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Mortality Differences by Dialysis Modality among Incident ESRD Patients with and without Coronary Artery Disease

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Abstract. It is unclear whether peritoneal dialysis (PD) compared with hemodialysis (HD) confers a survival advantage in end-stage renal disease (ESRD) patients with coronary artery disease (CAD). This hypothesis was tested in a national cohort of 107,922 patients starting dialysis therapy between May 1, 1995, and July 31, 1997. Data on patient characteristics were obtained from the Center for Medicare and Medicaid Services Medical Evidence Form (CMS) and linked to mortality data from the United States Renal Data System (USRDS). Patients were classified on the basis of CAD presence and followed until death or the end of 2 yr. Nonproportional Cox regression models estimated the relative risk (RR) of death for patients with and without CAD by dialysis modality using primarily the intent-to-treat but also the as-treated approach. Diabetic patients (DM) and nondiabetic patients (non-DM) were analyzed separately. Among DM, patients with CAD treated with PD had a 23% higher RR (95% CI, 1.12 to 1.34) compared with similar HD patients, whereas patients without CAD receiving PD had a 17% higher RR (CI, 1.08 to 1.26) compared with HD. Among non-DM, patients with CAD treated with PD had a 20% higher RR (CI. 1.10 to 1.32) compared with HD patients, whereas patients without CAD had similar survival on PD or HD (RR = 0.99; CI, 0.93 to 1.05). The mortality risk for new ESRD patients with CAD differed by treatment modality. In both DM and non-DM, patients with CAD treated with PD had significantly poorer survival compared with HD. Whether differences in solute clearance and/or cardiac risk profiles between PD and HD may explain these findings deserves further investigation.

Cardiac disease accounts for more than 50% of all deaths among ESRD patients (1). There has been much speculation about the cause of this increased burden of cardiovascular mortality. Proposed mechanisms include accelerated atherogenesis, lipid derangements, endothelial dysfunction, and inflammation (2–6). In addition, evidence is accumulating to suggest that dialysis modality may contribute to increased atherogenesis in this population (7). Both PD and HD may contribute individually to accelerated vascular disease through separate immune-mediated and nonimmune-mediated mechanisms, accelerate preexisting coronary artery disease, and precipitate fatal cardiac events (8,9).

A largely unexplored question is whether new ESRD patients with preexisting CAD would benefit preferentially from placement on either PD or HD, all else being equal. Both modalities have favorable and unfavorable characteristics that might either protect patients from accelerated cardiac disease or increase their susceptibility. On one hand, PD may offer patients better BP control, less hemodynamic shear stress, and avoidance of the peaks and troughs in uremic toxins that are common with HD (10). On the other hand, because of unfavorable lipid profiles and elevated serum glucose, PD may accelerate preexisting CAD through increased glycosylation and lipid oxidation (11–16). The selection of HD for patients with CAD may also have untoward effects on the coronary vasculature mediated by increased oxidative stresses and inflammatory mediators (17,18). However, notwithstanding these untoward effects, HD might provide patients with overall greater solute clearance and greater removal of potentially atherogenic uremic toxins compared with PD.

In studies of ESRD patients, mortality differences between PD and HD have been inconsistent (19–21). These differences may be partially due to the differences in patient selection between HD and PD or differences in patient characteristics between prevalent and incident ESRD patients (22). In the United States, we and others have shown that patients selected to PD tend to be younger and are less likely to have cardiovascular disease and other clinical comorbid conditions compared with HD patients (23,24). These differences in case-mix would favor greater survival on PD. Recent survival comparisons in new ESRD patients have suggested that PD might be

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the preferred modality, at least for the first 15 mo, after which HD confers a greater survival advantage (21). Whether the same holds true for new ESRD patients with CAD is unclear.

We hypothesized that patients with a history of CAD might benefit from PD compared with HD because of (*1*) improved volume regulation and BP control, (*2*) less hemodynamic shear stresses on the vascular wall as a result of fluid shifts during dialysis, and (*3*) less activation of the complement system and decreased oxidant stress. The purpose of this study was to explore this hypothesis in a national cohort of new ESRD patients and determine the association of modality with survival among patients with and without CAD before ESRD start.

Materials and Methods

Data

This study was a historical prospective cohort of new ESRD patients in the United States who were initiated on dialysis between May 1, 1995, and July 31, 1997. The data used in this analysis were obtained from the Center for Medicare and Medicaid Services (CMS) Medical Evidence Form, a government document that is completed for all new patients initiated on dialysis (25). The CMS form records data on demographic characteristics (age, gender, and race), causes of ESRD, date of first initiation of dialysis, mode of dialysis, and presence of several comorbid conditions and laboratory parameters at the time of dialysis initiation, including serum albumin, creatinine, urea, and hematocrit. An estimate of residual renal function was calculated for each patient using the Modification of Diet in Renal Disease (MDRD) formula (26), and body mass index (BMI) was calculated from the following equation: BMI = weight (kg)/height (m^2).

For the purposes of this study, the presence of CAD was defined as a history of prior coronary artery disease, myocardial infarction, angioplasty, or coronary artery bypass graft (CABG) from the CMS Medical Evidence Form. The study start date for all incident patients was defined as day 90 of ESRD. The reasons for this are twofold. First, many patients younger than 65 yr do not become eligible for Medicare for up to 90 d and therefore may have incomplete claims data before this. Second, the 90-d rule is important for patients whose final modality is PD but who have been placed temporarily on HD until PD training and PD catheter placement has been completed. These eligibility requirements are consistent with prior USRDS methods. The CMS form is a validated data collection instrument, and data arising from it has been published in prior studies (27,28).

The CMS data set was linked with the United States Renal Data System (USRDS), a renal registry that captures data on all patients undergoing dialysis in the United States. This allowed merging of data on date of death and date of renal transplantation by USRDS identification number for each member of the study. Patients were excluded from the analyses if they were less than 18 yr of age or if they had data missing on age, gender, race, indicators of CAD, or laboratory measures of interest, or if modality assignment could not be determined at day 90 of ESRD. Following exclusion, there were 107,922 patients available for further analyses.

Analytical Methods

The dependent variable was time to death. Time-dependent Cox regression equations were used to compare the mortality risks between HD and PD in patients with and without CAD. This modeling strategy was used because preliminary analyses demonstrated that the impact of dialysis modality on mortality varied with time ($P < 0.0001$ interaction), thereby violating proportionality assumptions of the Cox model. Accordingly, we compared patient survival times on PD with HD at successive 6-mo intervals in the follow-up period. The beginning of each 6-mo interval served as the start date, with the end date at 180 d. Patients were followed until death, loss to follow-up, or at the end of 2 yr, whichever came first.

We employed both an intent-to-treat and an as-treated model in assessing the association of treatment modality with mortality risk in patients with and without CAD. The intent-to-treat model was used to determine the association between the specified dialysis modality chosen at ESRD onset and subsequent mortality, irrespective of any future changes in modality. For these analyses, patients were not censored if they changed treatment modality during follow-up and patient death was assigned to the initial treatment modality. The as-treated model was used to determine the risk of death while being treated by a specified modality during the follow-up period. In the as-treated studies, patients were censored from contributing additional time at risk when they switched from one modality of treatment to another. Furthermore, the as-treated analyses allowed us to evaluate the mortality risks of patients who switched from one modality to another during the follow-up period by comparing survival times of patients who switched from PD to HD (HD_{new}) and from HD to PD (PD_{new}) with those remaining on PD (PDo) or HD (HDo) since ESRD start. Finally, we analyzed diabetics patients and nondiabetic patients in separate models because previous studies have shown nonproportional hazards in these two groups.

As PD patients with CAD were shown to differ significantly from HD patients with CAD with respect to nutritional, vascular, and several other potentially confounding factors, the relationship between modality and mortality risk was further explored in a series of sensitivity analyses. First, we tested the sensitivity of our results to additional known predictors of mortality by including measures of nutrition (serum albumin and BMI) and anemia (hematocrit), vascular disease (peripheral and cerebral vascular disease), tobacco use, level of renal function estimated at ESRD start using the Modification of Diet in Renal Disease Study Group equation, and a measure of pre-ESRD patient care (use of erythropoietin before ESRD start). Second, we evaluated the robustness of our measure of CAD by analyzing a subset of patients with a history of myocardial infarction (MI) recorded on the CMS Evidence Form and repeating the above analyses. Finally, we tested the sensitivity of the models to renal transplantation. The regression analyses were therefore repeated with and without censoring at transplantation. All statistical analyses were performed using SAS statistical software (version 8.0; SAS Institute, Cary, NC).

Results

Baseline Characteristics of Cohort and Distribution of Deaths during Follow-Up

Between the dates of May 1, 1995, and July 31, 1997, over 167,000 patients were initiated on dialysis in the United States. Of these, 107,922 had data on the variables of interest and were included in this study. Hemodialysis was the choice of therapy for 93,900 (87%) and PD the choice for 14,022 (13%). A history of CAD was recorded in 26% of new ESRD patients. The median follow-up was 12 mo; 27,149 (25.2%) patients died, 5423 (5%) were transplanted, and 3753 (3.5%) patients were lost to follow-up within the 2-yr period.

The distribution of patient characteristics for the entire study

population is given in Table 1. The average age at onset of ESRD was 61.5 ± 15 yr, 63% were white, 53% were male, and 44% developed ESRD as a consequence of diabetes. Table 2 compares the characteristics of patients with and without CAD by treatment modality. Patients with CAD initiated on PD were of younger age and had a greater fraction of white, male, and diabetic patients than those selected to HD. In general, PD patients with CAD had fewer comorbid medical conditions (congestive heart failure, peripheral vascular disease, lung disease, and neoplasm), higher values for nutritional indicators (serum albumin and body mass index), and greater level of residual renal function at ESRD start compared with their HD counterparts. The distribution of patient characteristics was similar for new ESRD patients without CAD with lower comorbidity burden seen in PD-selected patients.

Patient Survival by Modality

The distribution of deaths among patients with and without CAD according to dialysis modality is illustrated in Table 3. Patients with CAD treated with PD had a higher proportion of deaths during follow-up compared with HD-treated patients (36.1 *versus* 33.7%), whereas patients without CAD treated with PD had a lower fraction of deaths compared with those treated with HD (18.2 *versus* 22.7%). Similarly, among the subgroups of CAD, patients with a recorded history of MI, the proportion of patients who died during follow-up was higher in the PD-treated group. Adjusted Cox survival curves were estimated for PD-treated and HD-treated patients in each CAD category as shown in Figures 1 and 2. For patients with CAD, similar survival on either modality was observed up to 8 mo, after which the curves diverged with greater survival in HD-treated group. In contrast, among patients without CAD, the survival curves were almost superimposed and in fact crossed with an early survival benefit in favor of PD and a late survival advantage in favor of HD.

Mortality Risk Predictors in New ESRD Patients

The relationship between treatment modality and subsequent mortality risk was explored for the entire cohort, and the

Table 1. Characteristics of the study population at ESRD onset from the CMS Medical Evidence Report Form (n = 107,922)

Patient Characteristics	Study Population n = 107,922	HD n = 93,900	PD n = 14,022
Demographics			
Age of onset of ESRD (mean yr ± SD)	61.5 ± 15.3	62.3 ± 15.2	56.5 ± 15.2[f]
race			
% White	63.4	62	73.4[f]
% Black	31.1	32.6	20.8[f]
% Asian	3.7	3.6	4.2[e]
gender (% male)	53	52.8	53.8[d]
cause of ESRD (% diabetes)	44.3	44.0	46.1[f]
Laboratory values (mean ± SD)			
serum albumin (g/dl)	3.2 ± 0.7	3.2 ± 0.65	3.4 ± 0.64[f]
hematocrit (%)	28.1 ± 5.3	27.9 ± 5.3	29.3 ± 5.3[f]
GFR (MDRD) (ml/min)[a]	8.2 ± 2.9	8.1 ± 2.9	8.5 ± 2.9[f]
Comorbid conditions (% yes)			
diabetes (history and/or nephropathy)	39.3	39.4	38.7
hypertension	72.6	72.5	73.2
coronary artery disease[b]	25.9	26.4	22.7[f]
myocardial infarction	8.9	9.0	8.4[d]
cardiac arrest/dysrhythmia	6.4	6.5	5.3[f]
congestive heart failure	32.7	33.9	24.7[f]
cerebrovascular disease	8.9	9.3	6.7[f]
peripheral vascular disease[c]	14.6	15.0	12.1[f]
chronic obstructive lung disease	6.9	7.3	4.4[f]
tobacco use	6.2	6.2	6.4
AIDS	0.55	0.57	0.41[d]
neoplasm	4.9	5.2	3.0[f]
BMI (mean kg/m^2 ± SD)	25.7 ± 5.8	25.6 ± 5.9	25.9 ± 5.3[f]

[a] At first dialysis per MDRD formula (n = 34,585; HD = 29,676; PD = 4909) (26).
[b] Includes history of coronary artery disease, myocardial infarction, coronary artery bypass surgery, angioplasty, or abnormal angiography.
[c] Includes a history of peripheral vascular disease amputation, intermittent claudication, or absent pulses.
[d] $P < 0.05$, [e] $P < 0.01$, [f] $P < 0.001$ for bivariate comparisons.

Table 2. Characteristics of patients with and without coronary artery disease (CAD) by treatment modality at ESRD onset (n = 107,922)

Patient Characteristics	CAD Present (n = 27,997)		CAD Absent (n = 79,925)	
	HD (n = 24,818)	PD (n = 3179)	HD (n = 69,082)	PD (n = 10,843)
Demographics				
age of onset of ESRD (mean yrs ± SD)	68.6 ± 10.7	64.8 ± 11.5[e]	60 ± 16.0	54 ± 15.4
race				
% White	76.1	85.3[e]	56.8	70[e]
% Black	20	11.2[e]	37.2	23.7[e]
% Asian	2.6	2.5	4.0	4.7[d]
gender (% male)	56	62.1[e]	51.7	51.4
cause of ESRD (% diabetes)	52	58[e]	41.1	42.9[d]
Laboratory values (mean ± SD)				
serum albumin (g/dl)	3.2 ± 0.6	3.4 ± 0.6[e]	3.2 ± 0.67	3.5 ± 0.65[e]
hematocrit (%)	28.8 ± 4.9	30.2 ± 5.0[e]	27.6 ± 5.4	29.1 ± 5.4[e]
GFR (MDRD) (ml/min)[a]	8.6 ± 2.8	9.1 ± 2.9[e]	7.9 ± 2.9	8.2 ± 2.8[e]
Comorbid conditions (% yes or suspected)				
diabetes (history and/or nephropathy)	50.3	52.6[c]	35.4	34.7
hypertension	79	80	70.1	71.2[c]
cardiac arrest/dysrhythmia	14.5	13.8	3.6	2.8[e]
congestive heart failure	59	54[c]	24.7	16.2[e]
cerebrovascular disease	15.8	13.3[e]	6.9	4.8[e]
peripheral vascular disease[b]	31	29[c]	9.3	7.2[e]
chronic obstructive lung disease	13.3	9.7[e]	5.1	2.8[e]
tobacco use	6.9	7.1	6.0	6.1
AIDS	0.06	0.09	0.76	0.51[d]
neoplasm	5.8	3.7[e]	5.0	2.8[e]
BMI (mean kg/m^2 ± SD)	25.4 ± 5.6	25.8 ± 5.1[e]	25.7 ± 6.0	25.9 ± 5.4[e]

[a] At first dialysis per MDRD formula (26).
[b] Includes a history of peripheral vascular disease amputation, intermittent claudication, or absent foot pulses.
[c] $P < 0.05$, [d] $P < 0.01$, [e] $P < 0.001$ for bivariate comparisons for bivariate comparisons in each CAD category.

Table 3. Distribution of deaths among patients with and without CAD or MI by dialysis modality

	HD		PD	
	Number of Patients n	Number of Deaths n (%)	Number of Patients n	Number of Deaths n (%)
Coronary artery disease				
yes	24,818	8374 (33.7)	3179	1147 (36.1)
no	69,082	15,659 (22.7)	10,843	1969 (18.2)
Myocardial infarction				
yes	8451	2951 (34.9)	1172	446 (38.1)
no	85,449	21,082 (24.7)	12,850	2670 (20.8)

unadjusted and adjusted hazard ratios with 95% confidence intervals (CI) for each covariate are given in Table 4. In the adjusted analyses, the risk of death increased by 3% for every additional year of age. White patients had a 25% higher mortality risk compared with non-white patients. The relative risk of death was significantly greater for patients with known cardiovascular conditions: CAD (RR = 1.11; CI, 1.08 to 1.14), peripheral vascular disease (RR = 1.18; CI, 1.14 to 1.22), cerebral vascular disease (RR = 1.18; CI, 1.13 to 1.22), cardiac arrest/dysrhythmia (RR = 1.18; CI, 1.14 to 1.23), and cardiac failure (RR = 1.26; CI, 1.23 to 1.29) compared with those without these conditions at ESRD onset. Similar high mortality

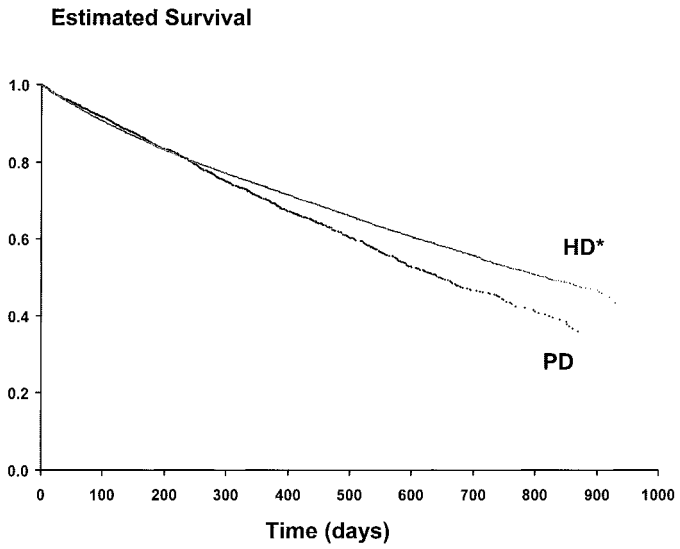

Figure 1. Adjusted Cox survival curves for new ESRD patients with coronary artery disease treated with peritoneal dialysis (PD) *versus* hemodialysis (HD). Adjusted for age at study start, gender, race, cause of ESRD, hypertension, congestive heart failure, peripheral vascular and cerebrovascular disease, tobacco use, chronic lung disease, AIDS, neoplasm, serum albumin, body mass index, hematocrit, estimated GFR, and pre-ESRD erythropoietin use. *$P < 0.0001$.

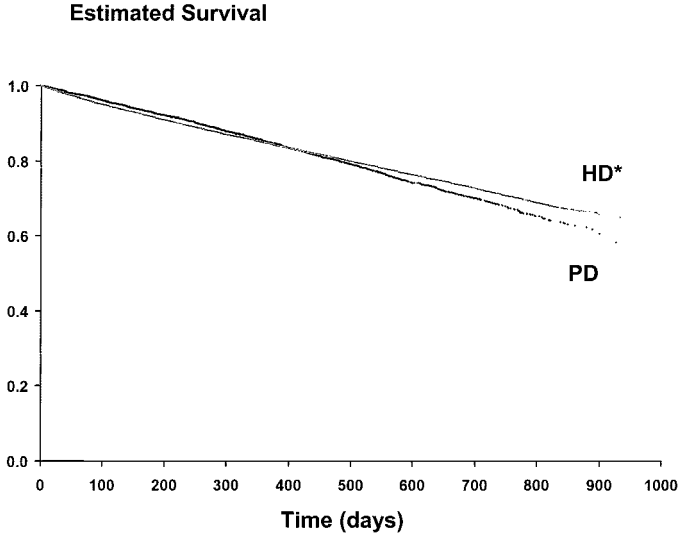

Figure 2. Adjusted Cox survival curves for new ESRD patients without coronary artery disease treated with PD *versus* HD. Adjusted for age at study start, gender, race, cause of ESRD, hypertension, congestive heart failure, peripheral vascular and cerebrovascular disease, tobacco use, chronic lung disease, AIDS, neoplasm, serum albumin, body mass index, hematocrit, estimated GFR, and pre-ESRD erythropoietin use. *$P = 0.03$.

risks were observed for patients with a diagnosis of AIDS (RR = 4.91; CI, 4.37 to 5.52) and cancer (RR = 1.42; CI, 1.36 to 1.49) at the start of ESRD. An unexpected observation was the association of higher hematocrit with increased mortality risk (RR = 1.01 per one–percentage point increase), a finding that persisted despite adjustment for several other laboratory measures and comorbid conditions. In contrast, the risk of death was significantly lower for patients with higher serum albumin (RR = 0.72 per 1 g/dl higher) and greater body mass index (RR = 0.98 per 1 kg/m^2 higher) as well as for those who were prescribed erythropoietin before ESRD start (RR = 0.86; CI, 0.84 to 0.89). The relative risk of PD *versus* HD varied significantly over time. The unadjusted analysis found a lower risk of death for PD-treated compared with HD-treated patients up to 12 mo follow-up, an equalization of risk at between 12 to 18 mo and significantly higher risk of death during 18 to 24 mo (RR = 1.11; CI 1.01 to 1.21). With adjustment, however, the benefit of PD over HD was observed only in the first 6 mo of dialysis, after which PD-treated patients experienced significantly higher mortality risk compared with their HD counterparts (RR = 1.15, 1.28, and 1.37 at each 6-mo interval, respectively; $P < 0.001$).

Mortality Risks of PD and HD in Patients with and without CAD: Intention-to-Treat

The finding of significant interactions between treatment modality, CAD, and survival as well as treatment modality, diabetes, and survival ($P < 0.001$ for each) permitted us to investigate these relationships further in a series of time-dependent Cox regression models stratified by diabetes and CAD. The unadjusted and adjusted RR estimates are presented in Table 5.

Among *diabetic patients with CAD*, the unadjusted mortality risk of PD *versus* HD varied over time and was significantly higher for PD patients between 6 and 24 mo of follow-up. With adjustment for differences in demographic factors, measures of nutrition, and cardiovascular conditions between PD and HD, an even stronger relationship was evident with higher risk for PD. A similar pattern in risk was observed among *diabetic patients without CAD.* Patients treated with PD had significantly higher mortality risks compared with HD between 6 and 24 mo of follow-up. The higher mortality risks of PD over HD in diabetic patients with CAD, however, were not significantly different from those in the non-CAD group (P for interaction ≥ 0.1).

Among nondiabetic patients, the modality × CAD interaction with mortality was highly significant ($P < 0.0001$), indicating that the impact of dialysis treatment on survival was different in patients with and without CAD. In the stratified analysis, patients with CAD treated with PD had significantly higher adjusted mortality risk compared with those who received HD between 6 and 30 mo of follow-up (RR = 1.28, 1.19, 1.62, and 1.40 at each successive 6-mo intervals, respectively). Similarly, the hazard ratios of PD *versus* HD in nondiabetic patients without clinical CAD also varied over time; in contrast, PD-treated patients experienced a lower mortality risk during the first 6 mo, similar risk between 6 and 12 mo, and significantly higher risk between 12 and 24 mo compared with HD-treated patients.

Table 4. Predictors of all-cause Mortality in new ESRD patients in the United States (n = 107,922)

Patient Characteristics	Unadjusted RR[a]	95% CI	Adjusted RR[a]	95% CI
Demographics				
age of onset of ESRD (yr)	1.04	1.035 to 1.037[h]	1.03	1.030 to 1.032[h]
White race (non-White)	1.53	1.49 to 1.57[h]	1.25	1.22 to 1.29[h]
male gender (female)	1.02	0.99 to 1.04	0.99	0.97 to 1.02
diabetic ESRD (all other causes)	1.10	1.08 to 1.13[h]	1.08	1.05 to 1.11[h]
Laboratory values				
serum albumin (per 1 g/dl)	0.75	0.73 to 0.76[h]	0.72	0.71 to 0.73[h]
hematocrit (per 1%)	1.02	1.015 to 1.020[h]	1.01	1.010 to 1.014[h]
GFR (MDRD) (per ml/min)[b]	1.08	1.07 to 1.08[h]	1.05	1.046 to 1.055[h]
Comorbidity (yes or suspected *versus* no)				
coronary artery disease[c]	1.68	1.64 to 1.73[h]	1.11	1.08 to 1.14[h]
cardiac arrest/dysrhythmia	1.86	1.78 to 1.93[h]	1.18	1.14 to 1.23[h]
congestive heart failure	1.72	1.68 to 1.76[h]	1.26	1.23 to 1.29[h]
cerebrovascular disease	1.58	1.53 to 1.64[h]	1.18	1.13 to 1.22[h]
peripheral vascular disease[d]	1.66	1.61 to 1.71[h]	1.18	1.14 to 1.22[h]
chronic obstructive lung disease	1.82	1.75 to 1.90[h]	1.24	1.19 to 1.29[h]
tobacco use	1.01	0.96 to 1.07	1.03	0.98 to 1.09
AIDS	2.62	2.33 to 2.95[h]	4.91	4.37 to 5.52[h]
neoplasm	1.81	1.73 to 1.90[h]	1.42	1.36 to 1.49[h]
BMI (per kg/m^2)	0.963	0.960 to 0.965[h]	0.98	0.974 to 0.978[h]
Pre-ESRD care				
erythropoietin use (yes *versus* no)	0.90	0.87 to 0.93[h]	0.86	0.84 to 0.89[h]
Dialysis modality PD (*versus* HD)[e]				
PD *versus* HD (reference)				
0 to 6 mo	0.69	0.65 to 0.73[h]	0.92	0.87 to 0.98[h]
6 to 12 mo	0.91	0.86 to 0.97[g]	1.15	1.08 to 1.23[h]
12 to 18 mo	1.06	0.99 to 1.13	1.28	1.19 to 1.38[h]
18 to 24 mo	1.11	1.01 to 1.21[f]	1.37	1.25 to 1.51[h]
0 to 24 mo	0.83	0.80 to 0.87[h]	1.11	1.07 to 1.16[h]

[a] Unadjusted and adjusted relative risks (RR) for all covariates in the study population.
[b] At first dialysis per MDRD formula (18).
[c] Includes history of coronary artery disease, myocardial infarction, coronary artery bypass surgery, angioplasty, or abnormal angiography.
[d] Includes a history of peripheral vascular disease amputation, intermittent claudication, or absent foot pulses.
[e] RR for PD *versus* HD were estimated at each successive 6-mo interval. A separate model found significant interactions between modality × coronary artery disease (CAD) ($P < 0.0001$) and modality × diabetes ($P < 0.0001$) when included in the adjusted model.
[f] $P < 0.05$, [g] $P < 0.01$, and [h] $P < 0.001$ compared with a RR of 1.00.

Mortality Risks of PD and HD in Patients with and without CAD: As-Treated Analysis

The results of the time-dependent as-treated analyses mirrored those of the intent-to-treat analysis and are presented in Table 6. *Among diabetic patients with CAD*, the adjusted mortality risk was significantly higher for PD patients who remained on this therapy during follow-up (PDo/HDo = 1.18; $P < 0.01$) and for patients who switched therapies either from PD to HD (HD_{new}/HDo = 1.68; $P < 0.001$) or from HD to PD (PD_{new}/HDo = 1.66; $P < 0.0001$) compared with those who remained on HD from ESRD start. A similar pattern was observed in *diabetic patients without CAD* who did not switch; PDo patients experienced an 11% higher mortality risk compared with HDo patients, and those who switched from PD to HD and from HD to PD had substantially higher mortality risks, by 56% and 45% respectively.

Among nondiabetic patients stratified by CAD, the results of the as-treated analysis again paralleled those of the intent-to-treat analysis. In the CAD subgroup, PDo patients had an 18% higher mortality risk compared with HDo patients during follow-up, and those who switched therapies had substantially greater risks, 43% (HD_{new}) and 58% (PD_{new}). In contrast, PDo patients in the non-CAD group had a 9% lower mortality risk compared with HDo patients following adjustment, and those who switched had significantly greater risks, 50% for HD_{new} and 24% for PD_{new}.

We performed several sensitivity analyses to test the validity of our results. First, we repeated the analyses using only that

Table 5. RR of death for PD *versus* HD among incident ESRD patients with and without preexisting coronary artery disease: intent-to-treat analysis

	Coronary Artery Disease *RR (PD/HD)*		No Coronary Artery Disease *RR (PD/HD)*		*P* for Interaction Term
	Unadjusted	Adjusted (CI)	Unadjusted	Adjusted (CI)	
Diabetic population					
0 to 6 mo	0.891	1.03 (0.90 to 1.18)	0.77[c]	1.04 (0.92 to 1.17)	0.8
6 to 12 mo	1.23[b]	1.37 (1.18 to 1.58)[c]	1.05	1.32 (1.16 to 1.49)[c]	0.5
12 to 18 mo	1.42[c]	1.57 (1.34 to 1.85)[c]	1.14[a]	1.35 (1.17 to 1.54)[c]	0.2
18 to 24 mo	1.27[a]	1.39 (1.11 to 1.75)[b]	1.11	1.31 (1.09 to 1.57)[b]	0.4
0 to 24 mo	1.07	1.23 (1.12 to 1.34)[c]	0.92[a]	1.17 (1.08 to 1.26)[c]	0.09
Nondiabetic population					
0 to 6 mo	0.85[a]	1.05 (0.91 to 1.20)	0.55[c]	0.83 (0.75 to 0.91)[c]	<0.001
6 to 12 mo	1.10	1.28 (1.10 to 1.49)[b]	0.71[c]	1.01 (0.90 to 1.12)	<0.001
12 to 18 mo	1.03	1.19 (0.98 to 1.44)	0.95	1.25 (1.11 to 1.41)[b]	0.8
18 to 24 mo	1.48[c]	1.62 (1.30 to 2.02)[c]	1.00	1.30 (1.12 to 1.50)[c]	<0.01
0 to 24 mo	1.01	1.20 (1.10 to 1.32)[c]	0.69[c]	0.99 (0.93 to 1.05)	<0.0001

[a] $P < 0.05$, [b] $P < 0.01$, and [c] $P < 0.001$ compared with RR of 1.00.

subgroup of patients who had a documented MI from medical record review. This was done to improve the specificity of our measure of CAD. The repeated analyses in both the MI and non-MI groups yielded results of similar magnitude and strength as in the original cohort. Second, concern has been expressed that the low sensitivity of the CMS form for certain comorbid conditions may lead to differential underreporting of these in PD and HD patients and may therefore bias survival analyses if they are used for adjustment. To overcome this concern, we repeated the regression analyses, including only those measures of comorbidity that could be recorded with accuracy, namely serum albumin (an index of cumulative comorbidity, inflammation, and perhaps nutrition), hematocrit, and BMI. The results of these analyses were similar to the original findings. Finally, we repeated our analyses with and without censoring at renal transplantation, which again yielded results similar to the original analysis.

Discussion

The question of which dialysis modality should be recommended to ESRD patients with a history of CAD is encountered frequently in clinical practice, as new patients at ESRD onset have a disproportionate burden of coronary disease (29). Given that cardiac mortality is the greatest contributor to overall mortality in this susceptible population, vigorous efforts are required to identify and correct potential factors that may exacerbate this problem. In this historical prospective study, we explored the hypothesis that PD might be the better choice for new ESRD patients with CAD, given its positive effect on hemodynamic stability, electrolyte balance, and BP control.

Contrary to this hypothesis, our study of almost 110,000 new ESRD patients showed that those with CAD had significantly poorer survival when placed on PD compared with HD over 2 yr of follow-up. Both diabetic patients and nondiabetic patients with CAD experienced substantially higher mortality on PD compared with HD. The benefit of HD over PD was not explained by differences between these two modalities in nutritional indices, anemia, or malignancy. Furthermore, the benefit of HD over PD was not accounted for by differences in preexisting vascular disease that may have precluded access for HD or level of renal function at the start of ESRD. These findings suggest that the utilization of PD in patient subgroups with documented CAD may adversely affect patient survival.

For *diabetic patients*, assignment to PD was associated with a greater risk of death in both the CAD and the non-CAD

Table 6. RR of death for PD *versus* HD among incident ESRD patients with and without preexisting coronary artery disease: as-treated analysis[a]

	Coronary Artery Disease Relative Risk		No Coronary Artery Disease Relative Risk	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Diabetic population				
HDo (ref)[a]	1.00	1.00	1.00	1.00
PDo[a]	1.02	1.18[e]	0.86[f]	1.11[d]
PD ▶ HD_{new}[b]	1.49[f]	1.68[f]	1.24[e]	1.56[f]
HD ▶ PD_{new}[c]	1.50[f]	1.66[f]	1.24[e]	1.45[f]
Nondiabetic population				
HDo (ref)[a]	1.00	1.00	1.00	1.00
PDo[a]	0.98	1.18[e]	0.63[f]	0.91[d]
PD ▶ HD_{new}[b]	1.24[d]	1.43[f]	1.14[d]	1.50[f]
HD ▶ PD_{new}[c]	1.39[f]	1.58[f]	1.02	1.24[f]

[a] The as-treated analyses compared the mortality risks of patients who switched from one modality to another during the follow-up with those remaining on PD (PDo) or HD (HDo) since ESRD start.
[b] (HD_{new}) = patients who switched from PD to HD.
[c] (PD_{new}) ± patients who switched from HD to PD.
[d] $P < 0.05$, [e] $P < 0.01$, [f] $P < 0.001$ compared with RR of 1.00. Model adjusted for all covariates listed in Table 2.

groups. The increased risk was evident as early as 6 mo after start of study (*i.e.*, 9 mo after onset of ESRD) and persisted throughout the 24 mo of follow-up. Although the magnitude of risk was greater for PD-treated patients in the CAD group (RR = 1.23; $P < 0.001$), it was not statistically different from that of PD-treated patients in the non-CAD group (RR = 1.17; $P < 0.001$). It is conceivable that our measure of CAD had limited specificity; therefore, a proportion of diabetic patients were mislabeled as not having CAD when in fact CAD was present. A recent paper by Longenecker *et al.* (30) argues against this. They found that the CMS 2728 form correctly classified patients CAD status with a 98% specificity. Furthermore, when we repeated the analyses in a subset of patients with a recorded history of MI, similar results were obtained. Nevertheless, we speculate that the clinical definition of CAD used for these analyses may have misclassified diabetic patients due to the silent nature of their coronary disease as well as their propensity to microvascular ischemia. Misclassification bias usually reduces the observed RR toward the null, (*i.e.*, toward RR = 1.0). This would suggest that the true RR might be larger than described here.

Among new ESRD *patients without diabetes*, the impact of treatment modality on survival differed significantly between CAD and non-CAD groups. For each group, we observed that patients assigned to HD had on average a greater number of comorbidities as well as lower hematocrit and serum albumin levels than those assigned to PD, suggesting a selection bias favoring lower mortality in the PD group. Despite these differences, both the intent-to-treat and as-treated analyses demonstrated higher mortality in PD (RR = 1.20 [$P < 0.001$] and RR = 1.18 [$P < 0.01$], respectively) compared with HD-treated patients with clinical CAD. In contrast, *nondiabetics patients without CAD* experienced similar survival on HD or PD. In fact, when one considered patients who did not switch therapies during follow-up, a small survival advantage was observed in favor of PD (PDo/HDo = 0.91; $P < 0.05$). These findings suggest that, for nondiabetics patients, caution should be exercised in recommending PD as the initial choice in those with proven CAD, whereas either modality may be recommended for those when CAD is absent.

Most published comparisons of PD and HD have considered outcomes based solely on intent-to-treat models (19,20,21). Although this approach addresses the question of optimal modality choice for patients at ESRD onset based on survival, it fails to consider changes in modality treatment over time and the outcomes of those who switch *versus* those who remain on the original assigned treatment. In this article, we report significantly greater mortality risks for both diabetic and nondiabetic patients who switch therapies during follow-up irrespective of their original modality assignment. Patients who switched from PD to HD (HD_{new}) had between a 43 to 68% higher risk of death compared with those remaining on HDo and between 3 to 5 times the risks of patients remaining on PDo, whereas those who switched from HD to PD (PD_{new}) had a correspondingly higher RR death (24 to 66%) compared with HDo patients and at least 3 times the risk of those remaining on PDo. Accordingly, increased vigilance should be given to ESRD patients who switch dialytic therapies, as they have a substantially increased risk of future mortality, independent of CAD status.

Several studies have suggested that PD confers benefit through a greater effect on BP control by continuous ultrafiltration across the peritoneal membrane, thereby preventing the large hemodynamic shifts that are seen with intermittent HD (31–33). It has been postulated that these large shifts in volume with HD may increase shear stress on vascular endothelial surfaces and facilitate plaque rupture (34,35). Clearly, such events would favor higher mortality in HD patients than PD patients. Similarly, the provision of PD also avoids the oscillations in serum electrolytes and uremic toxins of HD, which is generally thought to protect against serious electrolyte disturbances and the risk of fatal cardiac arrhythmias.

Despite the putative protective mechanisms associated with PD use, this analysis suggests worse survival among incident ESRD patients with CAD treated with PD. Although there are several mechanisms through which PD may increase mortality risk in this subgroup of patients, accelerated atherogenesis appears to be a strong possibility. Previous studies have demonstrated that certain cardiovascular conditions, including fatal stroke and left ventricular hypertrophy occur with greater frequency in patients treated with PD compared with HD (36–39). It has also been shown that patients treated with PD have higher levels of serum triglycerides, total cholesterol, LDL, and lower levels of high-density lipoproteins compared with HD-treated patients (12–14). Furthermore, comparisons of PD and HD patients have found greater increases in lipoprotein (a) levels in those treated with PD (12). Such evidence points to PD as being more proatherogenic.

Although it is postulated that BP control is more stable and less erratic in PD compared with HD-treated patients, some have found suboptimal control in over 85% of those treated with PD (40). Ultrafiltration failure and the development of high transport permeability over time may contribute to hypertension, fluid overload, and cardiomyopathy in PD-treated patients (35–39). These factors together may preferentially contribute to increased mortality rates in PD-treated patients with CAD. Additionally, higher mortality rates among new PD patients with CAD may result from inadequate small molecular solute clearance. Although measurements of clearance were not performed during the follow-up period, we speculated that if solute clearance were a distinguishing factor, mortality rates would be higher in PD-treated patients after 18 to 24 mo follow-up (*i.e.*, at a time when residual renal function was at a minimum). In support of this hypothesis, the magnitude of relative risk at the end of 2 yr was significantly greater than that after 1 yr.

There are several other unique characteristics associated with PD and HD, which may contribute either alone or in concert to observed mortality differences. Differences in levels of homocysteine, oxidative stresses, advanced glycosylation end-products, and soluble adhesion molecules between PD and HD may accelerate underlying atherogenesis and precipitate cardiovascular events (14,18,41). Finally, differences in healthcare delivery between HD-treated and PD-treated patients after

the initiation of dialysis may contribute to the greater observed mortality in PD-treated patients. On average, patients selected to PD are seen less frequently by their nephrology team compared with HD-treated patients. As a result, one may postulate that there is less attention given to modifiable cardiovascular risk factors such as hypertension and hyperlipidemia as well as a lower likelihood of identification of more life-threatening conditions such as myocardial infarction or dangerous electrolyte imbalances.

The findings reported here should be considered in the context of an observational study and its inherent limitations. One concern regarding the internal validity of this study is the presence of selection bias toward one modality over another (23). Although we adjusted for several of these differences between PD and HD, it is possible that other unidentified yet important differences between these two modalities, such as aspects of medical care, were not adjusted for in the final analyses. A second concern is the underreporting of specific comorbid conditions present in new ESRD patients from the CMS Medical Evidence form. This would raise the possibility of differential bias when comparing PD and HD patients, especially if underreporting of a condition occurs to a greater degree in one group compared with the other (30). We considered this limitation in a sensitivity analysis in which we adjusted only for objective measures of comorbidity such as serum albumin and hematocrit and found similar results. Furthermore, it is possible that our measure of CAD, which was chosen to capture all new patients with underlying CAD, lacked specificity. To improve specificity, we performed a subset analysis in which we analyzed only patients with a recorded history of a MI from the CMS data form. The findings from this subset analysis were consistent with the overall results. Finally, the limitations reported here would be largely overcome by a randomized clinical trial; however, such random assignment has not been feasible in ESRD populations of sufficient size.

We conclude from this large population-based study that the mortality risk for new ESRD patients with CAD differs with respect to treatment modality. Both diabetic and nondiabetic patients with CAD treated with PD had significantly higher mortality risk compared with HD patients following several levels of adjustment. The mechanism through which PD may contribute to this increased mortality risk in this subgroup is unclear, but greater levels of oxidant stress, advanced glycosylation end-products, and poor BP control may contribute to accelerated atherosclerosis and increased cardiovascular mortality. In contrast, nondiabetic patients without CAD had similar survival on PD or HD, suggesting that either modality may be recommended to this subgroup of patients. As there are no clear guidelines for the use of HD over PD in new ESRD patients, this study suggests that patients with a history of CAD who have no contraindications should be considered preferentially for HD.

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