Hemodialysis and Peritoneal Dialysis: Comparison of Adjusted Mortality Rates According to the Duration of Dialysis: Analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis 2

FABIAN TERMORSHUIZEN,* JOHANNA C. KOREVAAR,* FRIEDO W. DEKKER,† JEANNETTE G. VAN MANEN,† ELISABETH W. BOESCHOTEN,‡§ and RAYMOND T. KREDIET,‡ FOR THE NETHERLANDS COOPERATIVE STUDY ON THE ADEQUACY OF DIALYSIS STUDY GROUP

*Departments of *Clinical Epidemiology and Biostatistics and ‡Nephrology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; †Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; and §Dianet Dialysis Centers, Amsterdam and Utrecht, The Netherlands.*

Abstract. Various studies indicate that fair comparisons of mortality rates between hemodialysis (HD) patients and peritoneal dialysis (PD) patients are difficult because of differences in patient characteristics, because of nonconstant relative risks of death (RR), and because the survival times of patients who switch treatment modalities can be censored in different ways. The differences in mortality rates between HD and PD patients were investigated in an analysis in which these potential sources of bias were taken into account. The Netherlands Cooperative Study on the Adequacy of Dialysis is a multicenter, prospective, observational, cohort study in which new patients with ESRD are monitored until transplantation or death. A multivariate Cox regression analysis was used to analyze the mortality data according to treatment modality (HD, $n = 742$; PD, $n = 480$). No statistically significant differences in adjusted mortality rates between HD and PD patients were observed during the first 2 yr of dialysis. In the years thereafter, increases in mortality rates for PD patients and resulting decreases in RR in favor of HD were observed (*e.g.*, months 24 to 36, adjusted RR, 0.53; 95% confidence interval, 0.31 to 0.91). This tendency was observed especially among patients ≥60 yr of age and was not influenced by the censoring strategy. These results suggest that long-term use of PD, especially among elderly patients, is associated with increases in mortality rates. Further analyses are required to determine the potential role of dialysis adequacy in the observed long-term differences in mortality rates between HD and PD patients and to establish the possible survival benefits for PD patients who switch to HD in time.

Studies in which the mortality rates for patients undergoing hemodialysis (HD) were compared with the mortality rates for patients undergoing peritoneal dialysis (PD) yielded conflicting results. Some studies noted no difference in survival rates between patients treated with HD and patients treated with PD (1–3), whereas other studies demonstrated differences in favor of either HD (4) or PD (5–8). Various sources of bias may threaten the reliability of observational studies of outcomes with HD, compared with PD, which may explain the conflicting results in different studies.

First, differences in clinically important characteristics may exist between patients who start with HD and patients who start with PD (9,10). Adjustments for these differences are required for comparative studies, and not performing such adjustments may yield biased results (11–13). Second, various studies have indicated that the relative risk of death (RR) among HD patients, compared with PD patients, decreases with time after the initiation of dialysis (*i.e.*, in favor of HD), which makes survival analyses dependent on the length of follow-up monitoring (4–6). Consequently, studies among chronically treated patients may yield results that are clearly different from studies among new patients (3,14). Third, various studies have demonstrated significant differences in the RR for HD patients, compared with PD patients, among different subgroups of patients defined on the basis of age and diabetes mellitus status. Older age and the presence of diabetes mellitus may be associated with a RR in favor of HD patients; for younger patients, with or without diabetes mellitus, a RR in favor of PD patients was observed (3,11,12,15). These differences in outcomes with HD and PD in different subgroups of patients must

Received April 18, 2003. Accepted July 27, 2003.
Correspondence to Dr. Fabian Termorshuizen, Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands. Phone: +31-20-5663607; Fax: +31-20-6912683; E-mail: FTermorshuizen@cs.com
1046-6673/1411-2851
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000091585.45723.9E

be taken into account, to enable valid generalization of the results and comparison with other studies. Another source of confusion is the method of handling data for patients who switch from one modality to the other. It has been demonstrated that different strategies for censoring the survival times of patients who switch therapeutic modalities may influence the estimated RR for HD patients, compared with PD patients (5,14).

Comparative studies on survival rates with HD *versus* PD in which all of these potential sources of bias are taken into account are important for reaching evidence-based consensus regarding the form of dialysis that offers the best chance of survival for individual patients. We investigated the differences in mortality rates between HD and PD patients who participated in the Netherlands Cooperative Study on the Adequacy of Dialysis, and we assessed the effects of patient characteristics, the time since the start of dialysis, and the method of handling data for "modality switchers" on the results.

Materials and Methods

Patients

The Netherlands Cooperative Study on the Adequacy of Dialysis is a multicenter, prospective, observational, cohort study in which new patients with ESRD are consecutively included at the time of initiation of dialysis treatment and are monitored at 6-mo intervals until renal transplantation or death. Patients who are >18 yr of age and who begin chronic dialysis as the first renal replacement therapy (RRT) are eligible for the study. All invited patients give informed consent before inclusion. For this analysis, we selected patients who survived the first 3 mo of dialysis. The patients were classified according to the treatment modality at the 3-mo visit (baseline). Exclusion of the first 3 mo was performed to bypass analytical problems associated with late referral to the nephrologist, early modality switching, and acute renal failure. For 742 HD patients (of the 947 HD patients who survived the first 3 mo) and 480 PD patients (of the 542 PD patients who survived the first 3 mo), complete data sets on residual renal function, nutritional status, and hemoglobin and albumin concentrations at baseline were available; those patients were included in this analysis.

Data Collection Procedures

Data on demographic characteristics, primary kidney disease, and comorbidities were collected at the time of entry into the study. Data on residual renal function (residual GFR, renal Kt/V_{urea}, and urine production), nutritional status, biochemical parameters, and dialysis characteristics (current treatment modality, delivered Kt/V_{urea}, and ultrafiltration) were collected 3 mo after the start of RRT and at 6-mo intervals thereafter. Primary kidney disease was classified according to the codes of the European Renal Association-Dialysis and Transplantation Association (16). On the basis of the number of comorbid conditions, patients were classified as having no, intermediate, or severe comorbidity, according to the comorbidity index described by Davies *et al.* (17). Diabetic status was defined on the basis of diabetes mellitus being registered as the primary kidney disease or as a comorbid condition. For assessment of renal function, both urea and creatinine levels were measured in plasma and urine samples. For HD patients, the volume of urine produced in the long interdialytic interval was recorded. For PD patients, the volume of urine produced in a 24-h period was recorded. The residual GFR was calculated as the mean of renal creatinine and urea clearance, adjusted for body surface area (in milliliters per minute per 1.73 m^2). The renal Kt/V_{urea} was calculated as the renal urea clearance per week adjusted for the urea distribution volume, which was calculated according to the method described by Watson *et al.* (18). The nutritional status was scored with the seven-point scale of the subjective global assessment (SGA), which is a standardized method based on the clinical judgment of the dialysis nurse (19).

Statistical Analyses

Mortality Rates According to Modality and Time since the Initiation of Dialysis. Death rates were calculated according to the treatment modality and the time since the initiation of dialysis. The time since the initiation of dialysis was categorized into four periods, namely, 3 to 12 mo, 12 to 24 mo, 24 to 36 mo, and >36 mo. Follow-up monitoring ended at the time of transplantation, patient withdrawal, or September 1, 2002. In an as-treated (AT) analysis, follow-up monitoring ended at day 60 after the first transfer to the other treatment modality, if any. For patients who died within the 60-d period, the deaths were allocated to the original treatment modality, with the assumption that deaths occurring during this short period were likely associated with the modality of the preceding treatment episode. Therefore, only deaths occurring during or shortly after treatment with the original modality were taken into account (modality history assignment) (11,15). In an intention-to-treat (ITT) analysis, modality switches were ignored, and all registered deaths during the follow-up period were allocated to the treatment modality at the 3-mo visit (15).

The RR and associated 95% confidence intervals (CI) for HD patients, compared with PD patients, were estimated and tested with a Cox proportional-hazards model. Each patient's survival time was calculated from the 3-mo visit onward. Terms for modality-time period interactions were included in the model, to address the possibility of nonproportionality. In the model, the RR for HD patients, compared with PD patients, was estimated separately for each time period after the initiation of dialysis, with the assumption that the proportional-hazards assumption would hold true within each time period (20). The RR for HD patients, compared with PD patients, according to time period were estimated with both AT and ITT censoring strategies.

Multivariate Cox Proportional-Hazards Model. The Cox proportional-hazards model with terms for modality-time period interactions was extended with adjustments for the possible confounding effects of age, gender, primary kidney disease, Davies comorbidity index, SGA score, residual renal function, and hemoglobin and albumin concentrations at baseline. This analysis resulted in separate adjusted RR for each time period after the initiation of dialysis. This analysis was also performed with both censoring strategies.

Differences According to Subgroup. The Cox proportional-hazards model was further extended with a second-order term for interactions between modality and time period and subgroup. In this model, the RR for HD patients, compared with PD patients, was estimated separately for each combination of time period and subgroup. Different subgroup definitions were used. Subgroups were defined on the basis of age (<60 or ≥60 yr) and gender, on the basis of age (<60 or ≥60 yr) and the presence of diabetes mellitus, or on the basis of age (<60 or ≥60 yr) and the presence of one or more cardiovascular diseases (CVD). Time periods were dichotomized as 3 to 24 mo or 24 to 48 mo. Other, more refined, subgroup definitions were not used, to avoid inclusion of small numbers of patients and

death events in each stratum and data interpretation that would become too complicated. All analyses were performed with SAS statistical software, version 8.2 (SAS Institute, Cary, NC).

Results

Description

The characteristics of the HD and PD patients at the 3-mo visit are presented in Tables 1 and 2. HD patients were, on average, 10 yr older than PD patients. Compared with PD patients, HD patients more often demonstrated comorbid conditions. On average, worse nutritional status, lower hemoglobin concentrations, and lower residual renal function were observed for HD patients, in comparison with PD patients. No significant difference in serum albumin levels was observed.

The number of HD patients who died during the follow-up period was 239; the number of PD patients who died was 72 (AT censoring). Thirty HD patients (4.05%) were transferred to PD during the follow-up period. For PD patients, this number was much higher; 111 PD patients (23.1%) were transferred to HD during the follow-up period. The 2-yr technique survival rate for HD patients was 96%, and the 2-yr technique survival rate for PD patients was 74%. The number of HD patients who received renal transplants was 110 (15% of the original HD cohort), and those patients were censored at the time of transplantation. The number of PD patients who received transplants was 99 (21% of the original PD cohort). During the 18 mo after the initiation of RRT, 241 HD patients (32.5%) were accepted onto the renal transplant list; during that period, 88 HD patients (11.9%) declined to be placed on the list because of their own preferences (*i.e.*, not for medical reasons). For PD patients, the corresponding figures were 275 (57.3%) and 60 (12.5%).

The unadjusted 2-yr patient survival rate for HD patients was 73%; the unadjusted 2-yr survival rate for PD patients was 84% (AT censoring). The mortality rate for patients who were excluded from the analysis because of missing baseline data was higher than the mortality rate for patients who were included. Comparatively higher mortality rates for the excluded patients were observed for both HD and PD patients (HD, 2-yr survival rate of 63%, $n = 205$; PD, 2-yr survival rate of 67%, $n = 62$).

Follow-up data are presented in Table 3. The higher hemoglobin concentrations and the more favorable nutritional status for PD patients, compared with HD patients, remained during the follow-up period. Decreases in renal Kt/V_{urea} during the follow-up period were observed for both HD and PD patients. However, the difference in favor of PD that was established at baseline remained during the follow-up period. No significant differences in

Table 1. Patient characteristics at baseline, according to treatment modality (categorical data)[a]

	No. of Patients		P (χ^2 Test)
	HD	PD	
Age (yr)			0.0001
<45	89 (12.0%)	147 (30.6%)	
45 to 60	187 (25.2%)	173 (36.0%)	
60 to 70	203 (27.4%)	100 (20.8%)	
≥70	263 (35.4%)	60 (12.5%)	
Male gender	427 (57.6%)	313 (65.2%)	0.0074
Primary renal disease			0.0001
diabetes mellitus	111 (15.0%)	70 (14.6%)	
glomerulonephritis	77 (10.4%)	102 (21.3%)	
renal vascular cause	158 (21.3%)	58 (12.1%)	
all other	396 (53.4%)	250 (52.1%)	
Davies score at study entry			0.0001
no comorbidity	296 (39.9%)	286 (59.6%)	
intermediate	363 (48.9%)	161 (33.5%)	
high comorbidity	83 (11.2%)	33 (6.9%)	
Presence of diabetes mellitus	168 (22.6%)	87 (18.1%)	0.0578
Presence of CVD	293 (39.5%)	118 (24.6%)	0.0001
SGA score[b]			0.0001
≤4	109 (14.7%)	33 (6.9%)	
5	138 (18.6%)	56 (11.7%)	
6	281 (37.9%)	168 (35.0%)	
7	214 (28.8%)	223 (46.5%)	
Total	742 (100%)	480 (100%)	

[a] HD, hemodialysis; PD, peritoneal dialysis; CVD, cardiovascular disease; SGA, subjective global assessment.
[b] A higher SGA score is indicative of better nutritional status; (score of 6 or 7, well nourished; ≤4, malnourished).

Table 2. Patient characteristics at baseline, according to treatment modality (continuous data)[a]

	HD	PD	*P* (Wilcoxon Test)
Age (yrs)	62.3 ± 13.9	52.1 ± 14.7	0.0001
Serum albumin level (g/dl)	3.66 ± 0.48	3.64 ± 0.54	0.74
Hemoglobin level (g/dl)	10.7 ± 1.4	11.9 ± 1.6	0.0001
Residual GFR (ml/min per 1.73 m^2)	3.4 ± 2.8	4.1 ± 2.7	0.0001
Renal Kt/V_{urea} (weekly)	0.70 ± 0.58	0.82 ± 0.57	0.0001
Urine production (liters/d)	0.78 ± 0.66	1.1 ± 0.80	0.0001

[a] Values are mean ± SD.

Table 3. Follow-up data, according to treatment modality at baseline[a]

	3 mo	12 mo	24 mo	36 mo
No. at risk				
HD	742	572	372	232
PD	480	357	205	111
Davies score (intermediate/high) (%)				
HD	50.1/11.6	49.7/10.5	48.9/9.7	50.0/11.6
PD	34.2/7.1	34.7/7.6	32.7/8.8	34.2/4.5
Presence of cardiovascular morbidity (%)				
HD	40.8	42.3	45.4	48.7
PD	25.4	26.3	28.3	25.2
Hemoglobin level (g/dl)				
HD	10.7 (10.6 to 10.8)	11.4 (11.2 to 11.5)	11.3 (11.2 to 11.4)	11.3 (11.1 to 11.4)
PD	11.9 (11.8 to 12.1)	11.9 (11.7 to 12.0)	11.7 (11.5 to 11.9)	11.7 (11.4 to 12.0)
Albumin level (g/dl)				
HD	3.66 (3.62 to 3.69)	3.72 (3.68 to 3.76)	3.64 (3.59 to 3.68)	3.65 (3.59 to 3.71)
PD	3.64 (3.59 to 3.69)	3.66 (3.60 to 3.71)	3.62 (3.55 to 3.69)	3.57 (3.49 to 3.66)
SGA (scale of to 7)				
HD	5.7 (5.6 to 5.8)	6.0 (5.9 to 6.1)	6.1 (6.0 to 6.2)	6.1 (6.0 to 6.2)
PD	6.2 (6.1 to 6.3)	6.4 (6.3 to 6.4)	6.3 (6.2 to 6.4)	6.3 (6.1 to 6.5)
Renal Kt/V (weekly)				
HD	0.70 (0.65 to 0.74)	0.48 (0.44 to 0.53)	0.34 (0.29 to 0.40)	0.32 (0.22 to 0.43)
PD	0.82 (0.77 to 0.87)	0.64 (0.57 to 0.70)	0.55 (0.47 to 0.63)	0.53 (0.41 to 0.65)

[a] Measurements and follow-up times during treatment, according to the modality at 3 mo, were considered [as-treated (AT) censoring]. Values are means and 95% confidence intervals (CI).

serum albumin levels, either at baseline or during the follow-up period, were observed. A small decrease in serum albumin levels, from 3.62 g/dl at the 24-mo visit to 3.49 g/dl at the 42-mo visit, was noted for PD patients (42-mo data not shown). The Davies comorbidity scores remained stable during the course of follow-up monitoring. Among HD patients, a small increase in the percentage of patients with CVD was noted.

Characteristics of the HD and PD treatments are presented in Table 4. The decline in residual renal function (Table 3) was associated with an increase in the delivered Kt/V_{urea} for both HD and PD patients. For HD patients, this increase was associated with an increase in the number of HD sessions per week and the number of treatment hours. For PD patients, the use of higher glucose concentrations, icodextrin, and automated PD increased during the follow-up period.

Mortality Rates According to Modality and Time since the Initiation of Dialysis

The number of patients, patient-years, number of deaths, and unadjusted mortality rates according to treatment modality and duration of dialysis are presented in Table 5 and Figure 1 (AT censoring). During the periods of 3 to 12 mo and 12 to 24 mo, the unadjusted mortality rates for HD patients were significantly higher than the mortality rates for PD patients. During the periods of 24 to 36 mo and 36 to 48 mo, similar mortality rates were observed for HD patients, whereas the mortality rates for PD patients were higher than the mortality rates during the preceding time periods. Consequently, the crude RR for HD patients, compared with PD patients, decreased from 2.96 (95% CI, 1.75 to 5.00) during months 3 to 12 to 0.87 (95% CI, 0.46 to

Table 4. Treatment characteristics for HD and PD[a]

	3 mo	12 mo	24 mo	36 mo
HD				
delivered Kt/V_{urea} (weekly)	2.7 ± 0.8	3.2 ± 0.9	3.5 ± 0.8	3.6 ± 0.8
no. of weekly hours	9.3 ± 2.0	10.0 ± 2.0	10.6 ± 1.9	11.0 ± 1.8
frequency, ≥3 *versus* ≤2 times/wk (%)	57	68	79	82
PD				
delivered Kt/V_{urea} (weekly)	1.5 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	1.7 ± 0.4
CAPD *versus* APD (%)	89	72	69	67
glucose concentration (%)	1.9 ± 0.5	2.0 ± 0.6	2.1 ± 0.6	2.2 ± 0.6
icodextrin use *versus* no use (%)	7	14	22	22

[a] CAPD, continuous ambulatory PD; APD, automated PD. Values are mean ± SD.

Table 5. Numbers of patients, patient-years, and deaths, mortality rates, and crude RR[b] for HD patients, compared with PD patients, according to time since the initiation of dialysis (AT censoring strategy)

Time Period (mo)	Modality	No. of Patients	No. of Patient yrs	No. of Deaths	Mortality Rate (per 100 patient-yr)	RR[b] (95% CI)[a]
3 to 12	HD	742	496.5	78	15.7	2.96 (1.75 to 5.00)
	PD	480	320.3	17	5.3	
12 to 24	HD	571	471.4	71	15.0	2.17 (1.31 to 3.59)
	PD	356	275.2	19	6.9	
24 to 36	HD	369	297.7	52	17.4	1.23 (0.75 to 2.03)
	PD	204	155.5	22	14.1	
36 to 48	HD	228	249.1	38	15.2	0.87 (0.46 to 1.61)
	PD	111	83.1	14	16.8	

[a] A relative risk of death (RR) of <1 indicates a lower mortality rate for HD patients, compared with PD patients; a RR of >1 indicates a higher mortality rate for HD patients, compared to PD patients.

[b] Crude RR (and 95% CI) according to time period were estimated with a univariate Cox proportional-hazards model, (overall test for modality-time period interactions, Wald $\chi^2 = 11.21$; $df = 3$; $P = 0.0107$

1.61) during months 36 to 48. Similar results were observed with an ITT censoring strategy.

Multivariate Cox Proportional-Hazards Model

In Table 6, the adjusted RR for HD patients, compared with PD patients, are presented according to the time since the initiation of dialysis, as estimated with AT and ITT censoring strategies. After adjustment for age, gender, comorbidity, primary kidney disease, SGA score, hemoglobin concentration, serum albumin level, and renal Kt/V_{urea}, the RR for HD patients, compared with PD patients, during the periods of 3 to 12 mo and 12 to 24 mo were not statistically significantly different from 1. However, a significant RR in disadvantage of PD during the 2 yr thereafter became apparent after adjustment for baseline patient characteristics. The AT and ITT censoring strategies yielded similar results.

Similar results were observed when no adjustments were made for variables that might have been influenced by the treatment modality during the first 3 mo (SGA score, hemoglobin concentration, serum albumin level, and renal Kt/V_{urea}) and when patients with missing data for those variables were also included. A RR in favor of HD at more advanced stages was also observed when the analysis was restricted to patients who were accepted onto the renal transplant list or who refused for nonmedical reasons (for the period of 36 to 48 mo: RR, 0.23; 95% CI, 0.08 to 0.67; $n = 664$). This restriction was performed to investigate the possible confounding effect of the selection of patients with more health problems at later stages, which might be caused by the selective dropout of healthier patients because of transplantation. Eligibility for renal transplantation, which can be regarded as an additional marker of health status and the absence of severe comorbidity, seemed to be independently and significantly associated with lower mortality rates, as expected (RR, 0.42; 95% CI, 0.31 to 0.57). Inclusion of this variable in the models presented in Table 6 did not modify the RR with HD, compared with PD. Furthermore, the RR at later stages were not substantially modified when the analysis was restricted to patients who survived the first 2 yr of dialysis treatment and adjustments were made for the Davies comorbidity score and other patient characteristics at the 24-mo visit (*e.g.*, adjusted RR for HD patients, compared with PD patients, for months 36 to 48 with AT censoring, 0.32; 95% CI, 0.16 to 0.64).

Differences According to Subgroup

The results of the analysis with subgroups defined on the basis of age and the presence of diabetes mellitus are presented in

Table 7. For patients <60 yr of age without diabetes mellitus, no significant difference in mortality rates between HD patients and PD patients, either during the period of 3 to 24 mo or during the period of 24 to 48 mo, was observed. For patients <60 yr of age with diabetes mellitus, a statistically significantly higher mortality rate for HD patients, compared with PD patients, during the period of 3 to 24 mo was observed. The RR for HD patients, compared with PD patients, declined in favor of HD during the period of 24 to 48 mo but did not reach statistical significance. Among patients ≥60 yr of age, with diabetes mellitus or not, no significant difference in mortality rates between HD patients and PD patients during the period of 3 to 24 mo was observed. Among those patients, the RR for HD patients, compared with PD patients, declined in favor of HD during the period of 24 to 48 mo, irrespective of the presence of diabetes mellitus. The RR for HD patients, compared with PD patients, in favor of HD during the period of 24 to 48 mo reached the level of statistical significance for elderly patients without diabetes mellitus, irrespective of the censoring strategy.

RR significantly in favor of HD for the period of 24 to 48 mo among elderly patients were observed for both male and female patients and for both patients with one or more CVD and those without CVD, irrespective of the censoring strategy. For patients <60 yr of age with CVD, a decrease in the RR for HD patients, compared with PD patients, from 2.65 (95% CI, 0.71 to 9.91) during the period of 3 to 24 mo to 0.68 (95% CI, 0.18 to 2.59) during the period of 24 to 48 mo was observed, but none of those RR was significantly different from 1.00.

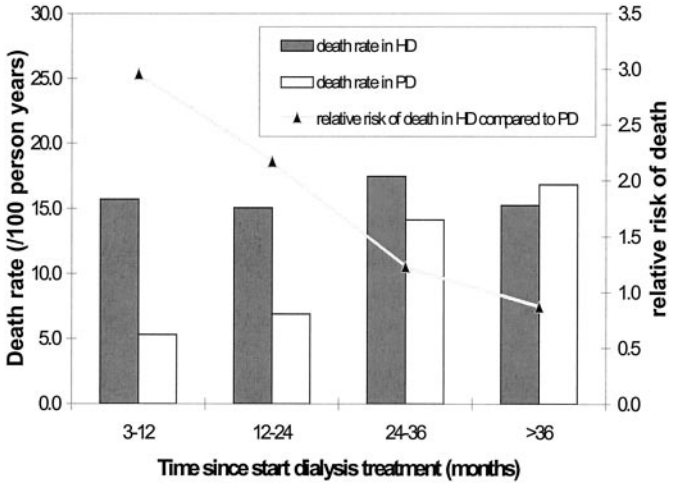

Figure 1. Unadjusted death rates and relative risk of death for hemodialysis (HD), compared with peritoneal dialysis (PD), according to time since the initiation of dialysis treatment (as-treated censoring).

Discussion

We investigated the RR for HD patients, compared with PD patients, with an observational study design. In this analysis, no statistically significant overall difference in mortality rates between HD and PD patients during the first 2 yr of dialysis treatment could be established, provided that adjustments were made for important differences in patient characteristics at the 3-mo visit. During the subsequent years, statistically significant differences in adjusted mortality rates in favor of HD were observed. This tendency toward greater relative mortality rates for PD patients with longer duration of treatment was observed especially for elderly patients, irrespective of diabetic status, gender, or the presence of CVD. For patients <60 yr of age with diabetes mellitus, a significant difference in mortality rates in favor of PD during the first 2 yr was observed, with a decline in RR in favor of HD in the subsequent years.

The most suitable study design for evaluation of differences in outcomes between treatment modalities would be a prospective, randomized, clinical trial. However, conducting such a study for ESRD could be regarded as extremely difficult, because of the special advantages and disadvantages associated with the modality choice for individual patients. Therefore, we are primarily left with the conscientious analysis of observational data from prospective studies in which special attention is paid to all sources of bias. The detailed follow-up data in the Netherlands Cooperative Study on the Adequacy of Dialysis database enabled us to assess the effects of patient characteristics, time since the initiation of dialysis, and modality switching on comparisons of mortality rates between HD and PD.

We observed a higher mortality rate for patients who were excluded from the analysis because of missing baseline data for important patient characteristics (residual renal function, nutri-

Table 6. Multivariate Cox proportional-hazards model for death with RR_c (and 95% CI) for HD patients, compared with PD patients, adjusted for age, gender, comorbidity, primary kidney disease, SGA score, hemoglobin concentration, serum albumin level, and renal Kt/V_{urea} at baseline, according to time since the initiation of dialysis and censoring strategy

Time Period (mo)	AT Censoring[a]		ITT Censoring[b]	
	Adjusted RR	95% CI	Adjusted RR	95% CI
3 to 12	1.44	0.83 to 2.50	1.32	0.80 to 2.18
12 to 24	1.04	0.61 to 1.77	1.06	0.66 to 1.72
24 to 36	0.53	0.31 to 0.91	0.55	0.34 to 0.87
36 to 48	0.29	0.16 to 0.57	0.42	0.24 to 0.73

[a] Overall test for interaction of modality and time period, Wald $\chi^2 = 17.74$; $df = 3$; $P = 0.0005$.
[b] Overall test for interaction of modality and time period, Wald $\chi^2 = 14.35$; $df = 3$; $P = 0.0025$. ITT, intention-to-treat.

Table 7. Multivariate Cox proportional-hazards model for death, with RR (and 95% CI) for HD patients, compared with PD patients, adjusted for age, gender, comorbidity, primary kidney disease, SGA score, hemoglobin concentration, serum albumin level, and renal Kt/V_{urea} at baseline, according to time since the initiation of dialysis, subgroup determined on the basis of age and the presence of diabetes mellitus, and censoring strategy

	AT Censoring[a]		ITT Censoring[b]	
	Adjusted RR	95% CI	Adjusted RR	95% CI
Age <60 yr/no diabetes mellitus				
3 to 24 mo (n = 488)	0.60	0.25 to 1.42	0.77	0.34 to 1.73
24 to 48 mo (n = 223)	1.15	0.35 to 3.81	0.77	0.31 to 1.94
Age <60 yr/diabetes mellitus				
3 to 24 mo (n = 108)	9.99	1.29 to 77.29	6.35	1.42 to 28.36
24 to 48 mo (n = 50)	0.60	0.13 to 2.72	0.41	0.13 to 1.32
Age ≥60 yr/no diabetes mellitus				
3 to 24 mo (n = 479)	1.28	0.71 to 2.30	1.03	0.62 to 1.72
24 to 48 mo (n = 250)	0.30	0.18 to 0.51	0.41	0.25 to 0.67
Age ≥60 yr/diabetes mellitus				
3 to 24 mo (n = 147)	1.45	0.67 to 3.14	1.28	0.65 to 2.52
24 to 48 mo (n = 50)	0.45	0.18 to 1.17	0.66	0.30 to 1.49

[a] Overall test for interaction of modality and time and subgroup, Wald χ^2 = 8.1927; df = 3; P = 0.0422.
[b] Overall test for interaction of modality and time and subgroup, Wald χ^2 = 5.9498; df = 3; P = 0.1141.

tional parameters, or hemoglobin levels). Exclusion of patients with comparatively greater risks of death may yield biased results. However, the higher mortality rate associated with exclusion was observed for both HD and PD patients. Furthermore, similar results were observed in an analysis without adjustment for the aforementioned patient characteristics but with inclusion of the patients with missing data. Although the mortality rates in absolute terms were biased downward, the mortality rates for HD and PD patients relative to each other were not.

We performed analyses with both AT and ITT censoring strategies. In an AT analysis, the outcomes during actual treatment with HD are compared with the outcomes during actual treatment with PD; therefore, the estimated RR may be regarded as a pure reflection of the efficacy of one modality relative to the other. However, when switching from PD to HD (which occurred for many PD patients) is associated with a higher mortality rate because of deteriorating clinical conditions, then an AT analysis may yield a RR spuriously in favor of PD (5). To address this possibility in part, deaths that occurred within 60 d after switching of treatment modalities were attributed to the original treatment (11). In an ITT analysis, switches to the other treatment modality are disregarded and all deaths are allocated to the original treatment. The results of such an analysis may be especially useful for counseling regarding survival rates after the choice to start with HD or PD, but the treatment modalities are not analyzed as separate entities. This may be an advantage, for example when long-term survival rates are better with initial PD followed by transfer to HD after a number of months or years (21). The beneficial effect of such a treatment strategy could be determined with an ITT analysis. Because the two censoring strategies address different research questions and are associated with different analytical pitfalls, investigators should perform both types of analyses (14). We did not observe substantial differences between the results of our AT and ITT analyses. This indicates that no important bias associated with modality switching was introduced. The majority of patients did not switch modalities during the follow-up period and, for those nonswitching patients, the different censoring strategies are similar by definition.

The increase in mortality rates for PD patients with longer follow-up times and the resulting decrease in the RR for HD patients, compared with PD patients, are in accordance with the findings of other studies (5,6,11,14,21). For example, in the Canadian registry-based study of new dialysis patients by Fenton *et al.* (5), an increase in mortality rates for PD patients, which resulted in a trend toward a RR in favor of HD during a 4-yr follow-up period, was reported. Therefore, survival studies among new patients may yield results that are different from those of studies among chronically treated patients. In the study by Bloembergen *et al.* (4) of chronically treated patients registered in the United States Renal Data System (1987 to 1989), a survival benefit in favor of HD was observed. However, in the reanalysis by Vonesh and Moran (3), in which the same chronically treated and more recent new HD and PD patients (1989 to 1993) were included, no substantial overall differences in mortality rates between HD and PD could be established. This was probably because of the inclusion of the survival benefit of early PD patients in the latter analysis and the exclusion of the early PD experience in the former one. This phenomenon had already been suggested in the analysis by Bloembergen *et al.* (4), because the duration of dialysis seemed to be a substantial risk factor for PD patients.

Our study indicates that differences in important patient characteristics, either at baseline or during the follow-up pe-

riod, do not explain the mortality rate difference between HD and PD after 2 yr of follow-up monitoring. At baseline, residual renal function, hemoglobin concentrations, and SGA scores were higher for PD patients; Davies comorbidity scores and the prevalence of CVD were lower for PD patients. A decline in residual renal function during the follow-up period was observed for both HD and PD patients. However, the differences in residual renal function and in the other parameters in favor of PD patients remained during the follow-up period. A comparatively high mortality rate for PD patients after 2 yr of follow-up monitoring was also observed when the analysis was restricted to patients who survived the first 24 mo of dialysis treatment and adjustments were made for comorbidity and other patient characteristics at the 24-mo visit. These observations indicate that a possible confounding effect attributable to the selection of patients with more health problems at later stages of PD treatment is less likely. This was supported by the finding that the results were not substantially modified when eligibility for transplantation was taken into account. Eligibility for transplantation may be regarded as a subtle marker of health status and the absence of severe comorbidity, suggesting selective dropout at the time of censoring because of transplantation. Unobserved differences associated with the choice of dialysis modality might have biased the outcomes in favor of one or the other treatment modality. However, these findings suggest that the increase in RR with long-term PD is possibly associated with the actual effects of this treatment modality. It is known that residual urine production is an important determinant of survival among dialysis patients (22,23). Decreases in urine production among PD patients necessitate higher peritoneal ultrafiltration rates, which require the use of high-glucose dialysis solutions. Exposure to such dialysis fluids, which also contain high concentrations of glucose degradation products, is likely to induce morphologic and functional abnormalities of the peritoneum (24,25). Loss of peritoneal ultrafiltration capacity is the most common clinical manifestation of peritoneal membrane alterations (26). The resulting overhydration is likely to be partly responsible for the high cardiovascular mortality rates for PD patients. Our finding of decreases in serum albumin levels for PD patients from the 24-mo visit onward might be attributable to this overhydration, because long-term PD is not associated with increases in peritoneal protein loss (27,28). The high cardiovascular mortality rate may also be attributable to peritoneal absorption of glucose degradation products that enhance the formation of advanced glycation end products, thus contributing to the progression of atherosclerosis (29). On the basis of these considerations, it can be speculated that reductions in exposure to glucose and glucose degradation products, in combination with the use of glucose polymers as osmotic agents, might improve the long-term results for PD.

A difference in mortality rates in favor of PD was observed in the first 1 yr of dialysis treatment. This difference (44% in the analysis with AT censoring) did not reach the level of statistical significance, which might be attributable to a lack of statistical power. A real mortality difference in favor of PD in the early stages of RRT may exist and may have clinical relevance. It could be argued that the intermittent nature of HD is associated with greater fluctuations in BP, with deterioration of residual renal function, and greater fluctuations in toxic solute and blood glucose levels. For example, in a study by Berlanga *et al.* (30), it was observed that PD was associated with a beneficial effect on residual renal function; in a study by Jansen *et al.* (31), it was observed that HD was associated with a further deterioration of residual renal function shortly after the initiation of RRT.

An approach in which HD and PD are regarded as complementary modalities and initiation with PD is followed by timely transfer to HD might be advocated, as was done by van Biesen *et al.* (21). The slightly higher adjusted RR for HD *versus* PD for time periods of >36 mo in our ITT analysis, in comparison with the AT analysis (RR, 0.42 *versus* 0.29) (Table 6), may indeed indicate that there was a survival benefit for a number of long-term PD patients after switching to HD. Further in-depth analyses are required to substantiate the roles of small-solute clearance (Kt/V_{urea}) and other important characteristics of dialysis (such as fluid removal, BP control, and clearance of other solutes) in long-term mortality rate differences and to establish the potential survival benefits of the complementary modality approach (21).

The tendency toward a mortality rate difference in favor of HD with longer follow-up times was observed particularly for elderly patients, with diabetes mellitus or not. This is partly in accordance with other reports. Held *et al.* (11) observed a higher risk of death for older diabetic patients treated with PD. However, the effects of age, diabetes mellitus, and follow-up times were not examined in one multivariate model, and it is difficult to compare those results with our findings. Vonesh and Moran (3) also observed an increased risk of death associated with PD among older diabetic patients, especially female patients, but no adjustments for comorbidities were performed. In a recent study by Winkelmayer *et al.* (12), an increase in mortality risk during the first 1 yr of PD treatment for patients ≥65 yr of age was observed.

We observed a statistically significant RR in favor of PD treatment in the first 2 yr among younger diabetic patients. This finding must be interpreted with caution, because unobserved patient selection might have contributed to the large mortality rate difference, and the number of young patients with diabetes mellitus was relatively small. It might be argued that the greater fluctuations in volume status and BP with HD are harmful, especially among patients with diabetes mellitus, because of the preexisting vascular damage and failing adaptive physiologic responses to sudden fluid removal associated with neuropathy. Furthermore, beneficial effects of continuous ambulatory PD on metabolic control have been reported (32). In later stages, the possible disadvantages associated with HD may be outweighed by problems associated with long-term PD. A RR in favor of PD among young diabetic patients with ESRD was also reported by Nelson *et al.* (15). The later decrease in the RR in favor of HD, as observed for elderly patients, may indicate that timely transfer to the other treatment modality may also be a useful treatment strategy for this subgroup of patients. For younger patients without diabetes

mellitus, the two treatment modalities seemed to be equivalent during both the early and later stages of dialysis treatment.

In conclusion, the results of this analysis indicate that long-term use of PD, especially among elderly patients, is associated with increases in mortality rates. Further analyses are required to determine the potential role of dialysis adequacy in the observed long-term differences in mortality rates between HD and PD patients and to establish the possible survival benefit for PD patients who switch to HD in time.

Acknowledgments

This work was supported by grants from the Dutch Kidney Foundation (Grant E.018) and the Dutch National Health Insurance Board (Grant OG97/005). The nursing staff of the dialysis centers and the trial nurses of the Netherlands Cooperative Study on the Adequacy of Dialysis, who collected most of the data, are gratefully acknowledged for their assistance. We thank Patrick M. Bossuyt, epidemiologist, for critically reviewing an earlier version of this manuscript. The Netherlands Cooperative Study on the Adequacy of Dialysis Study Group includes A. J. Apperloo, J. N. M. Barendregt, R. J. Birnie, M. Boekhout, W. H. Boer, E. F. H. van Bommel, H. R. Büller, F. T. de Charro, C. J. Doorenbos, W. T. van Dorp, A. van Es, W. J. Fagel, G. W. Feith, C. F. M. Franssen, L. A. M. Frenken, J. A. C. A. van Geelen, W. Geerlings, P. G. G. Gerlag, J. P. M. C. Gorgels, W. Grave, R. M. Huisman, K. J. Jager, M. A. M. Jansen, K. Jie, W. A. H. Koning-Mulder, M. I. Koolen, T. K. Kremer Hovinga, A. T. J. Lavrijssen, A. W. Mulder, K. J. Parlevliet, J. B. Rosman, J. L. C. M. van Saase, M. J. M. Schonk, M. M. J. Schuurmans, P. Stevens, J. G. P. Tijssen, R. M. Valentijn, G. Vastenburg, C. A. Verburg, C. E. Verhagen, V. M. C. Verstappen, H. H. Vincent, and P. Vos.

References

1. Gokal R, Jakubowski C, King J, Hunt L, Bogle S, Baillod R, Marsh F, Ogg C, Oliver D, Ward M: Outcome in patients on continuous ambulatory peritoneal dialysis and haemodialysis: 4-year analysis of a prospective multicentre study. *Lancet* 2: 1105–1109, 1987
2. Maiorca R, Cancarini GC, Zubani R, Camerini C, Manili L, Brunori G, Movilli E: CAPD viability: A long-term comparison with hemodialysis. *Perit Dial Int* 16: 276–287, 1996
3. Vonesh EF, Moran J: Mortality in end-stage renal disease: A reassessment of differences between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 10: 354–365, 1999
4. Bloembergen WE, Port FK, Mauger EA, Wolfe RA: A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 6: 177–183, 1995
5. Fenton SS, Schaubel DE, Desmeules M, Morrison HI, Mao Y, Copleston P, Jeffery JR, Kjellstrand CM: Hemodialysis *versus* peritoneal dialysis: A comparison of adjusted mortality rates. *Am J Kidney Dis* 30: 334–342, 1997
6. Collins AJ, Hao W, Xia H, Ebben JP, Everson SE, Constantini EG, Ma JZ: Mortality risks of peritoneal dialysis and hemodialysis. *Am J Kidney Dis* 34: 1065–1074, 1999
7. Gokal R, Figueras M, Olle A, Rovira J, Badia X: Outcomes in peritoneal dialysis and haemodialysis: A comparative assessment of survival and quality of life. *Nephrol Dial Transplant* 14[Suppl 6]: 24–30, 1999
8. Selgas R, Cirugeda A, Fernandez-Perpen A, Sanchez-Tomero JA, Barril G, Alvarez V, Bajo MA: Comparisons of hemodialysis and CAPD in patients over 65 years of age: A meta-analysis. *Int Urol Nephrol* 33: 259–264, 2001
9. United States Renal Data System: 1992 annual data report: Patient selection to peritoneal dialysis *versus* hemodialysis according to comorbid conditions. *Am J Kidney Dis* 20[Suppl 2]: S20–S26, 1992
10. Xue JL, Chen SC, Ebben JP, Constantini EG, Everson SE, Frazier ET, Agodoa LY, Collins AJ: Peritoneal and hemodialysis: I. Differences in patient characteristics at initiation. *Kidney Int* 61: 734–740, 2002
11. Held PJ, Port FK, Turenne MN, Gaylin DS, Hamburger RJ, Wolfe RA: Continuous ambulatory peritoneal dialysis and hemodialysis: Comparison of patient mortality with adjustment for comorbid conditions. *Kidney Int* 45: 1163–1169, 1994
12. Winkelmayer WC, Glynn RJ, Mittleman MA, Levin R, Pliskin JS, Avorn J: Comparing mortality of elderly patients on hemodialysis *versus* peritoneal dialysis: A propensity score approach. *J Am Soc Nephrol* 13: 2353–2362, 2002
13. Xue JL, Everson SE, Constantini EG, Ebben JP, Chen SC, Agodoa LY, Collins AJ: Peritoneal and hemodialysis: II. Mortality risk associated with initial patient characteristics. *Kidney Int* 61: 741–746, 2002
14. Vonesh EF, Schaubel DE, Hao W, Collins AJ: Statistical methods for comparing mortality among ESRD patients: Examples of regional/international variations. *Kidney Int* 57[Suppl 74]: S19–S27, 2000
15. Nelson CB, Port FK, Wolfe RA, Guire KE: Comparison of continuous ambulatory peritoneal dialysis and hemodialysis patient survival with evaluation of trends during the 1980s. *J Am Soc Nephrol* 3: 1147–1155, 1992
16. van Dijk PC, Jager KJ, de Charro F, Collart F, Cornet R, Dekker FW, Gronhagen-Riska C, Kramar R, Leivestad T, Simpson K, Briggs JD: Renal replacement therapy in Europe: The results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 16: 1120–1129, 2001
17. Davies SJ, Russell L, Bryan J, Phillips L, Russell GI: Comorbidity, urea kinetics, and appetite in continuous ambulatory peritoneal dialysis patients: Their interrelationship and prediction of survival. *Am J Kidney Dis* 26: 353–361, 1995
18. Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr* 33: 27–39, 1980
19. Visser R, Dekker FW, Boeschoten EW, Stevens P, Krediet RT: Reliability of the 7-point subjective global assessment scale in assessing nutritional status of dialysis patients. *Adv Perit Dial* 15: 222–225, 1999
20. Allison PD: *Survival Analysis Using the SAS System: A Practical Guide*, Cary, NC, SAS Institute Inc., 1995
21. van Biesen W, Vanholder RC, Veys N, Dhondt A, Lameire NH: An evaluation of an integrative care approach for end-stage renal disease patients. *J Am Soc Nephrol* 11: 116–125, 2000
22. Bargman JM, Thorpe KE, Churchill DN: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: A reanalysis of the CANUSA study. *J Am Soc Nephrol* 12: 2158–2162, 2001
23. Termorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT, NECOSAD Study Group: The relative importance of residual renal function compared to peritoneal clearance for patient survival and quality of life: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis* 41: 1293–1302, 2003

24. Hendriks PM, Ho-dac-Pannekeet MM, van Gulik TM, Struijk DG, Phoa SS, Sie L, Kox C, Krediet RT: Peritoneal sclerosis in chronic peritoneal dialysis patients: Analysis of clinical presentation, risk factors, and peritoneal transport kinetics. *Perit Dial Int* 17: 136–143, 1997
25. Davies SJ, Phillips L, Naish PF, Russell GI: Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J Am Soc Nephrol* 12: 1046–1051, 2001
26. Krediet RT, van Esch S, Smit W, Michels WM, Zweers MM, Ho-dac-Pannekeet MM, Struijk DG: Peritoneal membrane failure in peritoneal dialysis patients. *Blood Purif* 20: 489–493, 2002
27. Struijk DG, Krediet RT, Koomen GCM, Boeschoten EW, Hoek JK, Arisz L: A prospective study of peritoneal transport in CAPD patients. *Kidney Int* 45: 1739–1744, 1994
28. Struijk DG, Krediet RT, Koomen GCM, Hoek JK, Boeschoten EW, van der Reijden HJ, Arisz L: Functional characteristics of the peritoneal membrane in long-term continuous peritoneal dialysis. *Nephron* 59: 213–220, 1991
29. Zeier M, Schwenger V, Deppisch R, Haug U, Weigel K, Bahner U, Wanner C, Schneider H, Henle T, Ritz E: Glucose degradation products in PD fluids: Do they disappear from the peritoneal cavity and enter the systemic circulation? *Kidney Int* 63: 298–305, 2003
30. Berlanga JR, Marron B, Reyero A, Caramelo C, Ortiz A: Peritoneal dialysis retardation of progression of advanced renal failure. *Perit Dial Int* 22: 239–242, 2002
31. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT, NECOSAD Study Group: Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int* 62: 1046–1053, 2002
32. Grefberg N, Danielson BG, Berne C: Decreasing insulin requirements in CAPD patients given intraperitoneal insulin. *J Diabet Complications* 1: 16–19, 1987