Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands

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Considerable geographic variation exists in the relative use of hemodialysis (HD) vs peritoneal dialysis (PD). Studies comparing survival between these modalities have yielded conflicting results. Our aim was to compare the survival of Dutch HD and PD patients. We developed Cox regression models using 16 643 patients from the Dutch End-Stage Renal Disease Registry (RENINE) adjusting for age, gender, primary renal disease, center of dialysis, year of start of renal replacement therapy, and included several interaction terms. We assumed definite treatment assignment at day 91 and performed an intention-to-treat analysis, censoring for transplantation. To account for time dependency, we stratified the analysis into three time periods, >3–6, >6–15, and >15 months. For the first period, the mortality hazard ratio (HR) of PD compared with HD patients was 0.26 (95% confidence interval (CI) 0.17–0.41) for 40-year-old non-diabetics, which increased with age and presence of diabetes to 0.95 (95% CI 0.64–1.39) for 70-year-old patients with diabetes as primary renal disease. The HRs of the second period were generally higher. After 15 months, the HR was 0.86 (95% CI 0.74–1.00) for 40-year-old non-diabetics and 1.42 (95% CI 1.23–1.65) for 70-year-old patients with diabetes as primary renal disease. We conclude that the survival advantage for Dutch PD compared with HD patients decreases over time, with age and in the presence of diabetes as primary disease.

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The relative use of hemodialysis (HD) vs peritoneal dialysis (PD) for treatment of end-stage renal disease varies considerably across countries. In 2002, 0.5% of dialysis patients in Luxembourg underwent PD, whereas 48.4% used this modality in New Zealand.[1] Practice varies not only among but also within countries, as has been reported for the United States.[2] Although cultural factors and patient or physician preference may play a role, as well as reimbursement policy decisions, survival associated with both therapy modalities is an important consideration in the treatment decision.

Studies comparing patient survival on HD and PD, however, have yielded conflicting results. Possible explanations for these inconsistent results include underlying differences in the populations studied (e.g., incident vs prevalent patients, elderly vs general population), differences in methodology used (e.g., intention-to-treat vs as-treated), as well as unavailability of information on important confounders in several studies (e.g., presence and/or severity of co-morbid conditions). Although differences in measured clinical or demographic characteristics can be adjusted in multivariable regression analyses, confounding by unmeasured characteristics remains a threat to validity. It has been suggested that using information on the treatment center can be used to further reduce bias.[3,4] This can be conducted in several ways, such as through multivariable modeling, multilevel modeling, or including center information in exposure propensity scores.[5,6] Furthermore, the relative mortality risk of HD compared with PD patients may differ for various patient groups. In addition, the relative risks may change over time after the initiation of dialysis.[7–10]

In The Netherlands, a relatively high proportion of patients initiate renal replacement therapy (RRT) using PD. We conducted this study to compare mortality of incident HD and PD patients in the Netherlands, using Dutch registry data.

RESULTS

The RENINE Registry prospectively collected data of 20 687 patients who started RRT between 1 January 1987 and

31 December 2002. We discarded 2157 patients who died during the first 90 days of RRT. Of the remaining patients, we excluded 517 patients because they were younger than 18 years and another 19 patients who had more than one episode of recovery of renal function or death directly following a period of renal recovery. Of the remaining patients, there were 699 who had received a pre-emptive transplantation before or at day 91. We excluded 625 patients from centers treating fewer than 20 dialysis patients or fewer than five PD patients and another 27 patients for whom center information was not available. As a result, our final sample included 16 643 patients from 47 centers. Mean age was 59 years (s.d.: 15.3) and 58.8% were male. Descriptive characteristics of patients are shown in Table 1. The Kaplan–Meier survival plot (Figure 1) showed a higher crude survival for PD compared with HD patients (log-rank test: $P<0.001$).

Table 1 | Baseline characteristics of study cohort

	All patients	HD	PD	*P*-value
Number (%)	16 643	10 841 (65.1)	5802 (34.9)	
Age (s.d.) (years)	59.0 (15.3)	61.8 (14.6)	53.6 (15.0)	<0.001
Female gender (%)	41.2	42.5	38.7	<0.001
Primary renal disease (%)				<0.001
GN	13.7	11.1	18.5	
HT	11.4	11.7	10.8	
RVD	8.7	9.8	6.6	
DM	15.2	14.9	16.0	
Other	51.0	52.5	48.1	
Year of first RRT (%)				<0.001
1987–1990	17.0	18.0	14.9	
1991–1994	23.5	23.2	24.0	
1995–1998	28.6	28.3	29.0	
1999–2002	31.0	30.5	32.0	
Years of follow-up (s.d.)	2.38 (2.14)	2.42 (2.24)	2.32 (1.95)	0.007

DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HT, hypertension; PD, peritoneal dialysis; RRT, renal replacement therapy; RVD, renovascular disease.

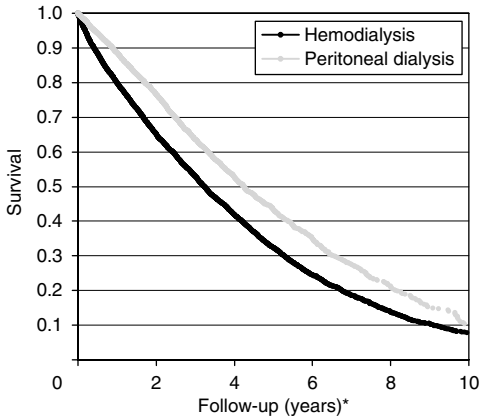

Figure 1 | Unadjusted survival of dialysis patients. Kaplan–Meier curves of survival of HD (black line) and PD (grey line) patients, censored for transplantation (log-rank test: $P<0.001$). *Follow-up censored for transplantation in years.

Multivariable regression analysis

In the univariable Cox model, dialysis modality was associated with survival: patients who initiated RRT using PD had a 30% lower mortality compared with HD patients (hazard ratio (HR) = 0.70; 95% confidence interval (CI): 0.67–0.74; $P<0.001$). The coefficients of all other univariable models were also statistically significant, both in the overall population and in the HD and PD groups (see Table 2). The coefficient for the year of starting RRT was not significant in the total population, because its effect was in opposite directions for HD and PD patients. With increasing year of start of RRT, the relative risk of dying increased for HD patients and decreased for PD patients. Center was a significant univariable predictor of modality ($P<0.001$, data not shown).

The multivariable Cox model, adjusted for age, gender, primary renal disease, year of first RRT, and treatment center but without interaction terms revealed that mortality of PD patients and HD patients did not differ (HR = 0.99; 95% CI: 0.94–1.05). Of the interaction variables tested in this multivariable model, however, four were statistically significant: age by modality (HD or PD) and diabetes as the primary cause of renal disease (PRD-DM) by modality, by age, and by gender (Table 3). An analysis using propensity scores was also undertaken and the results were virtually unchanged. Additional analyses using center size as a covariate yielded essentially identical results (not shown).

Several interactions with time were statistically significant in the multivariable Cox model indicating violations of the proportionality assumption. We tested various time-stratification strategies. Finally, we stratified time into three periods: >3–6, >6–15, and beyond 15 months. For each of these periods, the relative mortality risk of PD compared with HD patients appeared constant over time. In order to illustrate the change in relative hazards over time and to account for the variables that were effect modifiers of the treatment variable (age, PRD-DM), we calculated HRs of PD compared with HD patients for representative values of these variables.

Table 2 | Univariable associations with mortality

	HD		PD		All patients	
	HR	*P*-value	HR	*P*-value	HR	*P*-value
Age (per year)	1.04	<0.001	1.06	<0.001	1.05	<0.001
Female vs male gender	0.94	0.02	0.80	<0.001	0.91	<0.001
Primary renal disease versus GN[a]						
HT	1.47	<0.001	2.15	<0.001	1.72	<0.001
RVD	2.35	<0.001	3.80	<0.001	2.86	<0.001
DM	2.11	<0.001	3.49	<0.001	2.55	<0.001
Other	1.38	<0.001	1.61	<0.001	1.53	<0.001
Year of first RRT (per year)	1.02	<0.001	0.99	<0.001	1.00	0.18
PD vs HD	—	—	—	—	0.70	<0.001

DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HR, hazard ratio; HT, hypertension; PD, peritoneal dialysis; RRT, renal replacement therapy; RVD, renovascular disease.
[a]Compared with GN as reference group.

We used four ages, 40, 50, 60, and 70 years, for detailed presentation (Table 4). For the eight groups defined by these values of age and the presence vs absence of PRD-DM, the relative mortality risk of PD patients compared with HD patients increased over time, that is, the relative survival benefit diminished (Table 4). And for all time-strata, this relative PD survival benefit decreased with increased age and with the presence of PRD-DM. Among non-PRD-DM patients, the relative survival advantage associated with PD was highest for 40-year olds, although this relative advantage decreased over time, from an HR of 0.26 (95% CI: 0.17–0.41) in the time period of >3–6 months to an HR of 0.86 (95% CI: 0.74–1.00) in the period after 15 months. For 40- and 50-year-old patients with PRD-DM and for 50-, 60-, and 70-year-old patients without PRD-DM, the early relative survival advantage associated with PD disappeared over time. PD was even associated with worse relative survival after 15 months for 50-year-old PRD-DM patients (HR 1.17, 95% CI: 1.00–1.35) and 70-year-old patients without PRD-DM (HR 1.16, 95% CI: 1.07–1.25). Similarly, for 60- and 70-year-old patients with PRD-DM, PD was associated with a significantly worse relative survival (HR respectively 1.29, 95% CI 1.12–1.48 and 1.42, 95% CI 1.23–1.65) after 15 months, although there was no significant relative survival advantage for either modality up to 15 months.

To assess the impact of these HRs on actual cumulative survival, we constructed survival curves for these eight groups (Figure 2a–h). As can be deduced from these curves, the differences in absolute survival were similar as those with respect to the relative survival or HRs, with one exception. For 50-year-old patients without PRD-DM, we concluded from the HRs that the relative survival advantage disappeared over time, however, the cumulative survival benefit of PD remained over the entire observation period (Figure 2c).

Table 3 | Multivariable adjusted model

	HR	*P*-value
Age (per year)	1.05	<0.001
Female vs male gender	0.87	<0.001
Primary renal disease vs GN[a]		<0.001
HT	1.22	<0.001
RVD	1.68	<0.001
DM	5.65	<0.001
Other	1.31	<0.001
Year of first RRT (per year)	0.99	0.005
Dialysis center		<0.001
Peritoneal vs hemodialysis	0.43	<0.001
Age × dialysis modality	1.01	<0.001
DM × dialysis modality	1.22	0.002
Age × DM	0.98	<0.001
Gender × DM	1.20	0.002

DM, diabetes mellitus; GN, glomerulonephritis; HR, hazard ratio; HT, hypertension; RRT, renal replacement therapy; RVD, renovascular disease.
[a]Compared with GN as reference group.

Table 4 | Associations between dialysis modality and mortality

		HRs of PD vs HD (95% CIs)[a]		
Age	DM	>3–6 months	>6–15 months	>15 months
40	No	0.26 (0.17; 0.41)	0.51 (0.39; 0.68)	0.86 (0.74; 1.00)
40	Yes	0.40 (0.23; 0.68)	0.59 (0.44; 0.81)	1.06 (0.88; 1.26)
50	No	0.35 (0.25; 0.48)	0.62 (0.51; 0.76)	0.95 (0.85; 1.05)
50	Yes	0.53 (0.34; 0.83)	0.72 (0.56; 0.93)	1.17 (1.00; 1.35)
60	No	0.46 (0.37; 0.58)	0.75 (0.65; 0.87)	1.05 (0.97; 1.13)
60	Yes	0.71 (0.48; 1.04)	0.87 (0.71; 1.09)	1.29 (1.12; 1.48)
70	No	0.62 (0.50; 0.76)	0.92 (0.80; 1.05)	1.16 (1.07; 1.25)
70	Yes	0.95 (0.64; 1.39)	1.07 (0.85; 1.33)	1.42 (1.23; 1.65)

CI, confidence interval; DM, diabetes as primary renal disease; HD, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis.
[a]From models including age, gender, primary renal disease, year of start of RRT, center and the interaction terms age by modality, diabetes by modality, age by diabetes, and gender by diabetes.

DISCUSSION

In this comprehensive study of all patients who initiated chronic dialysis treatment between 1987 and 2002 in The Netherlands, unadjusted mortality of PD patients was 30% lower compared with HD patients. Multivariable adjustment for age, gender, primary renal disease, year of first RRT, and dialysis center, however, showed that the HR was not constant over time, but increased in favor of HD, with higher age, and in those whose primary renal disease was DM. In younger patients, PD was associated with superior survival in the first 15 months of RRT, independent of whether DM was the original renal disease. Among older patients, this association was only present for the first few months and only in those patients whose underlying renal disease was not DM. Independent of underlying renal disease, PD was associated with higher mortality after 15 months in patients older than 70 years of age. Examining the cumulative survival curves enables us to scrutinize the other aspect of this study, overall survival (Figure 2). For non-PRD-DM patients, PD was associated with a comparable (age 60 and 70) or better (age 40 and 50) overall survival compared with HD. Among PRD-DM patients, PD and HD showed equivalent survival among younger patients (age 40 and 50), but HD was associated with greater survival among older patients (age 60 and 70).

Our findings corroborate the existing literature on the decrease in relative survival of PD patients as compared with HD patients over time. Termorshuizen *et al.*[10] reported that mortality during the first two years was not different between HD and PD patients among participants of the NECOSAD study. However, they observed a higher relative mortality of PD patients after two years of treatment. Jaar *et al.*[11] came to similar conclusions in their recent study of 1041 incident dialysis patients in the US. Fenton *et al.*[7] concluded that Canadian PD patients had a significantly higher survival than HD patients, the effect being largest for the first two years on dialysis. Heaf *et al.*[9] reported a survival advantage for Danish PD patients for the first 1–2 years, but after 2.5 years this association was reversed in patients with diabetes.[8] Although these studies allow for different conclusions regarding the

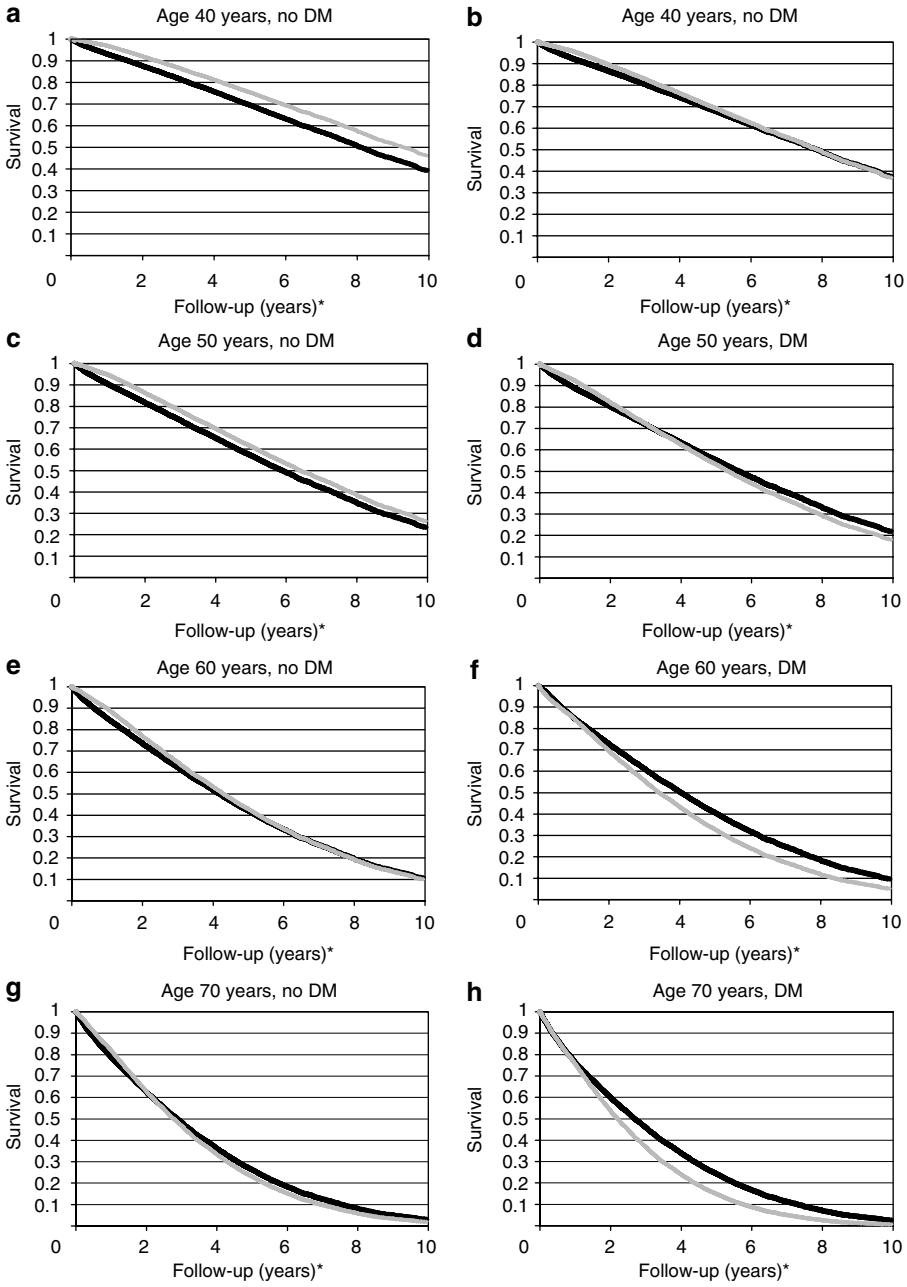

Figure 2 | Adjusted survival curves of HD and PD patients. (**a–h**) Curves of survival of HD (black line) and PD (grey line) patients, censored for transplantation, for various ages (years) and stratified by presence of diabetes mellitus (DM) being the primary renal disease. *Follow-up censored for transplantation in years.

presence of an initial survival advantage for PD patients, the time trends in survival differences are similar; the relative mortality risk of PD patients has consistently been reported to increase over time. Differences regarding the initial survival advantage of PD during the first years of dialysis in these studies might be explained by different analytical approaches, prognostic factors available for study, and regional differences in patient population and dialysis practice.

The initial survival advantage of PD patients in our study might be explained by HD patients having higher co-morbidity at initiation of dialysis therapy.[12] If HD patients with the highest burden of co-morbidity die early resulting in healthier HD patients surviving, mortality rates of HD patients would then decrease over time. PD patients, who are generally healthier than HD patients initially, would develop higher mortality over time as they accumulate other co-morbidities. Some of these aforementioned studies did correct for co-morbidity, however, and still observed time trends similar to our study.[7–10] Alternatively, the higher dose of delivered dialysis for PD patients initially might account for the time trend in relative mortality. Collins *et al.*[8]

reported, though, that initial delivered dose was not as different for HD and PD patients as had generally been believed. Finally, it has also been suggested that the short-term survival advantage of PD patients might be explained by better preservation of residual renal function in patients treated with PD as compared with patients treated with HD.[13] Residual kidney function has been shown to be an independent predictor of mortality for both HD[14] and PD[15] patients. As time progresses, residual kidney function declines and PD alone might not suffice to maintain adequate clearance. Therefore, some have advocated an Integrative Care Approach, starting RRT with PD and later switching to HD as residual renal function deteriorates.[9,16] To inform such an approach, it is important to consider both data on period-specific HRs and on cumulative survival over time. Even if one modality may be associated with greater mortality during later stages of RRT, the strategy may still be superior because of lower mortality during earlier time-periods, and vice versa.

In our study, we also found that the HR of PD compared with HD patients increased with age and in the presence of diabetes as primary renal disease. This effect modification had also previously been reported,[12,17–19] although contrasting findings were also described by Keshaviah *et al.*[20] The latter group described a similar two-year survival for HD and PD patients, independent of age and diabetic status, when adjusting for co-morbidity, serum albumin, and dialysis dose. This controversy might be explained by differences in the covariate adjustment: Keshaviah included dialysis dose as a covariate, whereas the other studies did not. Jaar *et al.*[11] did find age to be an effect modifier, whereas diabetes was not. In their study, initial dialysis dose as well as cardiovascular morbidity was among the included covariates. However, with a cohort of just over 1000 patients, their statistical power was rather limited to detect any effect modification on prognostic main effects. Our study confirms the findings of Vonesh *et al.* who analyzed 398 940 incident US dialysis patients from the United States Renal Data System. These authors also reported effect modification by age and diabetes and found a similar time trend in relative survival of HD compared with PD patients in age- and diabetes-stratified subgroups.[19]

Some limitations of our study deserve mention. The RENINE database does not include data on co-morbidity, but information on primary renal diagnosis is available. The most important co-morbid condition, diabetes, is likely well represented in the subgroup identified with diabetes as underlying renal disease, as diabetes and PRD-DM are likely to correlate strongly. Other factors that have been reported to affect dialysis mortality were also not available for study: ethnicity,[8,21] nutritional markers,[21–23] delivered therapy,[20] and transplant eligibility.[9]

Important factors, other than survival, in selecting dialysis modality for an individual patient would include HD and PD-associated quality-of-life and a patient's living arrangements and personal preference. Also the nephrologist's preference and the reimbursement system in a specific country are known to influence dialysis modality selection.[24,25] These aspects are beyond the scope of our study.

From our findings, we conclude that there is an initial survival advantage for PD patients compared with HD patients in The Netherlands. Over time, with advancing age, and in the presence of diabetes as primary disease, this relative survival advantage vanishes, and even reverses with time.

MATERIALS AND METHODS

Patients

We included all incident patients who started RRT between 1 January 1987 (start of prospective registration) and 31 December 2002 from the Dutch End Stage Renal Disease Registry (RENINE). We excluded patients younger than 18 years, patients who underwent RRT for less than 30 days, patients who had more than one episode of recovery of renal function, or who died directly following a period of renal recovery, patients who received a pre-emptive transplantation, patients who died during the first 90 days of RRT and patients from centers treating fewer than 20 dialysis patients or fewer than five PD patients. The outcome of interest was all-cause mortality, as registered by RENINE. The registry collects information on date and cause of death and verifies its information yearly with all centers.[26,27] From registry data, we also determined age and gender of patients. In the database, primary renal diagnosis was coded according to the classification of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA). We aggregated these into five categories: glomerulonephritis (PRD-GN), hypertension (PRD-HT), renovascular disease (PRD-RVD), diabetes mellitus (PRD-DM), and a category for all other renal diagnoses (PRD-OTH). Furthermore, we used registry data on dialysis modality, year of start of dialysis, and the center at which dialysis was started.

Analysis

We adopted an intention-to-treat perspective and considered the dialysis modality on day 91 to be the definite modality. We left-censored survival time for the first 90 days and right-censored at first transplantation or 31 December 2002, whichever occurred first. We compared Kaplan–Meier survival curves of HD and PD patients, using the log-rank test.

To estimate the independent comparison between PD and HD mortality by controlling for observed potential confounders, we used a multivariable regression adjustment approach. The first step was to estimate univariable Cox proportional hazards models for all available variables. Age and year of start of dialysis were entered into the model as continuous variables and all other variables as categorical variables. All statistically significant variables ($P<0.05$) from the univariable analyses were put into a multivariable Cox proportional hazards model. From the full multivariable model, we explored the significance of a quadratic term (age) and several two-way and three-way interaction terms. We tested for center effects by entering center as a categorical variable into the multivariable model.

In the final Cox model, we tested for violations of the proportional hazards assumption by testing for significance of time-dependent variables. As the proportionality assumption was violated for the main exposure variable, we applied time stratification, thus ensuring absence of time dependency within time strata. For all these analyses, we calculated HRs and 95% CI for PD relative to HD mortality within each time interval. In addition, we presented cumulative survival curves stratified by PD vs HD. An HR reflects a

relative survival difference for a period to which the HR pertains. Because the proportional hazards assumption was not satisfied, we calculated different HRs for different time periods. The long-term survival and life expectancy over the entire observation period are determined by the magnitude of the HRs and the duration of the period to which these ratios apply, in other words, by the cumulative effect of the different HRs. Absolute survival differences are therefore best reflected in differences in (the area under) the cumulative survival curves.

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