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Cardiac diseases in maintenance hemodialysis patients: Results of the HEMO Study

ALFRED K. CHEUNG, MARK J. SARNAK, GUOFEN YAN, MICHAEL BERKOBEN, ROBERT HEYKA, ALLEN KAUFMAN, JULIA LEWIS, MICHAEL ROCCO, ROBERT TOTO, DAVID WINDUS, DANIEL ORNT, ANDREW S. LEVEY, FOR THE HEMO STUDY GROUP

Veterans Affairs Salt Lake City Healthcare System and University of Utah, Salt Lake City, Utah; New England Medical Center, Boston, Massachusetts; Cleveland Clinic Foundation, Cleveland, Ohio; Duke University, Durham, North Carolina; Beth Israel Medical Center, New York, New York; Vanderbilt University, Nashville, Tennessee; Wake Forest University, Winston-Salem, North Carolina; University of Texas Southwestern Medical School, Dallas, Texas; Washington University, St. Louis, Missouri; and University of Rochester, Rochester, New York

Cardiac diseases in maintenance hemodialysis patients: Results of the HEMO Study.

Background. Cardiac disease is a common cause of death in chronic hemodialysis patients. A subanalysis of the data on cardiac diseases in the Hemodialysis (HEMO) Study was performed. The specific objectives were: (*1*) to analyze the prevalence of cardiac disease at baseline; (*2*) to characterize the incidence of various types of cardiac events during follow-up; (*3*) to examine the association of cardiac events during follow-up with baseline cardiac diseases; and (*4*) to examine the effect of dose and flux interventions on various types of cardiac events.

Methods. The HEMO Study is a randomized multi-center trial on 1846 chronic hemodialysis patients at 15 clinical centers comprising 72 dialysis units. The scheduled maximum follow-up duration was 0.9 to 6.6 years, with the mean actual follow-up of 2.84 years. The interventions were standard-dose versus high-dose and low-flux versus high-flux hemodialysis in a 2×2 factorial design.

Results. At baseline, 80% of patients had cardiac diseases, including ischemic heart disease (IHD) (39%), congestive heart failure (40%), arrhythmia (31%), and other heart diseases (63%). There were a total of 1685 cardiac hospitalizations, with angina and acute myocardial infarction accounting for 42.7% of these hospitalizations. There were 343 cardiac deaths during follow-up, accounting for 39.4% of all deaths. IHD was implicated in 61.5% of the cardiac deaths. Any cardiac disease at baseline was highly predictive of cardiac death during follow-up [relative risk (RR) 2.57; 95% CI 1.73–3.83]. There were no significant effects of dose or flux assignments on the primary outcome of all-cause mortality or the main secondary cardiac composite outcome of first cardiac hospitalization or all-cause mortality. Assignment to high-flux dialysis was, however, associated with decreased cardiac mortality and the composite outcome of first cardiac hospitalization or death from cardiac causes.

Conclusion. The HEMO Study identified IHD to be a major cause of cardiac hospitalizations and cardiac deaths. Future strategies for the prevention of cardiac diseases in the maintenance hemodialysis population should focus on this entity. Although high-flux dialysis did not reduce all-cause mortality, it might improve cardiac outcomes. This hypothesis needs to be further examined.

Key words: hemodialysis, cardiac disease, mortality, outcome, high flux, randomized trial.

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Cardiac disease is the leading cause of death among prevalent maintenance dialysis patients, accounting for approximately 45% of reported deaths in the United States [1, 2]. Compared with the general population, dialysis patients have a 10 to 20 times greater incidence of cardiovascular death [3]. This excess cardiac mortality is, in part, caused by a high prevalence of cardiac disease before initiation of dialysis [4, 5], and is likely caused by the high prevalence of cardiovascular risk factors in patients with progressive kidney disease [4–6]. In addition, dialysis patients with cardiac disease have a higher case-fatality rate than nondialysis patients with heart disease [7]. These data indicate an urgent need to identify the types of cardiac diseases, the risk factors for cardiac disease, and the strategies for prevention and treatment of cardiac diseases in patients with chronic kidney disease.

Despite the large and growing population of patients on maintenance hemodialysis in the United States, there has been a relative lack of large clinical databases describing the specific cardiac causes of mortality and hospitalization. Most of the available data in this regard are derived from retrospective analysis of administrative databases, which is fraught with limitations. In addition, the contributions of underlying cardiac diseases to subsequent cardiac events are unclear. Furthermore, there has been no large-scale prospective study that evaluated the

effects of dialysis dose or flux on cardiovascular morbidity and mortality. The Hemodialysis (HEMO) Study is the first large-scale prospective clinical trial involving 1846 maintenance hemodialysis patients randomized to either standard dialysis dose or high dialysis dose and low-flux or high-flux membranes [10]. In this report, we present the pre-existing cardiac diseases at baseline in this study, the incidence of various types of cardiac events during follow-up, and examine the association of these events with baseline cardiac diseases. Finally, we report the efficacy of the randomized interventions on specific cardiac outcomes (death and hospitalizations as a result of cardiac causes).

METHODS

Study design

The design and methods of the HEMO Study have been previously reported [8–10]. In brief, 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. The patients were aged 18 to 80 years old, undergoing in-center hemodialysis thrice weekly, and had been on dialysis for at least 3 months. Among other exclusion criteria were unstable angina and New York Heart Association Class IV congestive heart failure (CHF). Participants were evaluated during an 8- to 12-week baseline period between March 1995 and October 2000. They were excluded from randomization if they were unable to achieve an equilibrated urea dialysis dose (Kt/V) (eKt/V) [11] $\geq$1.35 within 4.5 hours, or if their residual kidney urea clearance was >1.5 mL/min/35 L of urea distribution volume.

Eligible patients were randomized between May 1995 and February 2001 to either a standard-dose (urea eKt/V 1.05) or high-dose goal (eKt/V 1.45), and to either a low-flux [mean β_2-microglobulin (β_2M) clearance <10 mL/min] or a high-flux (mean β_2M clearance >20 mL/min and ultrafiltration coefficient >14 mL/hr/mm Hg) dialyzer in a 2 $\times$ 2 factorial design with equal allocation. The mean achieved eKt/V, single-pool Kt/V (spKt/V), and urea reduction ratio (URR) during follow-up were 1.16 $\pm$ 0.08, 1.32 $\pm$ 0.09, and 66.3 $\pm$ 2.5%, respectively, for the standard-dose arm, and 1.53 $\pm$ 0.09, 1.71 $\pm$ 0.11, and 75.2 $\pm$ 2.5%, respectively, for the high-dose arm. The mean achieved β_2M clearances were 3.4 $\pm$ 7.2 mL/min and 33.8 $\pm$ 11.4 mL/min in the low-flux and high-flux arms, respectively. The durations of the dialysis sessions were 190 $\pm$ 23, 219 $\pm$ 23, 206 $\pm$ 28, and 203 $\pm$ 27 minutes for the standard-dose, high-dose, low-flux, and high-flux arms, respectively. Standards of general medical care for blood pressure control, calcium-phosphorus balance, anemia, and other parameters were monitored by a Quality of Care Committee. Data collection ended in December 2001. The maximum potential follow-up period for individual patients was 0.9 to 6.6 years, depending on the date of randomization.

Collection of baseline cardiac data

During the baseline period, evidence for existing or history of cardiac disease was collected by study coordinators and investigators using the Index of Disease Severity (IDS), one of the components of the Index of Coexisting Disease (ICED) [12]. In addition to the categories for other diseases, the IDS includes four categories for cardiac disease: ischemic heart disease (IHD), CHF, arrhythmias, and other heart diseases. Ascertainment of cardiac disease was accomplished by review of dialysis unit charts and hospital medical records, with particular attention paid to electrocardiogram (ECG), chest x-ray, and echocardiogram reports, which were available in 82%, 78%, and 41% of patients, respectively. A simple mention of cardiac disease in these records was sufficient for coding a diagnosis in the IDS. Each category of cardiac disease was scored from 0 to 3, with 0 indicating no disease in that category, and 3 indicating moderate or severe manifestations of the disease, despite treatment. For this report, we combined all patients with levels of 1 to 3 and classified them as positive for cardiac disease in that category.

Designation of clinical outcomes

The primary outcome of the HEMO Study was all-cause mortality. In the design of the study, the main secondary cardiac outcome was the composite end point of first cardiac hospitalization or all-cause mortality. Additional secondary cardiac outcomes included cardiac mortality, the composite of first hospitalization or death from cardiac disease [10], and hospitalization and deaths from four specific cardiac causes. The four cardiac causes of death were: (*1*) IHD; (*2*) CHF; (*3*) arrhythmias, and (*4*) other heart diseases. Their subcategories are presented in **Appendix I**. Sudden deaths were operationally defined as witnessed and unwitnessed unexpected deaths, with a preceding duration of symptoms less than 24 hours for witnessed deaths, and less than the interval since the last dialysis session for unwitnessed deaths. Sudden death was attributed to IHD if the patient had a past history of this condition, to arrhythmias if the patient had a past history of arrhythmias in the absence of IHD, and to other heart diseases if there were other causes of heart disease in the absence of IHD or arrhythmias.

Hospitalization was attributed to cardiac disease if it was precipitated or accompanied by any of the following: new onset or worsening angina, myocardial infarction, CHF, arrhythmias, or other heart diseases. The category of other heart diseases included hospitalizations for valvular diseases, pericarditis, and endocarditis. Each

hospitalization may be attributed to one or more cardiac cause.

Details of the methods used for the collection and validation of outcome data are presented in **Appendix II**.

Statistical analyses

Baseline characteristics were summarized by mean and standard deviations for continuous variables and by relative frequencies for categorical variables. These characteristics were compared between subgroups by chi-square tests or by pooled or unpooled *t* tests as appropriate.

Event rates were computed based on the ratio of the number of events during the ascertainment period to the total patient-years before the designated first event or the end of the ascertainment period. Event rates were expressed per 100 patient-years by multiplying these ratios by 100.

The relationships of baseline cardiac disease with the cardiac outcomes were examined by Cox regression models [14] for each outcome with stratification by the 15 Clinical Centers, and adjusted for the randomized treatment groups and the following seven prespecified baseline covariates: age, gender, race, diabetes, years on dialysis, ICED level computed excluding diabetes, serum albumin, and for the interaction of serum albumin with follow-up time [10]. The interaction of baseline albumin with follow-up time was included in the models to account for the expectation that the association of baseline albumin with the cardiac outcomes would decline over time.

The primary analysis was conducted by Cox regression of survival after randomization. Effects of randomized groups on mortality were tested with stratification by the Clinical Centers, and adjusted for the following seven prespecified baseline covariates as described above. Consistent with the calculation of event rates for mortality, follow-up was censored at the time of renal transplantation, but not transfers. The effects of the randomized groups on a designated cause of death was analyzed using the same basic Cox regression model, except that deaths from causes other than the designated cause were censored as competing risks. The effects of the randomized groups on the composite of first cardiac hospitalization or all-cause death, and on the composite of first cardiac hospitalization or cardiac death, were analyzed using the basic Cox model, with transfers censored in addition to renal transplantation.

The secondary outcome that incorporates cardiac death and total cardiac hospitalizations include multiple events in the same patient, and therefore could not be analyzed by the standard Cox regression model. Thus, this outcome was analyzed using several techniques for multiple events (the Andersen-Gill model, the marginal model suggested by Wei, Lin, and Weissfeld, the Gaussian frailty model, and the overdispersed Poisson regression model) [15]. Because results for comparisons between the flux arms were consistent among these techniques, only the results using the overdispersed Poisson regression model are presented.

Interactions between interventions and baseline cardiac diseases on outcomes were individually tested using extensions of the Cox models described above to determine if the interventions had different effects on cardiac outcomes in subgroups defined by the various baseline cardiac conditions.

RESULTS

Baseline characteristics

The demographics and other clinical characteristics of patients at entry to the study are shown in Table 1. The study cohort was in general slightly younger and comprised more blacks than the dialysis population in the United States [16]. These patients had been on dialysis for 3.7 ± 4.4 years before entry into the study, reflecting the exclusion criterion on significant residual kidney function. There were no differences ($P > 0.05$) in any of these variables between the two dose arms or between the two flux arms, indicating that the patients were well randomized [10].

Prevalence of cardiac disease at baseline

Cardiac diseases were common at baseline. Eighty percent of the patients had one or more type of cardiac diseases (Fig. 1). There was substantial overlap among the four specific categories of IHD, CHF, arrhythmia, and other heart diseases. For example, out of the 725 patients with IHD, 55% also had CHF, 46% had arrhythmia, and 74% had other heart diseases. Forty-two percent of patients with CHF also had arrhythmia. Within the category "other heart diseases," 46% had left ventricular hypertrophy (LVH) by echocardiographic criteria, 52% had LVH by electrocardiographic criteria, 57% had cardiomegaly on chest x-ray, 94% had at least one of these three findings that were suggestive of an enlarged heart, 39% had valvular disease, and 5% had pericarditis. Among the patients in the "other heart diseases" category, 46% also had IHD, 50% had CHF, and 38% had arrhythmia.

Differences in baseline cardiac diseases between demographic subgroups

Any cardiac disease (86.1% vs. 72.8%) and all four categories of cardiac disease were more ($P < 0.0001$) prevalent in older patients compared to those younger than 58 years. This difference was particularly pronounced in IHD and arrhythmia, in which the prevalence was twice as high in the older patients. There were no gender differences in cardiac diseases with the exception of

Table 1. Baseline characteristics of study cohort

Factors	All patients ($N = 1846$)	Patients without pre-existing cardiac disease ($N = 367$)	Patients with pre-existing cardiac disease ($N = 1479$)	P value (with vs. without cardiac disease)[e]
Age *years*	57.6 ± 14.0	51.9 ± 15.1	59.0 ± 13.4	0.0001
% Female	56.2	55.9	56.3	0.8727
% Black	62.6	56.7	64.1	0.0085
% Diabetic	44.6	32.7	47.5	<0.0001
ICED level[a]	2.0 ± 0.8	1.7 ± 0.8	2.1 ± 0.8	0.0001
% with cardiac disease	80.1	0	100	–
Years on dialysis	3.7 ± 4.4	3.9 ± 4.7	3.7 ± 4.3	0.5435
% Residual kidney clearance >0	32.9	35.4	32.3	0.2471
Post-dialysis wt *kg*	69.2 ± 14.7	69.5 ± 15.2	69.1 ± 14.6	0.6002
Post-dialysis total body total body water[b] *L*	34.9 ± 6.1	35.4 ± 6.4	34.8 ± 6.0	0.1148
Systolic BP[c] *mm Hg*	151.8 ± 22.1	149.8 ± 22.8	152.3 ± 22.0	0.0614
Diastolic BP[c] *mm Hg*	81.4 ± 13.0	82.9 ± 12.9	81.1 ± 13.0	0.0135
Serum creatinine[c] *mg/dL*	10.3 ± 2.9	11.1 ± 2.9	10.0 ± 2.8	0.0001
Serum total cholesterol[3] *mg/dL*	172.7 ± 40.7	170.4 ± 39.7	173.2 ± 40.9	0.2426
Serum albumin[c] *g/dL*	3.6 ± 0.4	3.7 ± 0.4	3.6 ± 0.4	0.0001
enPCR[d] *g/kg/day*	1.03 ± 0.24	1.07 ± 0.23	1.02 ± 0.24	0.0009

Presented are the mean ± SD or percentage.
[a]Index of Coexisting Disease (ICED) severity levels computed with diabetes excluded [12].
[b]Predialysis values. Total body water estimated from anthropometric measurements and demographic data [17].
[c]Predialysis values.
[d]Equilibrated normalized protein catabolic rate.
[e]*P* values were determined by either chi-square (for categorical variables) or *t* test (for continuous variable).

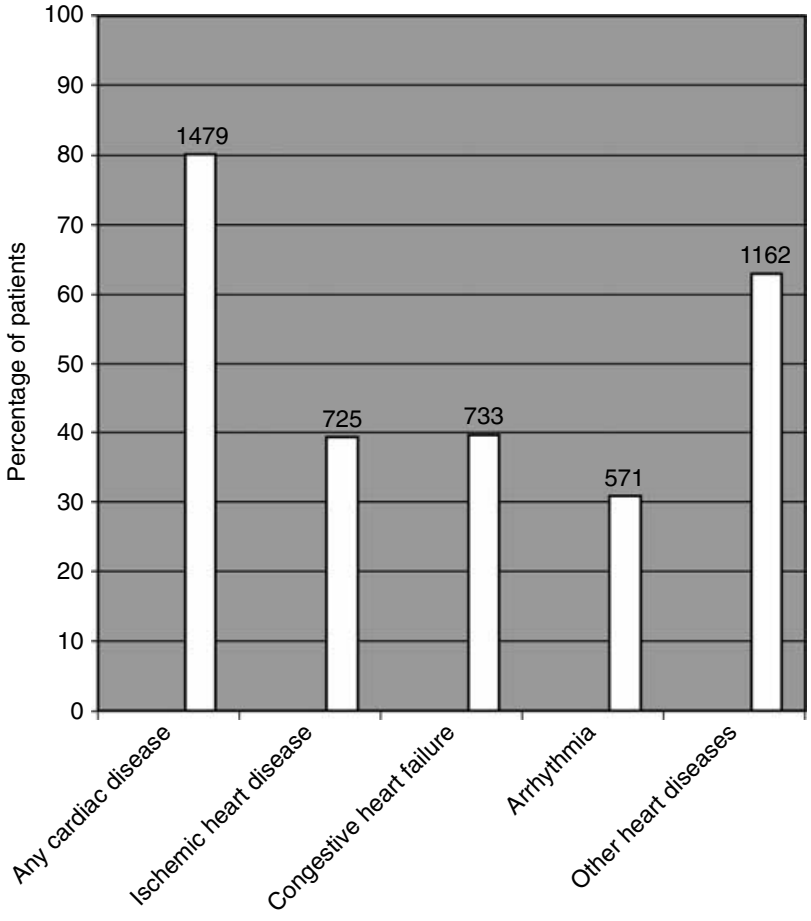

Fig. 1. Various types of cardiac disease at baseline. The number above each bar denotes the number of patients with that specific type of cardiac disease. There were a total of 1846 patients in the cohort, implying that many patients have more than one type of cardiac disease at baseline. The "other heart diseases" category included 534 patients with left ventricular hypertrophy on echocardiogram, 604 patients with left ventricular hypertrophy on electrocardiogram, 664 patients with cardiomegaly on chest x-ray, 448 patients with valvular diseases, and 62 patients with pericarditis.

Table 2. Rates of events involving cardiac deaths during follow-up

Event	No. of events	Rate (per 100 patient-year)
All-cause mortality	871	16.6
1st cardiac hospitalization or all-cause mortality	1079	28.5
1st cardiac hospitalization or cardiac death	835	22.0
Cardiac death	343	6.6
Death from ischemic heart disease	211	4.0
Death from congestive heart failure	36	0.7
Death from arrhythmia	59	1.1
Death from other heart diseases	37	0.7

arrhythmia, which was more prevalent (34.7% vs. 28.0%; $P = 0.0023$) in males. Blacks had less IHD (36.0% vs. 44.8%; $P = 0.0002$) and CHF (38.0% vs. 42.6%; $P = 0.0490$), but more other heart diseases (67.6% vs. 55.2%; $P < 0.0001$). Patients with diabetes had higher ($P < 0.0030$) prevalence of cardiac diseases in all categories than nondiabetics, with the exception of the other heart diseases category in which there was no difference. Patients on dialysis for >3.7 years had more arrhythmia (36.1% vs. 28.6%; $P = 0.0013$) and other heart diseases (69.8% vs. 59.8%; $P < 0.0001$), but less IHD (35.5% vs. 41.0%; $P = 0.0263$), compared with those dialyzed for ≤3.7 years.

Classifications and rates of outcomes involving cardiac deaths during follow-up

Eight outcome measures involving cardiac deaths were used in the analyses for this report (Table 2). Among these, all-cause mortality and the composite of first cardiac hospitalization or all-cause mortality were prespecified outcomes. Additional post-hoc analysis found that cardiac diseases accounted for 39.4% (343 out of 871) of all deaths. Among the cardiac deaths, IHD was determined to be the predominant cause and accounted for 61.5% (211 out of 343). There were 217 sudden deaths; 194 (89.4%) of which were considered to be related to various cardiac causes. The other 23 were sudden deaths of unknown causes.

Classifications and rates of cardiac hospitalizations during follow-up

There were 735 patients who were hospitalized for cardiac causes during the HEMO Study (Table 3). The total number of cardiac hospitalizations was 1685. The rates of first cardiac hospitalization and total cardiac hospitalization were 19.4 per 100 patient-years and 34.7 per 100 patient-years, respectively. Approximately 30% of all first and total cardiac hospitalizations carried more than one cardiac diagnosis. When angina and myocardial infarction were combined, this category of IHD accounted for 42.3% of the first cardiac hospitalizations and 42.7% of the total cardiac hospitalizations.

Table 3. Rates of subcategories of first and total cardiac hospitalizations

	No. of hospitalizations	Rate (per 100 patient-year)
First cardiac hospitalizations[a]		
Any cardiac cause	735	19.4
Angina	247	6.5
Myocardial infarction	127	3.3
Congestive heart failure	283	7.5
Arrhythmia	297	7.8
Other heart diseases	74	2.0
Only 1 cardiac hospitalization category	521	13.7
>1 cardiac hospitalization category	214	5.6
Total cardiac hospitalizations[b]		
Any cardiac cause	1685	34.7
Angina	616	12.7
Myocardial infarction	250	5.2
Congestive heart failure	693	14.3
Arrhythmia	639	13.2
Other heart diseases	174	3.6
Only 1 cardiac hospitalization category	1179	24.3
>1 cardiac hospitalization category	506	10.4

[a]First cardiac hospitalization refers to the first time the patient was hospitalized for the specified cardiac cause during follow-up.
[b]Total cardiac hospitalization refers to the total number of hospitalizations for the specified cardiac cause during follow-up.

Association of baseline cardiac disease burden with subsequent cardiac events

The association of cardiac diseases at baseline with subsequent cardiac events during follow-up was examined by Cox regression, after adjustment for baseline age, gender, race, diabetes, years on dialysis, serum albumin, randomized dose arm, and randomized flux arm and stratification for Clinical Centers. Any cardiac disease at baseline was a very strong predictor of all-cause mortality (RR = 1.84) and cardiac death (RR = 2.57), especially death from IHD (RR = 3.36) and CHF (RR = 6.32) (Table 4). The presence of IHD, CHF, arrhythmia, or other heart diseases at baseline was also predictive of subsequent all-cause mortality and cardiac death. The presence of CHF or other heart diseases at baseline increased the risk of death from CHF by 5- to 6-fold. The predictive values of baseline cardiac disease for cardiac events during follow-up were in general stronger without adjustment for covariates.

Effect of randomized dose and flux interventions on cardiac outcomes based on intent to treat

After adjustment for baseline factors with center stratification, the relative risk for all-cause mortality or any of the cardiac outcomes associated with the high-dose

Table 4. Association of baseline cardiac disease with various cardiac events during follow-up[a]

		Cardiac disease at baseline									
		Any cardiac disease $N = 1479$		Ischemic heart disease $N = 725$		Congestive heart failure $N = 733$		Arrhythmia $N = 571$		Other heart diseases $N = 1162$	
Cardiac event during follow-up	No.	RR[b]	95% CI[c]	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
All-cause mortality	871	1.84	1.47–2.29	1.32	1.14–1.53	1.51	1.31–1.74	1.43	1.23–1.65	1.52	1.30–1.79
1st cardiac hosp or ACM	1079	2.20	1.80–2.68	1.47	1.29–1.68	1.58	1.39–1.80	1.33	1.16–1.52	1.64	1.42–1.89
1st cardiac hosp or cardiac death	835	2.33	1.85–2.93	1.66	1.43–1.93	1.62	1.40–1.88	1.26	1.08–1.46	1.63	1.38–1.91
Cardiac death	343	2.57	1.73–3.83	2.02	1.59–2.56	1.65	1.31–2.08	1.44	1.14–1.82	1.67	1.29–2.15
IHD death[d]	211	3.36	1.89–5.98	2.82	2.05–3.87	1.40	1.04–1.87	1.42	1.05–1.92	1.49	1.08–2.06
CHF death[e]	36	6.32	0.83–48.01	1.71	0.81–3.60	5.05	2.13–11.97	1.75	0.86–3.57	5.95	1.75–20.19
Arrhythmia death	59	1.63	0.72–3.69	1.20	0.69–2.10	1.60	0.92–2.77	1.46	0.84–2.56	1.28	0.71–2.30
Death from other heart diseases	37	1.24	0.52–2.93	0.91	0.42–1.96	1.73	0.86–3.49	1.12	0.53–2.38	1.95	0.88–4.30

[a]Cox regression was performed with adjustment for baseline age, gender, race, diabetes, years on dialysis, serum albumin, randomized Kt/V group, and randomized flux group, and stratified for center.
[b]RR, relative risk of developing the cardiac event during follow-up.
[c]95% CI, 95% confidence interval.
[d]IHD death, death from ischemia heart disease.
[e]CHF death, death from congestive heart failure.

Table 5. Effect of randomized dose and flux arms on cardiac outcomes according to intent-to-treat

		Randomization to high Kt/V		Randomization to high flux	
Event	No. of events	RR[a]	95% CI[b]	RR[a]	95% CI
All-cause mortality	871	0.96	0.84–1.10	0.92	0.81–1.05
1st cardiac hosp or ACM	1079	0.99	0.88–1.12	0.90	0.80–1.01
1st cardiac hosp or cardiac death	835	1.00	0.87–1.15	0.87	0.76–1.00
Cardiac death	343	1.03	0.83–1.27	0.80	0.65–0.99
IHD death[c]	211	1.03	0.78–1.36	0.89	0.68–1.17
CHF death[d]	36	0.82	0.41–1.63	0.65	0.32–1.29
Arrhythmia death	59	1.20	0.71–2.03	0.67	0.40–1.14
Death from other heart diseases	37	1.12	0.58–2.15	0.71	0.36–1.37
Total cardiac hosp or cardiac death[e]	1878	1.06	0.90–1.26	0.89	0.75–1.05

[a]RR, relative risk; risk reduction rate = $(1 - \text{RR}) \times 100\%$.
[b]95% CI, 95% confidence interval.
[c]IHD death, death from ischemic heart disease.
[d]CHF death, death from congestive heart failure.
[e]Total cardiac hospitalization or cardiac death consisted of 1878 total events, which included 735 first cardiac hospitalizations, 827 subsequent cardiac hospitalizations, and 316 cardiac deaths.

intervention ranged from 0.82 to 1.20 compared with low dose; none of these comparisons was statistically significant (Table 5). The result on all-cause mortality was similar without adjustment for baseline factors.

In contrast, the relative risk for all-cause mortality and all examined cardiac outcomes associated with the high-flux intervention was consistently below 1.0, although the reduction was statistically significant (at $P < 0.05$) for only two outcome measures (Table 5). Specifically, the high-flux arm had an 8% (95% CI –5% to 19%) lower rate of all-cause mortality (primary outcome) and 10% (−1% to 20%) lower rate of first cardiac hospitalization or all-cause mortality (main secondary outcome) than the low-flux arm, but these differences were not statistically significant. The high-flux arm, however, was associated with a 20% reduction (95% CI 1% to 35%; $P = 0.042$) in cardiac death and a 13% reduction (95% CI 0% to 24%; $P = 0.045$) in the composite outcome of first cardiac hospitalization or cardiac death, which were statistically significant without adjustment for multiple comparisons. When the specific cardiac causes of death (IHD, CHF, arrhythmia, and other heart diseases) were analyzed individually, the high-flux intervention was associated with a risk reduction in all events, with effect sizes ranging from 11% to 35%. These decreases were, however, not statistically significant. High flux was also associated with a statistically insignificant (11%) decrease in the composite of total cardiac hospitalization or cardiac death.

The interactions between the presence or absence of cardiac disease (IHD or any cardiac disease) at baseline and the randomized interventions (dose or flux) on six of the eight outcomes listed in Table 3 were examined. Deaths from CHF and "other heart diseases" were not examined because of the small number of events in those categories. The results were adjusted for age, gender, race, diabetes, serum albumin level, and years on dialysis at baseline. Out of the 24 analyses performed (2 randomized interventions × 2 types of cardiac diseases ×

6 outcome measures), no strong, consistent effects were found. These analyses suggest that the presence or absence of cardiac disease at baseline did not modulate the effect of dialysis dose or flux on cardiac outcomes.

DISCUSSION

Summary of findings

The results of the present study indicate that (*1*) the prevalence of cardiac disease was high (80%) in chronic hemodialysis patients at baseline; (*2*) IHD was implicated in 61.5% of the cardiac deaths in this population; (*3*) the presence of any cardiac disease or specific types of cardiac disease at baseline was a risk factor for all-cause mortality and cardiac deaths; (*4*) randomization to the high-dose arm had no effect on cardiac outcomes. Although randomization to the high-flux arm did not have any significant benefit on the main secondary composite outcome of first cardiac hospitalization or all-cause death, it reduced cardiac deaths and the composite of first cardiac hospitalization or cardiac death in further analysis.

Baseline prevalence of cardiac disease

The HEMO Study confirms the high prevalence of IHD, CHF, and arrhythmias in hemodialysis patients [18, 19]. Despite the exclusion of patients with severe CHF and those with unstable angina, the prevalence of IHD and CHF (both ~40%) were higher than those reported in the United States Renal Data System (USRDS), which showed prevalence rates of ~20% for IHD and ~30% for CHF [20]. One reason for this difference may be the different methods of ascertainment of these cardiac conditions. In the HEMO Study, pre-existing cardiac conditions were ascertained using the ICED, based on the review of medical records by a trained study coordinator. Previous studies have shown that ICED is more sensitive in capturing the diagnosis of cardiac disease than the Medical Evidence Report Form 2728 of the Health Care Finance Administration, which is the basis of the data reported by the USRDS [20], with similar specificity [21]. In fact, the 80% prevalence of cardiac disease in the HEMO Study cohort could still be an underestimation of the true prevalence because only 41% of the subjects had cardiac echocardiography performed. Therefore, LVH might have been missed in some patients.

IHD as main cause of cardiac deaths

Cardiac deaths were common and accounted for 39.4% of all-cause deaths in the HEMO Study (Table 2). In the USRDS, cardiac causes account for a moderately higher fraction (45.2%) of all-cause deaths [1]. More importantly, 47.2% of the cardiac deaths in the USRDS were listed as cardiac arrest, while only 27.0% were attributed to acute myocardial infarction and atherosclerotic heart disease. In contrast, IHD was implicated in 61.5% of cardiac deaths in the HEMO Study (Table 2). In addition, IHD accounted for 42.7% of total cardiac hospitalizations (Table 3). This substantial difference in outcomes between the two databases could potentially be a result of the more careful data collection in the HEMO Study and differences in death classification. For example, 194 (89.4%) of the 217 sudden deaths were further classified to be caused by various cardiac causes (e.g., IHD) and accounted for 56.6% (194/343) of all cardiac deaths. In the USRDS, these sudden deaths might have been simply listed as "cardiac arrest, cause unknown" or "cardiac arrhythmia," without further classifications. The results of the death classification in the HEMO Study underscores the importance of IHD, and allows a sharper focus on future preventive strategies to improve the poor cardiovascular outcomes in maintenance hemodialysis patients. It should be reckoned that the nature of sudden deaths in both the HEMO Study and the USRDS has not been well characterized, and this topic deserves further investigations.

Baseline cardiac diseases predict cardiac deaths

Any cardiac disease and each specific type of cardiac diseases at baseline were highly predictive of death from all causes and from cardiac causes during follow-up. This type of detailed examination has not been previously reported in the dialysis population. These data suggest that, while the cardiovascular risk factors might continue or accelerate during the course of maintenance hemodialysis, the underlying disease burden plays an important role in determining cardiac mortality in this population. Thus, interventions to prevent and treat cardiac diseases should begin early in the course of kidney disease.

Effect of dialysis dose and flux on cardiac outcome

Some [22, 23], but not all [24], of the published observational studies have reported mortality reductions of approximately 20% between dose levels similar to the HEMO high and standard dose arms. The HEMO Study did not show a significant benefit of high dose in reducing all-cause mortality or cardiac events (Table 4). This result was consistent across various cardiac outcomes, with the average relative risk of the high dose goal compared with the standard dose goal being close to unity. These observations suggest that it would be difficult to substantially improve cardiac outcomes through increasing dialysis dose using the thrice-weekly treatment schedule as currently practiced in the United States. It remains unclear, however, if other techniques such as daily or nocturnal dialysis would have significant beneficial effects through additional increases in dialysis dose and fluid removal.

Our results also did not show any significant benefit of high-flux dialysis on the main composite cardiac outcome

(first cardiac hospitalization or all-cause mortality) (Table 5). However, high flux was associated with statistically significant (at $P < 0.05$ level) reduction in cardiac death (20%) and the composite outcome of first cardiac hospitalization or cardiac death (13%). In patients who had been on dialysis over 3.7 years before the study, the risk reduction in cardiac death associated with high flux was even greater (37%; $P = 0.016$) [25]. These results raise the possibility that high-flux dialysis may have a beneficial effect on certain cardiac outcomes, especially in patients on long-term dialysis. A sample size that is larger than the 1846 patients randomized in the HEMO Study may be necessary to clearly demonstrate a benefit of high-flux dialysis on all-cause mortality and other clinical outcomes. It is also conceivable that β_2-microglobulin clearances that are substantially greater than that achieved in the high-flux arm of the HEMO Study (34 mL/min) [10] and could be achieved through techniques such as the use of certain types of high-flux dialyzers, hemodiafiltration, or sorbent technologies would result in improved cardiac outcomes in a more comprehensive fashion.

Strengths and limitations

A major strength of this study regarding the prevalence of cardiac diseases and the incidence of cardiac events is that the data were carefully collected by trained study coordinators and examined by blinded investigators. Hence, this clinical database is probably more accurate than the national administrative databases that are often used in other studies. The details that are available in this database also allow for additional analyses that are not possible using most administrative databases. Second, this is the first randomized controlled trial that examined the effect of dialysis dose and flux on long-term cardiac outcomes.

There are also several limitations of the present analysis. First, clinical databases tend to be smaller than the administrative databases, and therefore entail smaller sample sizes and lower statistical power in general. Second, our database is derived from a clinical trial with its attendant subject exclusion criteria. For example, the percentage of blacks (62.6%) was higher than those reported in the USRDS. Thus, generalization of these results to the United States hemodialysis population should take this caveat into account. Third, because of practical considerations, the methods used to determine baseline cardiac disease burden are different from those used to prospectively determine cardiac events during follow-up. The fourth limitation relates to the lack of uniform laboratory tests that were required for the diagnosis of cardiac events in the HEMO Study. For example, serum troponin levels were not a requirement for the diagnosis of acute myocardial infarction. However, the Outcome Review Committee developed written uniform criteria to assign the primary cause of hospitalization or death, and to adjudicate the cardiac events. The fifth limitation relates to the issue of multiple statistical comparisons of effects between the randomized interventions; appropriate caution should therefore be exercised in the interpretation of results of the additional analyses.

CONCLUSION

Cardiac diseases are major causes of mortality in maintenance dialysis patients. Because of the potential of improving certain cardiac outcomes, the routine use of high-flux dialysis deserves further investigation. It should also be acknowledged that neither high-dose dialysis nor high-flux dialysis, as practiced in the HEMO Study, led to a large reduction in cardiac events. Alternative or additional strategies are needed in order to reduce cardiac morbidity and mortality in the maintenance hemodialysis population. In view of the high prevalence of cardiac diseases at baseline, the present study also underscores the importance of detection and treatment of cardiovascular diseases at earlier stages of chronic kidney disease.

APPENDIX I. Classifications of cardiac causes of death

1. Ischemic heart disease (IHD)
   - Sudden death caused by IHD
   - Acute myocardial infarction
   - Angina (secondary only*)
   - Atherosclerotic heart disease (secondary only*)
   - Other acute and subacute forms of IHD
   - Old myocardial infarction (secondary only*)
   - Other forms of chronic IHD (secondary only*)
2. Congestive heart failure (CHF)
   - CHF
   - CHF or pulmonary edema caused by exogenous fluid overload
   - Cardiogenic pulmonary edema
   - Cardiogenic shock
3. Arrhythmia and conduction problems
   - Sudden death caused by arrhythmia, not IHD
   - Atrioventricular conduction block
   - Sick sinus syndrome
   - Atrial fibrillation
   - Ventricular tachycardia
   - Other cardiac arrhythmia and conduction disorders
   - Hyperkalemia
4. Other heart diseases and conditions
   - Sudden death (caused by heart conditions other than IHD or arrhythmia)
   - Pericarditis
   - Endocarditis (also classified as infectious outcome)
   - Myocarditis
   - Pericardial effusion (secondary only*)
   - Cardiac tamponade
   - Aortic valve stenosis or insufficiency (secondary only*)
   - Mitral valve stenosis, regurgitation, or prolapse (secondary only*)
   - Other valvular defect (secondary only*)
   - Prosthetic valve malfunction (secondary only*)
   - Cardiomyopathy (without IHD)

*"Secondary only" refers to diseases or conditions that could only be a secondary or contributing cause of death and not the primary cause.

APPENDIX II. Collection and validation of outcome data

Procedure of outcome data collection

Each hospitalization or death during follow-up was classified by the investigator at the Clinical Center using a classification system devised by the HEMO Study and reported to the Data Coordinating Center. The data that form the basis for the reports were collected by the Clinical Center study coordinators and included hospital records, ICD-9 codes, clinic and dialysis unit notes, diagnostic tests including ECG, echocardiograms, other imaging studies, and cardiac catheterization, patient or family accounts, physician accounts, death certificates, and death notification forms to the USRDS. Therefore, the coding could be based on a simple mention in the record alone during baseline, but not during follow-up. Mandatory comments from the investigator at the Clinical Center were sent to the Data Coordinating Center for each hospitalization or death. A hospitalization event was defined as an overnight stay in the hospital.

Vital statistics and classification of cause of death were captured on all 1846 randomized patients by maintaining contact with the dialysis units to which the patients were transferred. However, resources did not permit classification of hospitalizations after patients were transferred to dialysis units not participating in the study. Thus, the definitions of the ascertainment periods for mortality and hospitalizations differed slightly. For each patient, the ascertainment period for all-cause mortality and for mortality from specific causes extended from the day of randomization until (a) renal transplant, (b) death, or (c) the end of the study on December 31, 2001. The ascertainment period for hospitalizations was the day of randomization until either (a), (b), (c), or (d) transfer to a nonparticipating hemodialysis facility, or to an alternative modality of dialysis. A total of 194 patients left the study before the scheduled end of follow-up because of kidney transplantation, and 198 others transferred to a nonparticipating facility or alternative dialysis modality. The mean durations of the mortality and hospitalization ascertainment periods were 2.84 and 2.63 years, respectively.

Classification of deaths and quality control

Information from the Clinical Centers regarding deaths and first hospitalizations for cardiac disease or infection was reviewed by the Clinical Center principal investigator, and an outcome was first adjudicated at that center. All available information was then sent to the Outcome Review Committee, along with the outcome classification and comments by the Clinical Center investigators. The Committee was comprised of investigators from Clinical Centers who were blinded to the arm of randomization for the case under review. Causes of death were classified into 24 categories, four of which were cardiac causes, as presented in Appendix I [13].

All death classifications by the Clinical Centers required independent audits by two members of the Outcome Review Committee assigned by the Data Coordinating Center [13]. Both auditors had access to the Clinical Center's diagnosis at the time of the audit. Agreement on the category of the primary cause of death was required. If either or both reviewers disagreed with the Clinical Center investigator, the cause of death was adjudicated during a conference phone call of the Outcome Review Committee by simple majority vote.

Classification of hospitalizations and quality control

Agreement between the Clinical Center investigator and a member of the Outcome Review Committee was also required for the classification of main secondary outcomes, which included first cardiac and first infectious hospitalizations. When there was disagreement, resolution was attempted by discussion between these individuals, followed by adjudication by the full Outcome Review Committee as necessary.

There were a total of 7822 hospitalizations during follow-up. Of these, 1600 were initially identified by the Clinical Center as first cardiac or first infectious hospitalizations. Of these 1600, 897 were initially classified by the Clinical Center as hospitalizations due to any cardiac cause, and 305, 147, 355, 353, and 128 were classified as angina, myocardial infarction, CHF, arrhythmias, and other heart diseases, respectively. The Outcome Committee review process confirmed 90%, 84%, 93%, 82%, 86%, and 66% of the initial Clinical Center classifications for any cardiac cause, angina, myocardial infarction, CHF, arrhythmias, and other heart diseases, respectively (correct classification by Clinical Centers). The proportions of the 1600 reviewed hospitalizations that were not identified by the Clinical Center as caused by a cardiac cause but which were later classified as cardiac hospitalizations by the Outcome Committee were 3%, and 1%, 1%, 2%, 2%, and 1% for angina, myocardial infarction, CHF, arrhythmias, and other heart diseases, respectively (false-negative classification by Clinical Centers).

For quality control purposes, a random sample of approximately 4% was selected using a computer algorithm from a set of all hospitalizations excluding those in the previous set of 1600 (i.e., the set that were not initially identified as a first cardiac or infection hospitalization by the Clinical Centers). This random sample was generated uniformly over time from the 15 Clinical Centers from January 31, 1996, to the end of the Study, resulting in the selection of 279 out of 6222 hospitalizations. These hospitalizations were then reviewed by the Outcome Committee using the same process that was used for the 1600 potential first cardiac or first infection hospitalizations. In this random sample, 91%, 71%, 60%, 100%, 82%, and 50% of the hospitalizations attributed respectively by the Clinical Centers to any cardiac cause, angina, myocardial infarction, CHF, arrhythmias, and other heart diseases were confirmed by the Outcome Review Committee (correct classification by Clinical Centers). The proportions of the hospitalizations in the random sample of 279 that were not identified by the Clinical Centers but which were later classified as cardiac hospitalizations by the Outcome Committee were 4%, 1%, 0%, 2%, 1%, and 1% for any cardiac cause, angina, myocardial infarction, CHF, arrhythmias, and other heart diseases, respectively (false-negative classification by Clinical Centers).

Overall rates of correct classification and false-negative classification by the Clinical Centers for all hospitalizations were obtained by the appropriately weighed averages of corresponding rates for the 1600 reviewed potential first cardiac or first infectious hospitalizations and for the random sample of 279. Finally, treating the Outcome Review classification as the reference standard, the sensitivity and specificity of the Clinical Center classifications were obtained by applying Bayes' rule. The sensitivity for the diagnosis of cardiac hospitalization initially reported by the Clinical Centers was estimated to be 87% for any cardiac cause, and 90%, 87%, 80%, 86%, and 68% for new onset or worsening angina, myocardial infarction, CHF, arrhythmia, and other heart diseases, respectively. The specificity was 97% for any cardiac cause, and 98%, 99%, 99%, 99%, and 99% for new onset or worsening angina, myocardial infarction, CHF, arrhythmia, and other heart diseases, respectively.

Final ascertainment of outcomes

Outcomes based on classifications of the cause of death and the composite outcomes of first cardiac hospitalization or death and of first cardiac hospitalization or cardiac death were derived from the final Outcome Committee classification. However, outcomes defined by specific causes of cardiac hospitalizations were, in some instances, defined using the Clinical Center classifications only because the hospitalizations might not have been initially determined to be first cardiac or first infectious hospitalizations, and thus were not reviewed by the Outcome Committee. For example, 356 hospitalizations were designated as first hospitalizations for angina by the Clinical Center review; of these, 285 were reviewed by the Outcome Committee, but the remaining 71 were not designated for review because they were preceded by another cardiac hospitalization. Overall, 80%, 73%, 78%, 79%, and 74% of hospitalizations designated by the Clinical Centers as first angina, first myocardial infarction, first CHF, first arrhythmia, or first other heart disease hospitalizations were subsequently reviewed by the Outcome Committee. Finally, overall rates of cardiac hospitalizations (including multiple hospitalizations for each patient) were determined entirely from the Clinical Center classifications because Outcome Committee review was available for only a small proportion of the total hospitalizations.

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Reprint requests to Alfred K. Cheung, M.D., 85 North Medical Drive East, University of Utah, Salt Lake City, UT 84112.
E-mail: alfred.cheung@hsc.utah.edu

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