.5$ mL/min (per 35 L urea volume) are excluded from the study since residual kidney function complicates the interpretation of both the dialysis dose and flux interventions. The 1.5 mL/min cutoff represents 2–3% of the urea clearance of a person with normal renal function. Patients satisfying the Kru and other entry criteria (Table 2) are evaluated on the full battery of study assessments (Table 3), including hematological and biochemical studies from local laboratories, vascular access conditions, comorbidity, quality of life, functional status, dietary intakes from 2-day food records, appetite, and anthropometry.

To confirm that the patients can attain the high Kt/V goal, at approximately the fourth week of baseline the DCC provides a modified dialysis prescription for each patient to target an eKt/V of 1.45 (see kinetic modeling logistics below). Patients who achieve a delivered eKt/V ≥ 95 1.30 for two of three consecutive modeled dialyses, satisfy the entry criteria of Table 2, and complete all baseline procedures within 14 weeks are eligible for randomization by the DCC after signing an informed consent.

Measurement Schedule

Table 3 summarizes the time schedule of the major study measurements in baseline and follow-up after randomization. Once randomized, the regular follow-up measurement schedule applies for each patient until death or dropout due to renal transplantation, a switch to an alternative method of dialysis other than HD, or transfer to a dialysis unit not participating in the study. Mortality information for the primary analysis is collected regardless of renal transplantation, therapy switches, or transfers.

The Index of Coexisting Disease (ICED) [41] is used to quantify the level of comorbidity at baseline, and annually throughout follow-up. The final ICED score is calculated based on separate indices of disease severity for each of 19 disease categories and for each of nine physical impairments. Functional status is also evaluated using the Karnofsky Index based on assessments by dialysis unit staff and study team [42]. Quality of life is evaluated using the Short Form-36 (SF-36) [43], in conjunction with the Kidney Disease and Quality of Life Questionnaire (KDQOL), an extended quality-of-life questionnaire developed

Table 3 Schedule of Data Procurement in Baseline and Follow-up

Type of Measurement	Baseline Frequency	Follow-up Frequency
Demographic information/history	Once	—
<i>Routine</i> kinetic modeling	≥4 weekly measurements	Monthly
<i>Extensive</i> kinetic modeling with urea rebound*	—	Months 4 and 36
Limited dialysis information from non-kinetic modeling days	—	Every 2 months
Timed urine collection	Once	Annually for patients producing > 50 mL of urine per day
Serum β_2 microglobulin	—	High flux: months 1, 2, 3, 4, and every 2 months thereafter; Low flux: every 6 months
Access related conditions	Once	Every 6 months
Medications	Once	Every 6 months
Local biochemistry	Once	Every 6 months
Detailed comorbidity assessment	Once	Annually
Detailed quality of life assessment	Once	Annually
Functional status	Once	Annually
2-day food records	Once	Annually
Appetite assessment	Once	Annually
Anthropometry	Once	Annually
Hospitalization	On discharge from hospital	On discharge from hospital
Death	On occurrence of death	On occurrence of death

* Extensive kinetic modeling sessions include 8 blood samples collected at designated times during and after dialysis, including a 30-minute postdialysis sample. An additional 60-minute postdialysis blood sample is obtained in approximately 200 volunteers.

specifically for dialysis patients [44], and Campbell's Index of Well-Being [45]. Each of the quality of life questionnaires is completed by the patient, with assistance from study team personnel if necessary.

Dietary food records are collected by the clinical centers using 2-day diary-assisted recall. These are analyzed for nutrient composition by clinical center dietitians using a version of the nutrient analysis software Nutritionist IV customized for the study [46]. Anthropometric measurements include height, weight, midarm and calf circumferences, skinfold thicknesses, and elbow breadth.

Logistics of Dialysis Dose Intervention

Urea kinetic modeling data are collected for at least four baseline dialysis sessions and for at least one dialysis session per month during follow-up. For each kinetic modeling session, the clinical centers draw predialysis and

postdialysis blood samples and record information related to the dialysis session in the database. The blood samples are shipped via overnight mail to a central biochemistry laboratory (CBL), which analyzes the samples for BUN, albumin, and $\beta_2\text{M}$. The CBL electronically transmits a file containing the day's results to the DCC. Automated software at the DCC performs the kinetic modeling calculations and e-mails patient-specific reports which summarize and interpret the results and provide instructions for future actions to the clinical centers.

The functions of the kinetic modeling reports transmitted by the DCC include:

1. *Dialysis prescriptions.* These reports specify multiple possible prescriptions, each targeted to the patient's randomized eKt/V goal of 1.05 or 1.45. They are transmitted by the DCC to the clinical centers when a patient is randomized, and are updated as necessary throughout follow-up. Based on a current estimate of the patient's volume of urea distribution V , the prescription reports provide an array of combinations of blood flow rate, dialysate flow rate, dialyzer model, and treatment time which are consistent with the patient's target eKt/V . To smooth out variations in estimates of V from individual modeling sessions, the estimates of V are averaged over the latest four kinetic modeling sessions in the standard Kt/V arm and the latest six modeling sessions in the high Kt/V arm. Extreme values are excluded if the coefficient of variation exceeds 10%.
2. *Adherence of the clinical center to the DCC prescriptions.* The adherence of the clinical center to the DCC prescription is assessed by comparing the eKt/V prescribed by the clinical center to the target of 1.05 or 1.45 corresponding to the patient's randomized Kt/V group. If the clinical center follows one of the options provided by the DCC prescription report, their prescribed eKt/V will match the 1.05 or 1.45 target to within a small rounding error. However, clinical centers may fail to adhere to the DCC prescription reports for a variety of reasons, including an unwillingness of the patient to remain in the dialysis clinic for the time required by the DCC prescription, inadequate blood flow in the patient's vascular access to achieve the required blood flow rate, or a desire by the patient or the patient's physician for a different dialysis dose than the study target.
3. *Assessment of the dialysis dose actually delivered.* Several measures of delivered dialysis dose are reported, including spKt/V and eKt/V .
4. *Identification of problems with the delivery of dialysis.* Unusually large variations in the modeled estimates of V are used to identify problems with the delivery or the measurement of the dialysis dose. Problems indicated by large variations in the estimated V include difficulties with blood flow due to access stenosis or thrombosis which reduce the delivered dialysis dose, clotting of the dialyzer, errors in blood sampling, or incorrectly reported treatment parameters.

Central Measurement of Dialyzer K_0A

The capacity of a dialyzer to remove urea is characterized by a clearance parameter denoted K_0A . For a particular model of dialyzer to be used in the

follow-up phase of the HEMO Study, at least five dialyzers of the same model, but different manufacturing lots, must be first submitted to a central laboratory (University of Utah) which measures the K_0A using a standardized methodology [47]. A minimum average K_0A of 500 mL/min is required for all dialyzer models to maintain a relatively uniform level of high-efficiency dialysis in each treatment group. Dialyzer models must also satisfy criteria related to the flux intervention, as described below.

Logistics of Flux Intervention

The conduct of the flux intervention is complicated by the practice of reuse of dialyzers for multiple dialysis sessions with reprocessing techniques that alter the clearance of β_2M . To maintain consistency with clinical practice in the United States, the HEMO Study allows dialyzers to be reused for up to 20 dialyses after the first use. At the start of the study, it was expected that reuse may increase or decrease β_2M clearance depending on the dialyzer/reprocessing combination. However, the specific effects of each reprocessing method on each type of dialyzer were unknown. Since the number of dialyzer/reprocessing combinations was too large for each combination to be evaluated prior to the study, a two-step process for approving dialyzers was established. This approval process is implemented by a subcommittee of the study investigators (the Flux/Membrane Committee).

In the first step, dialyzers are tentatively approved based primarily on their performance at first use, before reprocessing. Approval is based on existing data, or on data from special studies arranged by the Flux/Membrane Committee if no existing data are available. To be approved for the low flux intervention, the mean of five independent β_2M clearance measurements at first use must be <10 mL/min. A dialyzer can be tentatively approved for the high flux intervention if both of the following conditions are satisfied: (1) the ultrafiltration coefficient (an index of water permeability) specified by the manufacturer is ≥ 14 mL/h per mm Hg, and (2) the mean of five first-use β_2M clearance measurements is >20 mL/min. A dialyzer may also be tentatively approved for use with a specific reprocessing method in the high flux arm if it satisfies condition (1) and the mean β_2M clearance of five separate dialyzers exceeds 20 mL/min when averaged over reuses 0, 5, 10, 15, and 20 with that reprocessing method. As of July 1, 1999, eight dialyzer models were approved for the low flux arm, and 13 for the high flux arm.

In the second step of the approval process, the β_2M clearances of all dialyzers used in the study are monitored as a function of the number of reuses for each reprocessing technique. The Flux/Membrane Committee periodically reviews these data, and applies restrictions to particular dialyzer/reuse combinations if it becomes clear that these combinations adversely affect the separation in β_2M clearance between the flux groups.

Maintenance of Dietary Standards

Under the direction of a Nutrition Coordinating Center, the HEMO Study dietitians monitor the kinetically modeled nPCR and reported calorie intake and recommend increased protein and energy intakes if nPCR < 1 g/kg/d

or reported calorie intake < 28 kcal/g/d. The patient is offered nutritional supplements if the low values of nPCR or calorie intake persist following intervention by the HEMO Study dietitian. Nutritional counseling and, if necessary, nutritional supplements, are also provided in response to formal action items triggered by a serum albumin decline of $\geq 10\%$ from the mean baseline value and by an undesired reduction of ≥ 2.5 kg or 5% of postdialysis weight for 2 consecutive months.

Classification of Outcomes

The Outcome Review Committee consisting of 10–12 study investigators is responsible for assuring a uniform classification of causes of death and hospitalizations which are relevant to the secondary composite outcomes specified earlier.

For each death, the clinical center provides an initial classification and forwards relevant documentation to the DCC. The documentation includes a narrative summary by the principal investigator of the events leading to the death, the U.S. Medicare Death Notification Form, the autopsy report (if available), and the final discharge summary for patients who died in the hospital. The DCC assigns two members of the Outcome Review Committee to serve as primary reviewers, and sends them the obtained information along with relevant data on demographics, comorbidity, and laboratory values from the study database. If the two Outcome Review Committee members agree with each other on the primary cause of death, the agreed-upon classification is the final HEMO Study classification. If the two reviewers do not agree, documentation is sent to the full Outcome Review Committee, and the final classification is determined by a majority vote of the committee.

The clinical centers also provide initial classifications of hospitalizations. After discharge, the clinical center sends the DCC the ICD-9 code [48], the hospital discharge summary, and the local study team's assessment of the primary cause of the hospitalization using a classification system devised by the HEMO Study. The DCC database checks each postrandomization hospitalization to determine if it is a patient's first cardiovascular or first infection hospitalization. For these hospitalizations, the DCC sends one member of the Outcome Review Committee the compiled information and other pertinent data. The reviewer classifies the hospitalization according to the study coding scheme. If the reviewer and the clinical center principal investigator agree as to the primary cause of the hospitalization, the common classification is regarded as the final HEMO-Study classification. If agreement cannot be reached, documentation is sent to the full Outcome Review Committee, and the final classification is determined by a majority vote of the committee.

QUALITY CONTROL

In addition to standard quality control procedures implemented by the CBL and the clinical centers, the HEMO Study uses several additional quality control mechanisms. Quality assurance for clinical center personnel includes central annual training sessions where study coordinators are trained to carry out study procedures, including collection of kinetic modeling data, interpretation

of kinetic modeling reports provided by the DCC, standardized coding of comorbidity information, and data collection for hospitalizations and deaths. Coordinators and key-entry personnel are trained and certified in forms completion, data entry into the main study database, and error correction. HEMO Study dietitians are trained to obtain diary-assisted dietary recalls, perform nutritional counseling, and use the nutritional software package Nutritionist IV. The dietitians are also certified to take anthropometry measurements. Site visits were conducted for each clinical center during the first 2 years of the study. These included detailed review of recruitment procedures and a data audit [49]. Site visits were also conducted to review procedures at the CBL and the DCC.

The DCC provides monthly reports which monitor the performance of the clinical centers with regard to recruitment, adherence to the kinetic modeling and flux interventions, completeness of data collection and key entry, and adherence to standards of general medical care specified in the protocol. As described earlier, the kinetic modeling reports provide feedback on difficulties with the dialysis dose intervention on an individual patient basis. Every second month the clinical centers provide selected information for two nonmodeled dialysis sessions, which are randomly selected by the DCC, to evaluate whether results reported for modeled dialysis sessions are similar to dialysis sessions without kinetic modeling.

Re-key verification is required for entry of forms into the central Oracle database. The central database implements range checks on most items and includes consistency checks within and between forms. To monitor the accuracy of coding of diet diaries, the DCC annually selects a random 5% sample of diary-assisted dietary recalls for reanalysis by the NCC. Deviations exceeding 10% on selected dietary variables are identified and discussed between the dietitian who collected the data and the NCC for resolution of ambiguities.

External split-sample quality control of the CBL is conducted by each clinical center on two kinetic modeling sessions per year. The predialysis and postdialysis blood samples are split and shipped separately to the CBL by the clinical center, and the duplicate results are compared.

STATISTICAL ANALYSES

Primary Analysis

The primary statistical analysis will be conducted using Cox regression to test the effectiveness of the treatment interventions on duration of survival from the date of randomization. The Cox regression model includes indicator variables to represent the effects of the treatment interventions and baseline covariates to control for previously identified prognostic factors. The covariates specified for the primary analysis are: (1) age at randomization, (2) diabetic status (diabetic versus nondiabetic), (3) sex, (4) race (black versus nonblack), (5) years of dialysis at randomization, (6) a comorbidity index constructed from the ICED scale with diabetes excluded, (7) baseline serum albumin, and (8) the interaction between baseline serum albumin and time since randomization. The analysis will be stratified by clinical center. Most of these covariates have

been identified as predictors of survival in previous studies using large databases for patients with ESRD (e.g., the United States Renal Data System (USRDS) and the Patient Statistical Profile system for National Medical Care, Inc. [27]). The interaction term with baseline serum albumin is included due to the expectation that the baseline serum albumin measurements may be more strongly associated with the patients' survival rate shortly after randomization than later in follow-up.

In accordance with the 2×2 factorial design, both the main effects of the Kt/V and flux interventions and the interaction between these interventions will be tested, recognizing that the power to detect an interaction between the interventions is limited [50]. Under an intent-to-treat strategy, patients will be analyzed according to their randomized groups regardless of compliance. In addition, survival of patients who transfer to nonparticipating centers or to modes of dialysis other than HD will be analyzed without censoring. Under this approach, effects on survival of transfers or switches in modality of dialysis therapy are interpreted as consequences of the degree of patient compliance with the respective treatment interventions. This strategy will reduce the statistical power of treatment comparisons if the effects of the original HD interventions do not persist following transfer. However, censoring transfers and dialysis modality switches would have risked introducing bias in the treatment comparisons, since the decision to switch or transfer may be related to the prognosis of the patient.

A related complication is that published rates of renal transplantation [51] suggest that approximately 10% of HEMO Study patients are likely to receive cadaveric renal transplants during follow-up. Cadaveric renal transplantation is largely determined by the serendipitous availability of a viable kidney, and in this respect may not be strongly related to health status for most patients. Thus survival will be censored at the time of renal transplantation. However, since renal transplants are not provided to patients in exceptionally poor health, the decision to censor transplants may lead to an underestimation of a beneficial effect of an intervention if a disproportionate number of the healthier patients on that intervention receive renal transplants and are thus censored. The inclusion of baseline prognostic factors in the Cox model will help to control for bias due to associations of transplantation with baseline patient characteristics.

Secondary Analyses

Similar Cox regression models including the same baseline covariates will be used to test the effects of the interventions on the cardiovascular, infection, and declining serum albumin composite outcomes defined earlier. Because hospitalization and serum albumin data are not collected after transfer or modality switches, the analyses of the secondary composite outcomes will be censored at these events. Non-access hospitalization rates will be analyzed using Poisson regression and with multivariate generalizations of the Cox model [52, 53].

Interactions of both interventions with various patient factors which have been suggested in the literature will be tested. In particular, it has been suggested that higher levels of Kt/V are necessary in whites (as compared with blacks) [54], females and smaller patients [55], and in patients with higher

levels of comorbidity such as diabetes [13]. Other possible interactions include a smaller beneficial effect of the dialysis dose and flux interventions in patients who retain some level of native residual renal function. Such tests for interactions will be interpreted with caution due to the limitations in statistical power and inflation of type I error rates due to multiple tests.

Longitudinal methods will be used to relate the treatment interventions to changes in continuous outcomes (e.g., anthropometric measures, dietary intake variables, biochemical and kinetic measures of nutritional status, quality of life indices) and ordinal outcomes (e.g., the ICED score) [56, 57]. Methods which account for informative censoring will be used to control for bias in estimated changes in other outcomes resulting from censoring due to deaths and drop-outs [58].

Interim Analyses

Formal interim analyses are presented annually to the External Advisory Committee to monitor patient safety, review the conduct of the study, and determine if one or both arms of the study should be terminated early due to clear evidence of a benefit of one of the interventions. The spending function approach of Lan and DeMets [59] as adapted to survival data has been used to construct a formal stopping rule based on an O'Brien-Fleming boundary.

POWER ANALYSIS

Assumptions

Estimates of the power for the primary analysis of mortality were derived using a data set provided by the Health Care Financing Administration (HCFA) with data on mortality, transfers, and modality switches over a 5-year period for all U.S. dialysis patients entitled to medicare on January 1, 1986. These data were used to model the expected event rates in the HEMO Study with Cox regression equations relating the rates of mortality, renal transplantation, and dialysis modality switches to five of the prognostic factors: age, gender, race, years of dialysis, and diabetic status. Separate Cox regressions were obtained for the originally randomized patients (assumed to represent a prevalence sample) and the later replacement patients (assumed to correspond to new dialysis patients with ESRD for 3–12 months). The baseline hazard functions in the Cox regressions for mortality in the HCFA data set were approximately constant over time for both the prevalent patients and the new dialysis patients. Thus, constant hazard rates were assumed for mortality. On the other hand, decreasing baseline hazard functions were observed for the rates of renal transplantation and modality switches. The Cox regression models were updated by multiplying the estimated hazard functions by constant factors to bring the overall event rates into accordance with an updated survey of U.S. dialysis patients provided in the 1995 USRDS Annual Data Report [51]. Estimates of the prevalence of risk factors for the HEMO Study were adjusted based on a survey conducted at the start of the Full-Scale Study in the dialysis units participating in the HEMO Study.

Table 4 Power of Primary Analysis of Mortality*

Mortality Rate Reduction from USRDS	Mortality Rate in Low Kt/V-Low Flux Group [†]		Treatment Effect Size	Total Number of Patients in Trial [‡]	Power for 900 Concurrent Patients
	Initial Patients	Replacements			
20%	16.3%	17.2%	30%	1737	94%
20%	16.3%	17.2%	25%	1763	84%
20%	16.3%	17.2%	20%	1788	65%
30%	14.3%	15.1%	30%	1682	91%
30%	14.3%	15.1%	25%	1704	79%
30%	14.3%	15.1%	20%	1727	61%
40%	12.3%	12.9%	30%	1625	85%
40%	12.3%	12.9%	25%	1644	74%
40%	12.3%	12.9%	20%	1662	52%

* Other key assumptions: 1.5 years initial accrual; 5 years additional follow-up; lag time of 6 months; 4% annual transfer/dropout rate; rates of transplant and dialysis modality switches based on USRDS; censoring of transplants; no censoring of transfers or dialysis modality switches; treatment effect size applies to both factors; 2-sided significance level of 5%.

[†] Mortality rates at the time of randomization.

[‡] Indicated are the estimated total numbers of randomized patients to maintain 900 concurrent patients after the initial 1.5-year accrual period.

The rates of renal transplantation and modality transfers from this procedure were assumed to apply in each treatment group, while the projected mortality rates were assumed to apply to the low Kt/V - low flux group, which can be viewed as the “control” group. In the remaining treatment groups, mortality was modeled by multiplying the hazard functions by factors corresponding to hypothesized treatment effects. An initial lag time of 6 months was assumed for both the original and the replacement patients, with the log hazard rate decreasing linearly in the more intensively treated groups until the full hypothesized reduction in mortality rate is reached at 6 months. When considering the main effect of one of the interventions, the same effect was assumed for the other intervention. After dialysis modality switches or transfers, survival hazard rates were assumed to immediately revert to those of the low Kt/V - low flux group. This is a “worse case” scenario of no carryover of the treatment effects for these patients. In addition to modality switches, a 4% annual rate of dropout or transfer to nonparticipating centers was assumed.

Simulation Results

Using the distributions of covariates and hazard rates specified above, the power to detect hypothesized effects of the study interventions was estimated based on 2000 independent simulations for each of several scenarios.

The results of the power calculations for mortality are presented in Table 4. The power calculations are provided under the assumption that the mortality rate observed in the low Kt/V - low flux membrane group will be 20%, 30%, or 40% lower than in the USRDS. A lower mortality rate is expected in the study than in the general population because mortality rates in clinical trials have historically been lower than those in the general patient population.

Depending on the mortality rate reduction in the low Kt/V - low flux group from the USRDS, the power to detect an annual mortality rate reduction of 30% ranges from 85–94%, and the power to detect an annual mortality rate reduction of 25% ranges from 74–84%.

SUMMARY

The HEMO Study is the first randomized multicenter clinical trial addressing hemodialysis delivery since the NCDS was completed in 1981. The study uses a 2×2 factorial design to investigate the effects on mortality and morbidity of two factors related to the dialysis prescription: dialysis dose (or Kt/V) and membrane flux. Approaches taken to confront several methodological obstacles to achieving the objectives of the study were reviewed. To deal with constraints on resources, a recruitment scheme was devised in which patients who die or drop out are replaced by newly randomized patients to maintain a target of 900 concurrently active randomized patients over 5 years after a 1.5-year accrual period. To maximize clinical relevance, dialysis dose and treatment time are confounded in the design of the dialysis dose intervention, and a class of membranes with low biocompatibility was excluded from the low flux arm of the study. Urea kinetic modeling results from a Pilot Study were used to devise new methods for monitoring and adjusting dialysis dose in the Full-Scale Study. The design has adequate power to detect mortality rate reductions of 25% for both interventions. Presentation of the primary results of the trial is planned shortly after the end of patient follow-up in late 2001.

The HEMO Study is supported by grants from the National Institute of Digestive and Kidney Diseases. Some study dialyzers have been provided by Baxter Healthcare Corporation (McGaw Park, IL) and Fresenius Medical Care-North America (Lexington, MA). Nutritional supplements have been provided by Ross Laboratories (Columbus, OH) and vitamins by R&D Labs, Inc. (Marina del Rey, CA).

REFERENCES

1. United States Renal Data System, USRDS 1999 Annual Report, Chapter II: Incidence and Prevalence of ESRD. Bethesda MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1999:25–38.
2. United States Renal Data System, USRDS 1999 Annual Report, Chapter X: The Economic Cost of ESRD and Medicare Spending for Alternative Modalities of Treatment. Bethesda MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1999:145–164.
3. United States Renal Data System, USRDS 1999 Annual Report, Chapter V: Patient Mortality and Survival. Bethesda MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1999:73–88.
4. Held PJ, Brunner F, Odaka M, et al. Five-year survival for end-stage renal disease patients in the United States, Europe and Japan, 1982 to 1987. *Am J Kidney Dis* 1990; 5:451–457.
5. Collins A, Hanson G, Umen A, Kjellstrand C, Keshaviah P. Changing risk factor demographics in end-stage renal disease patients entering hemodialysis and the impact on long-term mortality. *Am J Kidney Dis* 1990;15:422–432.
6. Eknoyan G, Levey AS, Beck GJ, et al. The Hemodialysis (HEMO) Study: Rationale for selection of interventions. *Semin Dial* 1996;9:24–33.

7. Parker TF, Laird NM, Lowrie EG. Comparison of the study groups in the National Cooperative Dialysis Study and a description of morbidity, mortality and patient withdrawal. *Kidney Int* 1983;23(Suppl):S42–S49.
8. Harter HR. Review of significant findings from the National Cooperative Study Dialysis Study and recommendations. *Kidney Int* 1983;23(Suppl 13):S107–S112.
9. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription on patient morbidity: Report of the National Cooperative Dialysis Study. *New Engl J Med* 1981;305:1176–1180.
10. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985;28:526–534.
11. Depner TA. *Prescribing Hemodialysis: A guide to urea kinetic modeling*. Boston: Kluwer Academic Publishers; 1991.
12. Hakim RM, Breyer J, Ismail N, Schulman G. Effects of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 1994;23:661–669.
13. Collins A, Liao M, Umen A. Urea index (Kt/V) and other predictors of hemodialysis patient survival. *Am J Kidney Dis* 1994;23:272–282.
14. Parker TF, Husni L, Huang W, Lew N, Lowrie EG. Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. *Am J Kidney Dis* 1994;23:670–680.
15. Held PJ, Port FK, Wolfe RA, et al. The dose of hemodialysis and patient mortality. *Kidney Int* 1996;50:550–556.
16. National Kidney Foundation-Dialysis Outcomes Quality Initiative. Clinical practice guidelines for hemodialysis adequacy. *Am J Kidney Dis* 1997;30(Suppl):S22–S63.
17. Pedrini LA, Zereik S, Rasmy S. Causes, kinetics and clinical implications of post-hemodialysis urea rebound. *Kidney Int* 1988;34:817–825.
18. Spiegel DM, Parker PL, Babcock S, Contiguglia R, Klein M. Hemodialysis urea rebound: The effect of increasing dialysis efficiency. *Am J Kidney Dis* 1995;25:226–229.
19. Depner T, Beck G, Daugirdas J, Kusek J, Eknoyan G. Lessons from the Hemodialysis (HEMO) Study: An improved measure of the actual dialysis dose. *Am J Kidney Dis* 1999;33:142–149.
20. Daugirdas JT, Depner TA, Gotch FA, et al. Comparison of methods to predict equilibrated Kt/V in the HEMO Pilot Study. *Kidney Int* 1997;52:1395–1405.
21. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. *Kidney Int* 1994;46:830–837.
22. Josephson MA, Fellner SK, Dasgupta A. Improved lipid profiles in patients undergoing high flux hemodialysis. *Am J Kidney Dis* 1992;20:361–366.
23. Van Ypersele de Strihou C. Beta-2-microglobulin amyloidosis: Effect of ESRD treatment modality and dialysis membrane type. *Nephrol Dial Transplant* 1996;11 (Suppl 2):147–149.
24. Makita Z, Radoff S, Rayfield EJ, et al. Advanced glycosylation end products in patients with diabetic nephropathy. *New Engl J Med* 1991;325:836–842.
25. Jorstad S, Smeby LC, Balstad T, Wideroe TE. Generation and removal of anaphylotoxins during hemofiltration with 5 different membranes. *Blood Purif* 1988;6:325–335.
26. Leypoldt JK, Cheung AK, Carroll CE, et al. Effect of dialysis membranes and middle molecule removal on chronic hemodialysis patient survival. *Am J Kidney Dis* 1999; 33:349–355.
27. Lowrie EG, Lew NL. Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990;15:458–482.
28. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *New Engl J Med* 1993;329:1001–1006.

29. Rostand SG, Brunzell JD, Cannon RO, Victor RG. Cardiovascular complications in renal failure. *J Am Soc Nephrol* 1991;2:1053–1062.
30. Parfrey PS, Harnett JD, Barre PE. The natural history of myocardial disease in dialysis patients. *J Am Soc Nephrol* 1991;2:2–12.
31. United States Renal Data System, USRDS 1999 Annual Report, Chapter VI: Causes of Death. Bethesda MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1999:89–100.
32. Hakim RM, Levin N. Malnutrition in hemodialysis patients. *Am J Kidney Dis* 1993; 21:124–137.
33. Lindsay RM, Spanner E. A hypothesis: The protein catabolic rate is dependent upon the type and amount of treatment in dialyzed uremic patients. *Am J Kidney Dis* 1989;5:382–389.
34. Stein A, Walls J. The correlation between Kt/V and protein catabolic rate—a self-fulfilling prophecy. *Nephrol Dial Transplant* 1994;9:743–745.
35. Greene T, Depner TA, Daugirdas JT. Mathematical coupling and the association between Kt/V and PCR_n. *Semin Dial* 1999;12 (Suppl):S20–S28.
36. Daugirdas JT, Schneditz D. Overestimation of hemodialysis dose (delta Kt/V) depends on dialysis efficiency (K/V) by regional blood flow and conventional 2-pool urea kinetic analyses. *ASAIO J* 1995; 41: M719–M724.
37. Charra B. Does empirical long slow dialysis result in better survival? *ASAIO J* 1993; 39:819–822.
38. Charra B, Caemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. *Kidney Int* 1992;41:1286–1291.
39. Schulman GM, Hakim RM. Recent advances in the biocompatibility of haemodialysis membranes. *Nephrol Dial Transplant* 1991;2(Suppl 6):10–13.
40. Hakim RM. Assessing the adequacy of dialysis. *Kidney Int* 1990;37:822–832.
41. Greenfield S, Nelson E. Recent developments and future issues in the use of health status assessment measures in clinical settings. *Med Care* 1992;30:23–41.
42. 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* 1991;44:83–89.
43. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). *Med Care* 1992;30:473–481.
44. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL™) instrument. *Qual Life Res* 1994;3:239–338.
45. Campbell A, Converse PE, Rodgers WL. The quality of life of hemodialysis and transplant patients. *Kidney Int* 1982;22:286–291.
46. Nutritionist IV For Windows. First DataBank Division, The Hearst Corporation; 1995.
47. Leyboldt JK, Cheung AK, Agodoa LY, et al. Hemodialyzer mass transfer coefficients for urea increase at high dialysate flow rates. The Hemodialysis (HEMO) Study. *Kidney Int* 1997;51:2013–2017.
48. Longenecker JC, Klag MJ, Coresh J, et al. Validation of comorbid conditions on the ESRD medical evidence report by medical record review: The CHOICE Study. *J Am Soc Nephrol* 2000;11:520–529.
49. Ornt D, Kusek JW, Dockery J, et al. Assessment of data quality in an NIH-sponsored multicenter clinical trial: The HEMO Dialysis (HEMO) Study. Second Joint Meeting for Clinical Trials and International Society for Clinical Biostatistics; 1997; Boston MA.
50. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. *New Engl J Med* 1987;317:426–432.

51. United States Renal Data System, USRDS 1995 Annual Report. Bethesda MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995.
52. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 1989;84:1065–1073.
53. Anderson PK, Gill RD. Cox's regression model for counting processes: A large sample study. *Ann Stat* 1982;10:1100–1120.
54. Owen WF Jr., Chertow GM, Lazarus JM, Lowrie EG. Dose of hemodialysis and survival differences by race and sex. *JAMA* 1998;280:1764–1768.
55. Kopple JD, Zhu X, Lew NL, Lowrie EG. Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 1999;56:1136–1148.
56. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963–974.
57. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1982;73:13–22.
58. Follman D, Wu M. An approximate generalized linear model with random effects for informative missing data. *Biometrics* 1995;51:151–168.
59. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:669–673.

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