Impact of Dialysis Dose and Membrane on Infection-Related Hospitalization and Death: Results of the HEMO Study

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Abstract. Infection is the second most common cause of death among hemodialysis patients. A predefined secondary aim of the HEMO study was to determine if dialysis dose or flux reduced infection-related deaths or hospitalizations. The effects of dialysis dose, dialysis membrane, and other clinical parameters on infection-related deaths and first infection-related hospitalizations were analyzed using Cox regression analysis. Among the 1846 randomized patients (mean age, 58 yr; 56% female; 63% black; 45% with diabetes), there were 871 deaths, of which 201 (23%) were due to infection. There were 1698 infection-related hospitalizations, yielding a 35% annual rate. The likelihood of infection-related death did not differ between patients randomized to a high or standard dose (relative risk [RR], 0.99 [0.75 to 1.31]) or between patients randomized to high-flux or low-flux membranes (RR, 0.85 [0.64 to 1.13]). The relative risk of infection-related death was associated ($P < 0.001$ for each variable) with age (RR, 1.47 [1.29 to 1.68] per 10 yr); co-morbidity score (RR, 1.46 [1.21 to 1.76]), and serum albumin (RR, 0.19 [0.09 to 0.41] per g/dl). The first infection-related hospitalization was related to the vascular access in 21% of the cases, and non–access-related in 79%. Catheters were present in 32% of all study patients admitted with access-related infection, even though catheters represented only 7.6% of vascular accesses in the study. In conclusion, infection accounted for almost one fourth of deaths. Infection-related deaths were not reduced by higher dose or by high flux dialyzers. In this prospective study, most infection-related hospitalizations were not attributed to vascular access. However, the frequency of access-related, infection-related hospitalizations was disproportionately higher among patients with catheters compared with grafts or fistulas.

Infection is the second most common cause of death (after cardiovascular disease) among hemodialysis patients (1,2) and is a frequent cause of hospitalization (3). Mortality due to sepsis occurs about 250-fold more commonly among hemodialysis patients than among the general population (4). There is limited literature analyzing the type and frequency of serious infections among hemodialysis patients. Most reported studies are retrospective and have identified diabetes, older age, co-morbidity, hypoalbuminemia, and the use of a temporary dialysis catheter as the major, independent risk factors for serious infections (1,3–7).

Observational studies have suggested that a higher dialysis dose and use of a high-flux membrane may each decrease the likelihood of infectious events (1,8), but these potential benefits have not been evaluated in randomized studies. The HEMO Study was a large, prospective, multicenter study in which chronic hemodialysis patients were randomized to receive either standard-dose or high-dose dialysis and to use high-flux or low-flux dialyzers, and clinical outcomes tracked prospectively (9). A predefined secondary aim of the study was to determine whether dialysis dose (clearance of small molecules) or membrane flux (clearance of larger molecules) affected infection-related deaths or hospitalizations.

The present report (1) evaluates the frequency and specific etiologies of infection-related deaths and hospitalizations in this defined patient population (2), assesses whether a higher Kt/V or high-flux dialyzer decreased the likelihood of serious infections, and (3) determines what other baseline clinical factors affect infectious outcomes.

Materials and Methods

Study Design

The design and methods of the HEMO Study have been reported previously (9). In brief, the HEMO Study was a multicenter, prospective, randomized, 2×2 factorial clinical trial that evaluated the effect of dialysis dose and flux on the morbidity and mortality of hemodialysis patients. The study was approved by the Institutional Review Board at each of 15 clinical centers associated with 72 participating dialysis units, and all patients gave written informed consent.

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Baseline

The subjects were enrolled in the baseline phase between March 1995 and October 2000 and randomized between May 1995 and February 2001. Eligibility requirements for baseline enrollment included age between 18 to 80 yr, receiving in-center hemodialysis thrice weekly, and on hemodialysis $>$ 3 mo. Demographic and clinical information was collected at baseline. Patients were excluded during baseline if (*1*) their residual urea clearance in a 24 to 46-hr urine collection was $>$ 1.5 ml/min per 35 L of urea volume, (*2*) their serum albumin (nephelometry) was $<$ 2.6 g/dl, (*3*) they failed to achieve the high target dialysis dose in $\leq$ 4.5 h on two of three consecutive monitored dialysis sessions, (*4*) they had serious comorbid medical conditions, including active malignancy or infection, unstable angina, or end-stage cardiac, pulmonary, or hepatic disease, or (*5*) they were scheduled for a living donor kidney transplant.

Interventions

Patients meeting the inclusion and exclusion criteria were randomized to the study interventions in a 2 $\times$ 2 factorial design with equal allocation. Each patient was randomized to receive either a standard (eKt/V 1.45) or high (eKt/V 1.05) dialysis dose, and to dialyze with either a low-flux (32 β_2-microglobulin clearance $<$ 10 ml/min) or high-flux (32 β_2-microglobulin clearance $>$ 20 ml/min) membrane. Unmodified cellulose dialyzers were excluded. The target dialysis dose was achieved by manipulating dialyzer clearance, dialysis blood flow, and treatment time (minimum $\geq$ 2.5 h). Adherence to dose intervention was monitored by monthly urea kinetic modeling. β_2-microglobulin clearance was measured every 2 mo for high-flux dialyzers and every 6 mo for low-flux membranes. Dialyzer reuse was permitted, but the number of reuses was limited in the high-flux arm to meet the target β_2M clearance. The mean achieved equilibrated Kt/V (eKt/V) was 1.53 $\pm$ 0.09 in the high-dose group and 1.16 $\pm$ 0.08 in the standard-dose group; the single pool Kt/V (spKt/V) was 1.71 $\pm$ 0.11 and 1.32 $\pm$ 0.09, respectively. The mean achieved β_2-microglobulin clearances were 3.4 $\pm$ 7.2 ml/min and 33.8 $\pm$ 11.4 ml/min in the low-flux and high-flux groups, respectively. Other than the study interventions, the dialysis and medical management of the patients conformed to current standards of care. Data collection ended in December 2001. The mean patient followup for mortality was 2.84 yr.

Definition of Clinical Outcomes

The primary study outcome was all-cause mortality. Three main secondary outcomes were evaluated: first cardiac hospitalization or all-cause death, first infection-related hospitalization or all-cause death, and first declining albumin event ($>$ 15% decrease from baseline) or all-cause death. A fourth main secondary outcome was the rate of non–access-related hospitalizations. Other outcomes included cause-specific mortality and composites of death and first hospitalizations for cardiac disease or infection.

Determination of Clinical Outcomes

Each hospitalization of a study subject was reported by the clinical center, following review of the discharge summary, pertinent medical records, and diagnostic tests. For each death, the clinical center provided the death certificate, USRDS death notification form, and a brief narrative summary prepared by the local principal investigator. All infection-related hospitalizations or deaths were subclassified as "bacteremia or sepsis," "deep tissue infection," or a combination of both. In addition, each infectious outcome was categorized as being access-related or non–access-related. Finally, the clinical center assigned specific medical diagnosis codes from a predefined list for each hospitalization (up to four diagnoses were permitted).

An Outcome Review Committee, comprising investigators blinded to the patient's randomization group, performed independent audits of all clinical center reports of deaths and first cardiac or infection-related hospitalization. All mortality reviews required independent audits of the clinical center's death report by two members of the committee. Agreement on the category of the primary cause of death was required. When the reviewers disagreed, the cause of death was adjudicated during a conference call of the Outcome Review Committee.

All first infection-related or cardiac hospitalization reports were audited by one member of the Outcome Review Committee. This review process required agreement between the Clinical Center's principal investigator and the Outcome Review Committee member as to the classification of the cause of hospitalization. When agreement could not be reached between the Outcome Review Committee member and the Clinical Center investigator, the case was adjudicated by the Outcome Review Committee. To evaluate the accuracy of the review process, the level of agreement between the diagnosis reported by the Clinical Center and the Outcome Committee was examined. When the clinical center determined that a hospitalization was due to infection, the Outcome Committee agreed 96% of the time. The Outcome Committee also concurred with the clinical center classification of the first hospitalization as "bacteremia or sepsis," "deep tissue infection," and "access-related hospitalization" in 92%, 95%, and 88% of cases. When the clinical center did not report an infectious etiology for the hospitalization, the Outcome Committee disagreed in only 4% of the time.

Subsequent infection-related and cardiac hospitalizations were not routinely audited by the Outcome Committee. To further assess the validity of the classification in those instances, a random subset of subsequent hospitalizations was adjudicated by the Outcome Committee. The sensitivity and specificity of the clinical center's diagnosis of infectious hospitalization was 92% and 99%, respectively, when the Outcome Committee's diagnosis was taken as the gold standard. On this basis, we concluded that the Clinical Center classification could be accepted with a high degree of confidence in those instances that were not audited by the Outcome Committee.

Each month, the clinical center completed a form for each study patient specifying what type of vascular access (fistula, graft, or catheter) was being used for dialysis. For the purpose of this analysis, we assumed that the type of access specified in the form preceding a death or hospitalization was the one in use at the time of the infectious event.

Statistical Analyses

The effects of the dose and flux interventions were investigated for two classes of infectious outcomes. The first class consisted of outcomes defined by a single event for each patient. These included (*1*) all-cause mortality, (*2*) the main secondary composite outcome including the first infection-related hospitalization or death from any cause, (*3*) infection-related death, (*4*) the first infection-related hospitalization, and (5) the composite outcome including the first infection-related hospitalization or infection-related death. The time from randomization to the second outcome can be interpreted as the duration of survival free of infection-related hospitalization, while the third, fourth, and fifth outcomes specifically address only infection-related events. Each of these outcomes was defined on the basis of the classifications of the HEMO Study Outcome committee, as described above.

Table 1. Baseline characteristics of the HEMO Study cohort[a]

Factors	All patients (n = 1846)
Age, yr	58 ± 14
Female (%)	56.2
Black (%)	62.6
Diabetic (%)	44.6
Duration of dialysis, yr	3.7 ± 4.4
ICED score[b]	2.0 ± 0.8
Cardiac disease (%)	80.1
Coronary artery disease (%)	39
Congestive heart failure (%)	40
Post-dialysis weight (kg)	69 ± 15
Serum albumin (g/dl)	3.6 ± 0.4
Systolic BP (mmHg)[c]	152 ± 22
Diastolic BP (mmHg)[c]	81 ± 13

[a] Values are means ± SD or percentages.
[b] Index of Coexisting Disease severity score computed with diabetes excluded.
[c] Pre-dialysis values.

The effects of the randomized interventions on each of these outcomes was evaluated using Cox regression (10), stratified by clinical center and controlling for the seven pre-specified baseline covariates: age, gender, race, years on dialysis, diabetes, Index of Coexisting Disease (ICED) score computed excluding diabetes (11,12), and serum albumin. The interaction of baseline albumin with follow-up time was also included as a covariate to account for a reduction in the association of baseline albumin with mortality rate over time. Kidney transplants were censored for each outcome. In addition, the time of transfer to a nonparticipating dialysis unit or alternative dialysis modality was treated as a censoring event for the second, fourth, and fifth outcomes, which included hospitalization events; non–infection-related deaths were censored for the third and fifth outcomes, which included infection-related deaths; and all deaths were censored for the fourth outcome. The analyses with censored deaths must be viewed in a competing risk framework, in which the censored deaths are regarded as competing risk.

The second class of outcomes included multiple events for patients having more than one occurrence of the designated infection-related hospitalization. These outcomes were (*1*) all infection-related hospitalizations, (*2*) all infection-related hospitalizations that were access-related, (*3*) all infection-related hospitalizations that were non–access-related, (*4*) all infection-related hospitalizations presenting as deep-tissue infections, and (*5*) all infection-related hospitalizations presenting as bacteremia or sepsis. The effects of the randomized treatment interventions on each of these outcomes were evaluated using overdispersed Poisson regression analysis (13) while controlling for clinical center and the same seven baseline covariates described above, with deaths, transplants, and transfers censored.

Event rates for both classes of outcomes defined above were defined as the ratio of the total number of events to the total patient years of follow-up for that outcome, using the same rules for censoring as in the Cox and Poisson regressions described above.

The relationships of access type with infection-related death and with the composite outcome including the infection-related hospitalization or infection-related death were evaluated by Cox regressions relating the indicated outcomes to the access type designated on the monthly kinetic modeling form as a time-dependent covariate. These Cox regression models included the seven pre-specified baseline factors and randomized treatment group as covariates.

The relationship of the conditional probability that a patient's infection-related hospitalization resulted in death to the randomized treatment groups and the seven pre-specified baseline factors was investigated using multiple logistic regression. Deaths occurring within 3 d of discharge were attributed to the infection-related hospitalization in this analysis.

All analyses of the effects of the interventions were intent-to-treat. Kaplan-Meier survival curves (14) were constructed for the composite

Table 2. Frequency of infection-related outcomes

Event	Total Number of Events	Rate[a]
Deaths (all causes)	871	16.6%
1st infection-related hospitalization or death (all causes)	1104	29.9%
Infection-related death	201	3.8%
1st infection-related hospitalization	783	21.2%
1st infection-related hospitalization or infection-related deaths	802	21.7%
All hospitalizations	7757	159.8%
All infection-related hospitalizations	1698	35.0%
Access infection-related hospitalizations	395	8.1%
Non-access infection-related hospitalizations	1303	26.8%
Deep tissue infection-related hospitalizations (irrespective of whether also classified as bact. or sepsis)	1302	26.8%
Deep tissue infection-related hospitalizations only	927	19.1%
Bacteremia or sepsis infection-related hospitalizations (irrespective of whether also classified as deep tissue)	771	15.9%
Bacteremia or sepsis infection-related hospitalizations only	396	8.2%
Both deep tissue and bact or sepsis hosps.	375	7.7%

[a] Events per patient-year.

Table 3. Breakdown of infection-related events by disease category

Disease Category	All Infection-Related Hospitalizations[a]			1st Infection-Related Hospitalizations[a]			Infection-Related Deaths		
	Freq	Percent[b]	Annual Rate	Freq	Percent[b]	Annual Rate	Freq	Percent	Annual Rate
Cardiac disease	48	2.8	1.0	23	2.9	0.6	10	5.0	0.2
Peripheral vascular disease	176	10.4	3.6	67	8.6	1.8	27	13.4	0.5
Diabetes mellitus and endocrine disorders	101	5.9	2.1	40	5.1	1.1	3	1.5	0.1
Respiratory disease	372	21.9	7.7	184	23.5	5.0	41	20.4	0.8
Hepatobiliary disease	21	1.2	0.4	14	1.8	0.4	6	3.0	0.1
Musculoskeletal or connective tissue dis	70	4.1	1.4	33	4.2	0.9	5	2.5	0.1
Gastrointestinal	106	6.2	2.2	52	6.6	1.4	8	4.0	0.2
Nonvascular nervous system disease	7	0.4	0.1	4	0.5	0.1	3	1.5	0.1
Urinary tract disease	62	3.7	1.3	31	4.0	0.8	3	1.5	0.1
Hemodialysis vascular access complications	392	23.1	8.1	196	25.0	5.3	34	16.9	0.6
Infections of unknown source[c]	587	34.6	12.1	250	31.9	6.8	61	30.3	1.2

[a] A single hospitalization may receive up to four diagnosis codes, such that the same hospitalization may be counted more than once. Only infection-related diagnosis codes are counted in each category.
[b] Percent is calculated out of the total number of all infection-related hospitalizations (1698), or total number of 1st inf. hospitalizations (783).
[c] Includes septic shock, bacteremia, or abscess not falling into another disease category.

outcome including first infection-related hospitalization or all-cause death. Statistical differences between survival curves were determined by the log rank test. All reported *P*-values are two-sided, without adjustment for multiple comparisons.

Results

The HEMO Study randomized 1846 chronic hemodialysis patients, and they had a mean follow-up for mortality of 2.84 yr. A summary of the demographic and clinical characteristics of the study cohort is presented in Table 1. The study population tended to be younger than the US hemodialysis population. The proportion of black patients was higher, reflecting the demographics of the participating dialysis units.

In the course of the study, 871 patients died, providing an annual death rate of 16.6%. An infectious etiology was responsible for 201 deaths, or 23.1% of all deaths in the study (Table 2). The annual rate of infection-related death was 3.8%. There were 1698 infection-related hospitalizations, giving an annual rate of 35.0%. Of these, 55% were classified as deep tissue infections only, and 45% as having bacteremia or sepsis. In addition, 23% of all infection-related hospitalizations were considered access-related, and 77% non–access-related.

The most common disease categories responsible for infection-related death, first infection-related hospitalization, and all infection-related hospitalizations included respiratory disease (20.4 to 23.5%), vascular access infections (16.9 to 25.0%), and infection of unknown source (30.3 to 34.6%) (Table 3).

Table 4. Percent of infection-related hospitalizations that ended with death[a] by any cause

Disease Category	All Infectious Hospitalizations		1st Infectious Hospitalizations	
	Freq	%	Freq	%
Cardiac disease	48	29.2	23	30.4
Peripheral vascular disease	176	10.3	67	17.9
Diabetes mellitus and endocrine disorders	101	9.9	40	10.0
Respiratory disease	372	17.5	184	15.8
Hepatobiliary disease	21	14.3	14	14.3
Musculoskeletal or connective tissue dis	70	11.4	33	9.1
Gastrointestinal	106	17.9	52	23.1
Nonvascular nervous system disease	7	0.0	4	0.0
Urinary tract disease	62	9.7	31	3.2
Hemodialysis vascular access complications	392	6.9	196	7.1
Infections of unknown source[b]	587	26.6	250	25.6

[a] Deaths within 3 d after the discharge date are included.
[b] Includes septic shock, bacteremia, or abscess not falling into another disease category.

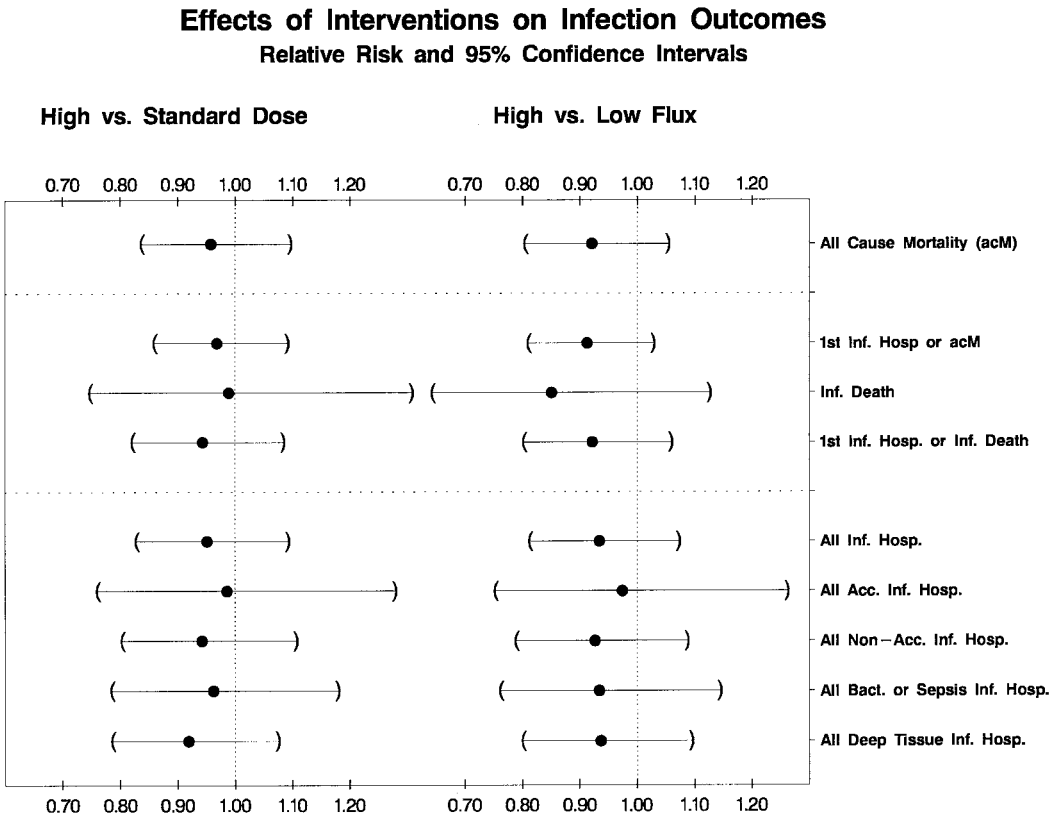

Figure 1. 95% confidence limits for the effects of the treatment Interventions. Relative risks compare the high-dose with the standard-dose group and the high-flux with the low-flux group. Shown are the primary outcome (mortality), infection-related deaths, infection-related hospitalizations, and selected additional secondary outcomes. Analyses are stratified by clinical center, and adjusted for baseline age, gender, race, duration of dialysis, diabetes, ICED score, excluding diabetes, and serum albumin.

Among patients with an infection-related hospitalization due to cardiac disease, 25.0% had coexisting vascular access infection. Conversely, 3.1% of infection-related hospitalizations that were access-related had a coexisting cardiac infection. The overall probability of death during an infection-related hospitalization was 15%, but it varied greatly according to the disease category (Table 4): 30% for cardiac infections, 17% for respiratory infections, and only 7% for vascular access-related infections.

The overall likelihood of death was not significantly different among patients randomized to the high dose *versus* standard dose, nor did it differ between patients randomized to the high-flux *versus* low-flux dialysis (Figure 1). Similarly, infection-related deaths, first infection-related hospitalizations, composite infectious outcomes, and rate of all infection-related hospitalizations or major classes of infection were not significantly reduced by a high dose or by high-flux membranes (Figure 1). Finally, infection-free survival was similar between patients randomized to a high or standard Kt/V and similar between patients with high-flux and low-flux membranes (Figure 2).

In a multivariable analysis, including the two randomization variables (dialysis dose and flux), as well as seven predefined baseline clinical variables, only diabetes, hypoalbuminemia, and high co-morbidity score (ICED) predicted a higher rate of infection-related hospitalization (Table 5). A similar analysis identified patient age, baseline serum albumin, ICED code, and number of years on dialysis as significant predictors of infectious deaths (Table 5). Finally, among the seven prespecified clinical variables, the RR of death during an infection-related hospitalization was affected significantly only by patient age (RR, 1.44 [1.21 to 1.72] per 10 yr; $P < 0.001$) and baseline serum albumin (RR, 0.46 [0.25 to 0.84] per g/dl; $P = 0.01$).

Only about one fifth of all first infection-related hospitalizations were considered to be access-related (Table 2). Among the subset of first infection-related hospitalizations that were access-related, the class of infection differed according to the type of vascular access. When the patient was dialyzing with a catheter, the infection was classified as "bacteremia or sepsis" 90% of time; in contrast, when the patient was dialyzing with a fistula or graft, this class of infection was observed 54 and 55% of the time, respectively (Figure 3).

Although catheters represented just 7.6% of the vascular accesses in the study, catheters were used in 32% of the access-related infections. A time-dependent Cox regression analysis, adjusted for clinical center and the seven predefined clinical variables, found a significantly higher likelihood of infection-related death among patients dialyzing with catheters compared with those dialyzing with fistulas (RR, 2.30 [95% CI, 1.45 to 3.64]; $P < 0.001$]. Similarly, the likelihood of first

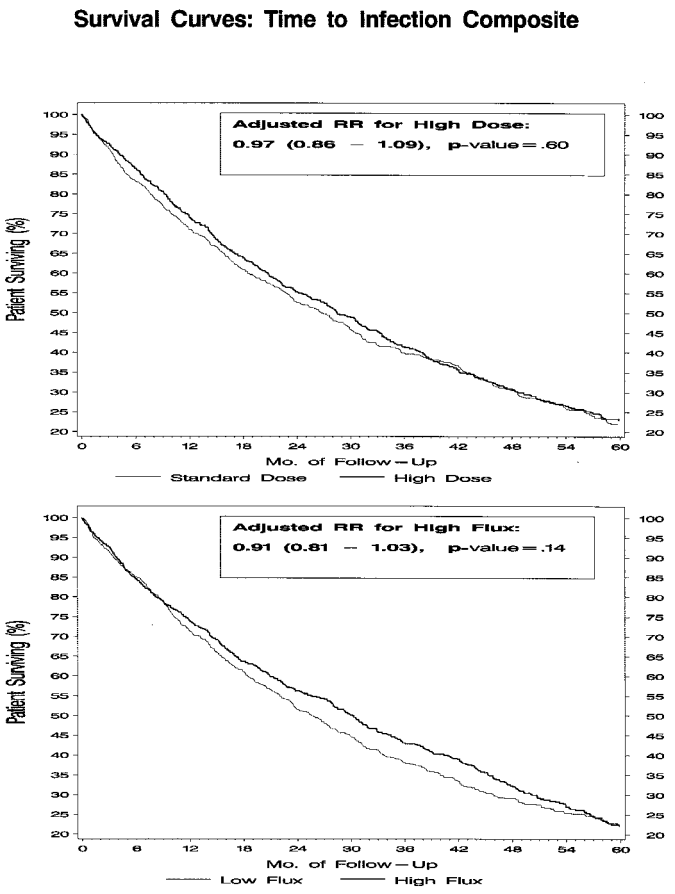

Figure 2. Survival curves for infection-free survival by randomized treatment group. After adjustment for the baseline factors, the high-dose group had a 3% lower rate for the composite of first infection-related hospitalization or all-cause death (95% CI, −9% to +14%; $P = 0.60$) than the standard-dose group, and the high-flux group had an 9% lower rate (95% CI, −3% to +19%; $P = 0.14$) than the low-flux group.

infection-related hospitalization or infection-related death was significantly higher for patients dialyzing with catheters compared with those dialyzing with fistulas (RR, 1.85 [95% CI, 1.47, 2.33]; $P < 0.001$).

Discussion

The HEMO Study confirms the high frequency of infections among chronic hemodialysis patients. Serious infections accounted for almost one fourth of all deaths. This proportion is about twice as high as the 12% of deaths estimated previously on the basis of retrospective analysis of the HCFA Death Notification Form (1,8). The higher proportion of infection-related deaths in the current study may be due to the prospective nature of data collection or to differences in the classification of causes of death. The 3.8% annual rate of infection-related deaths in the HEMO Study is comparable to the 3.2% rate reported for all US hemodialysis patient deaths between 1996 and 1998 (2).

Previous studies suggesting a beneficial effect of higher flux or higher Kt/V on infectious outcomes have been hampered by being nonrandomized, retrospective, or small sample size. In a large observational study of USRDS patients, Bloembergen *et al.* (1) reported a 9% lower relative risk of infection-related death for each 0.1-unit increase in single-pool Kt/V. The observational nature of their study precludes drawing conclusions about causality. In contrast, the present, prospective, randomized clinical trial did not observe a beneficial effect of higher dialysis dose (single pool Kt/V, 1.71 *versus* 1.32) on infectious outcomes (Figures 1 and 2). The present study does not preclude the possibility of patients with a Kt/V approximately 1.3 having fewer infectious events than those with an even lower Kt/V. However, it does not support the utility of exceeding current K/DOQI guidelines for hemodialysis adequacy (Kt/V $\geq$ 1.20) (15) for prevention of serious infections.

In vitro studies suggest a defect in polymorphonuclear cell function in uremic patients (16,17), that is improved by the use of high-flux dialysis membranes (18). An observational analysis of a large cohort of USRDS patients found that infection-related deaths were 31% lower among patients dialyzing with high-flux synthetic membranes compared with patients dialyzing with low-flux, unmodified cellulose membranes (8). In contrast, a recent prospective study evaluating bacteremia among chronic dialysis patients did not find a higher frequency of infections among patients dialyzing with cellulose membranes (5). The present, prospective, randomized clinical trial observed no advantage of high-flux dialyzers compared with low-flux membranes (β_2M clearances, 33.8 $\pm$ 11.4 ml/min *versus* 3.4 $\pm$ 7.2 ml/min, respectively) on infectious outcomes (Figures 1 and 2). Bioincompatible, unsubstituted cellulose dialyzers were excluded; it is therefore not possible to draw conclusions from the current study about their effect on infections.

The HEMO Study excluded patients with advanced age, those with severe comorbidity, and those with severe access problems that precluded achievement of the high-dose dialysis target. The possibility that a higher dose of dialysis or the use of high-flux membranes may benefit these patient subsets cannot be excluded.

The HEMO Study confirms previous reports showing an increased risk of serious infectious events among diabetic patients, older patients, individuals with serious co-morbidity, patients with hypoalbuminemia, and those using catheters for access (1,3–7). Hypoalbuminemia, a particularly striking risk factor for infectious events in the present study, is frequently a marker of inflammatory conditions in hemodialysis patients (19–21), which may predispose those patients to a higher risk of death or hospitalization.

Catheters were an important predictor of infection-related hospitalizations in the HEMO study. In agreement, Hoen *et al.* (5) observed that catheters were present in 36% of their patients with access-related infections, even though only 6% of the dialysis population was dialyzing with catheters. The increased risk of infection-related deaths among patients dialyzing with catheters in the present study is in agreement with a recent retrospective analysis (6). Because the prevalence of catheter use in the HEMO Study (7.6%) was far lower than its prevalence in the US hemodialysis population (approximately

Table 5. Effect of randomization group and 7 predefined clinical variables on infection-related hospitalization and death rate

Parameter	Rate of Inf Hospitalizations[b] (1698 Events)		Inf Deaths[c] (201 Events)	
	RR	95% CI	RR	95% CI
High-Kt/V group	0.95	(0.83 to 1.09)	0.99	(0.75 to 1.31)
High-flux group	0.93	(0.81 to 1.07)	0.85	(0.64 to 1.13)
Age (per 10 yr)	1.01	(0.95 to 1.07)	1.47[d]	(1.29 to 1.68)
Diabetic	1.45[d]	(1.24 to 1.69)	1.26	(0.93 to 1.72)
Baseline albumin (per 0.5 g/dl)	0.73[d]	(0.66 to 0.82)	0.43[d]	(0.29 to 0.64)
Baseline comorbidity score (per ICED unit)[a]	1.25[d]	(1.14 to 1.37)	1.46[d]	(1.21 to 1.76)
Black race	1.04	(0.87 to 1.24)	0.84	(0.59 to 1.18)
Gender (female)	1.03	(0.89 to 1.20)	1.00	(0.74 to 1.36)
Years dialysis	1.01	(1.00 to 1.03)	1.04	(1.00 to 1.07)

[a] ICED, Index of Coexisting Disease.
[b] The effect of the randomized treatment intervention on this outcome was evaluated using overdispersed Poisson regression analysis while controlling for the seven prespecified baseline covariates listed.
[c] The effect of the randomized treatment intervention on this outcome was evaluated using Cox regression analysis, stratified by clinical center and controlling for the seven prespecified baseline covariates listed, as well as the interaction between baseline serum albumin and follow-up time. The relative risk for the interaction term was 1.21 (95% CI, 1.06 to 1.38), indicating that there was a progressive weakening of the effect of baseline albumin over time, with its relative risk alternative toward 1.0 by 21% per year of followup.
[d] $P < 0.001$.

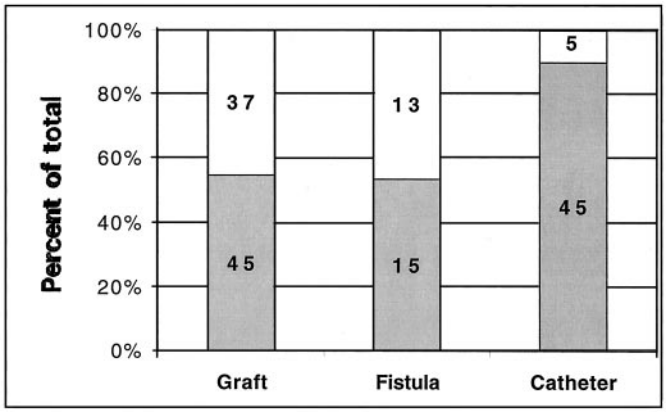

Figure 3. First infection-related hospitalization that was access-related, classified by type of vascular access and type of infection (gray bars, bacteremia or sepsis; white bars, deep tissue infection only). The number of patients is listed inside the bars. Access classification was missing for 12 hospitalizations. The class of infection differed significantly between patients dialyzing with catheters and those dialyzing with a fistula or graft ($P < 0.001$). The numbers of affected patients are indicated in the bars.

20%) (22–24), the burden of catheter-associated infection is likely much higher in the general US dialysis population.

In conclusion, neither increasing the dialysis dose above current DOQI guidelines nor switching to high-flux dialyzers is likely to reduce infection-related deaths or hospitalizations in hemodialysis patients. Although only about 20% of all infection-related hospitalizations are access-related, they may represent the subgroup that is most preventable by changing practice patterns. The other risk factors, including age, diabetes, co-morbidity, dialysis vintage, and hypoalbuminemia, are not readily modifiable. A concerted effort to reduce the proportion of dialysis patients dialyzing with catheters could substantially reduce the frequency of infection-related hospitalizations, particularly those classified as bacteremia or sepsis.

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