

Mortality studies comparing peritoneal dialysis and hemodialysis: What do they tell us?

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Several recent large-scale epidemiological studies comparing mortality among end-stage renal disease (ESRD) patients receiving hemodialysis (HD) versus peritoneal dialysis (PD) show conflicting results. In this paper, we undertake a critical review of these studies. Our goal is to determine if there are any consistent trends in outcomes between HD and PD within select subgroups of patients once methodological differences have been accounted for. A total of six large-scale registry studies and three prospective cohort studies conducted in the United States (US), Canada, Denmark, and the Netherlands were reviewed. Summary findings from these studies are presented for comparative purposes.

Additional summary analyses based on previously reported data on 398 940 incident US Medicare patients are included for the purpose of comparing results from this population of patients to those of the other select studies when similar methods of analysis are applied. Results are summarized in terms of the relative risk of death for PD versus HD (RR[PD:HD]). Differences in results between the nine studies can be attributed to the degree of case-mix adjustment carried out and to the use of different subgroups when comparing mortality between HD and PD. When these differences are accounted for, we found a remarkable degree of synergism in results between the registry studies and, to a lesser degree, the prospective cohort studies. PD was generally found to be associated with equal or better survival among non-diabetic patients and younger diabetic patients in all four countries. However, among older diabetic patients, results varied by country. The Canadian and Danish registries showed no difference in survival between PD and HD among older diabetics while in the US, HD was associated with better survival for diabetics aged 45 and older. All studies show a time-dependent trend in the RR of death with PD generally associated with equivalent or better survival during the first year or two of dialysis. However, results on longer-term survival varied according to study and to different subgroups within studies. Subgroup analyses in the prospective cohort studies were limited by small numbers of patients resulting in

highly varied and somewhat controversial results when compared to the larger registry-based studies. Based on our review of recent publications and additional analyses of US Medicare data, we conclude that overall patient survival is similar for PD and HD but that important differences do exist within select subgroups of patients, particularly those subgroups defined by age and the presence or absence of diabetes.

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Over the past decade, a number of publications from around the world have compared outcomes between end-stage renal disease (ESRD) patients receiving in-center hemodialysis (HD) versus those receiving home-based peritoneal dialysis (PD).^{1–19} At times, results of these studies appear to be at odds with one another sending mixed and confusing messages to the nephrology community. In some cases, discrepancies in results have been shown to be attributed to methodological differences such as the use of prevalent versus incident patients,^{1,13,15} proportional versus non-proportional hazards models,^{5,6,14,15} and the degree of case-mix adjustment.^{2–6,19} In other cases, however, there appear to be very minor differences in methodology yet results appear to be quite different. The goals of this paper are to critically review both the methods and results of some of the more recent publications and, when possible, compare those results against one another and against United States (US) Medicare data when similar analytical techniques are used. Our primary purpose is to identify those segments of the ESRD population for which results are generally concordant across studies and also those segments of the ESRD population for which discordant results between studies merit further investigation.

RESULTS

US Registry Studies

We first summarize results from four recent publications based on US Medicare data.^{1–4} Each of these studies adjusted for case-mix differences in some or all of the demographic, clinical, and laboratory factors recorded on the Center for Medicare and Medicaid Services (CMS) Medical Evidence

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Form 2728. Demographic characteristics included gender, race, age, and employment status. Clinical characteristics included cause of ESRD categorized as diabetes mellitus (DM) versus all other causes (non-DM), co-morbidity as measured by the presence or absence of congestive heart failure (CHF), cardiac arrest/dysrhythmia, ischemic heart disease/MI (or coronary artery disease, CAD), cerebrovascular disease, peripheral vascular disease, COPD, current smoking status, cancer, DM (secondary to primary cause of ESRD), and inability to ambulate or transfer. Included under clinical characteristics are baseline glomerular filtration rate and body mass index. Laboratory values measured were serum albumin and either hematocrit^{2,3} or hemoglobin.⁴ All studies used proportional and non-proportional hazards regression to estimate time-independent (or average) and time-dependent relative risks (RRs) together with 95% confidence intervals (CI). Two of the studies used an interval Poisson model^{1,4} to estimate time-dependent RRs while the other two used a Cox model;¹⁻³ both types of models have been shown to yield essentially equivalent results.²⁰ Likewise, all four studies used the USRDS 90-day rule for inclusion of incident-based patients, meaning that patients must have survived the first 90 days on dialysis to be eligible for analysis.

The first study we consider is that by Collins *et al.*¹ in which 117 158 incident US Medicare patients (HD = 99 048 (85%); PD = 18 110 (15%)) from 1994 to 1996 were followed through 30 June 1997. This study was, to the best of our knowledge, the first US registry-based study to compare PD and HD outcomes on the basis of a large national cohort of incident patients. At the time of this study, co-morbidity and laboratory values were not yet available through Medical Evidence Form 2728. Consequently, case-mix adjustments were confined to demographic (age, race, gender) and limited clinical characteristics (DM versus non-DM). The results of an as-treated Cox regression analysis, in which patients were censored 60 days after a change in modality, showed that except for female DM patients over the age of 55, PD was associated with an equal or lower risk of death compared to HD (Table 1). Indeed, the strengths of this study lie in its use of a national cohort of incident-only patients, the use of interval Poisson regression to estimate time-dependent RRs, and the performance of subgroup analyses with patients stratified according to DM, gender, and age. By using incident-only patients in combination with estimation of time-dependent RRs, the authors were able to demonstrate some of the significant flaws associated with prior prevalence-based analyses.^{13,15} Moreover, through subgroup analysis, this study confirmed the presence of age and DM as significant modifiers of treatment effect in that the relative risk of death for PD relative to HD (RR[PD:HD]) was shown to vary with both age and DM as in previous studies.^{10,11,13,15-18} A major weakness of the Collins study was its lack of case-mix adjustment for known risk factors.

The next two studies we consider are those by Ganesh *et al.*² and Stack *et al.*³ As both studies use the same population of patients and the same analytical methods, we

review these studies together. Both studies examined the impact of treatment modality on 2-year survival among a national cohort of 107 922 incident US Medicare patients (HD = 93 900 (87%); PD = 14 022 (13%)) who began dialysis between 1 May 1995 and 31 July 1997. Utilizing information taken from the CMS Medical Evidence Form 2728, each study compared survival between PD and HD adjusting for all of the demographic, clinical, and laboratory values identified above. As shown in both papers, PD patients in the US were generally younger and healthier (e.g., less overall co-morbidity, higher serum albumin, higher hematocrit) than their HD counterparts making it crucial that adjustments be made for baseline differences in both demographic and clinical characteristics. Using Cox regression, an intent-to-treat (ITT) comparison of survival found PD to be associated with an 11% higher risk of death (RR(PD:HD) = 1.11; 95% CI 1.07-1.16). Both studies also report results from subgroup analyses in which patients were stratified according to cause of ESRD (DM versus non-DM) and to either CAD² or CHF.³ The average RRs and associated 95% CI from these subgroup analyses are summarized in Table 2. Both studies also reported results of as-treated analyses that were qualitatively similar to the ITT analyses except for those non-DM patients who remained on PD and who did not have the given co-morbid condition. In this case, PD was associated with a significantly lower risk of death compared to HD (no CAD: RR = 0.91, $P < 0.05$; no CHF: RR = 0.90, $P < 0.01$).

These two studies share many of the same strengths as noted above for the study by Collins *et al.*¹ In addition, they improve on the Collins study by incorporating case-mix adjustments for differences in various clinical and laboratory characteristics. Furthermore, both studies identify co-morbidity as measured by the presence of either CAD or CHF as a factor that significantly modifies the effect of treatment modality on patient outcomes. However, a key weakness in both the Ganesh *et al.* and Stack *et al.* studies is that no allowance was made for an effect modification due to age (i.e., an age by modality interaction); something that was identified in a number of prior studies including the study by Collins *et al.*^{1,5,10,11,13,15} For example, prior US-based studies have shown that older DM patients tend to have better outcomes on HD while younger DM patients tend to have

Table 1 | Average RRs and associated 95% CI from Collins *et al.*¹

Patient group	As-treated RRs (PD:HD)	
	Non-DM	DM
Male, <55 year	0.72 (0.67-0.77)*	0.86 (0.81-0.92)*
Male, ≥55 year	0.87 (0.83-0.92)*	1.03 (0.96-1.10) ^{NS,a}
Female, <55 years	0.61 (0.59-0.66)*	0.88 (0.82-0.94)*
Female, ≥55 years	0.87 (0.84-0.91)*	1.21 (1.17-1.24)*

CI, confidence interval; DM, diabetes mellitus; HD, hemodialysis; PD, peritoneal dialysis; RR, relative risk.

* $P < 0.05$, NS=not significant ($P > 0.05$).

^aCI was estimated based on Figure 8 of Collins *et al.*¹

Table 2 | Average RRs and associated 95% CI from Ganesh et al.² and Stack et al.³

Study	Patient group	ITT RRs (PD:HD)	
		Non-DM	DM
Ganesh et al. ²	No CAD	0.99 (0.93–1.05) ^{NS}	1.17 (1.08–1.26)**
	CAD	1.20 (1.10–1.32)**	1.23 (1.12–1.34)**
Stack et al. ³	No CHF	0.97 (0.91–1.04) ^{NS}	1.11 (1.02–1.21)*
	CHF	1.24 (1.14–1.35)**	1.30 (1.20–1.41)**

CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; HD, hemodialysis; ITT, intent-to-treat; PD, peritoneal dialysis; RR, relative risk.

NS, not significant ($P > 0.05$). * $P < 0.05$; ** $P < 0.001$ compared to an RR of 1.00.

better outcomes on PD.^{1,10,15} Since older patients are more likely to have CAD or CHF, there may be some level of confounding between age and co-morbidity, as indeed appears to be the case based on patient characteristics of both the Ganesh et al.² and Stack et al.³ papers (Table 2). As noted by Vonesh et al.,⁴ this might lead to age-adjusted RRs among patients with CAD or CHF that are strongly influenced by RRs for older patients.

Finally, in the recent study by Vonesh et al.,⁴ an attempt was made to identify those factors that have the greatest impact on modifying the effect of treatment modality on survival. Based on outcomes data from a national cohort of 398 940 incident US Medicare patients (HD = 352 706 (88%); PD = 46 234 (12%)) who began dialysis between 1995 and 2000, Vonesh et al.⁴ identified cause of ESRD (DM versus non-DM), age, and the presence or absence of one or more co-morbid conditions as those factors that significantly modify the effect of treatment modality on patient survival. Factors used to adjust for case-mix differences at baseline in the Vonesh et al.⁴ study were the same as those identified in the Ganesh et al.² and Stack et al.³ studies except that hemoglobin was used in place of hematocrit. Another difference was that a cohort effect was included in which patients were classified according to the cohort periods 1995–1997 (same as Ganesh et al. and Stack et al.) and 1998–2000. This was carried out to adjust for possible temporal changes in medical practice patterns. Having classified patients into 12 subgroups on the basis of DM, age, and general co-morbidity, Vonesh et al.⁴ used both proportional and non-proportional hazards models to compare adjusted patient survival between PD and HD. The average RRs and associated 95% CI (with correction for multiple comparisons) are summarized in Table 3. Included are the average age-adjusted RRs obtained by pooling across the three age groups. We did this so we could compare the RRs of DM and non-DM patients with and without general co-morbidity to the DM and non-DM patients with or without CAD or CHF as reported in the Ganesh et al.² and Stack et al.³ studies (Table 2).

As the study by Vonesh et al.⁴ attempts to synthesize key results and methodologies from the previous three studies, it shares the same essential strengths as those studies. It

Table 3 | Average RRs and associated 95% CI from Vonesh et al.⁴

Patient group	Co-morbid conditions	Age	ITT RRs (PD:HD)	
			Non-DM	DM
None		18–44	0.81 (0.70–0.93)***	0.82 (0.70–0.95)**
		45–64	0.89 (0.80–0.98)**	1.09 (1.00–1.18)*
		≥65	0.89 (0.83–0.95)***	1.16 (1.08–1.26)***
		Average	0.88 (0.83–0.92)***	1.08 (1.03–1.14)***
One or more		18–44	0.84 (0.67–1.06) ^{NS}	0.91 (0.76–1.08) ^{NS}
		45–64	0.99 (0.90–1.09) ^{NS}	1.23 (1.15–1.31)***
		≥65	1.04 (0.99–1.10) ^{NS}	1.25 (1.18–1.32)***
		Average	1.02 (0.98–1.07) ^{NS}	1.22 (1.17–1.27)***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, not significant ($P > 0.05$) compared to an RR of 1.00.

CI, confidence interval; DM, diabetes mellitus; HD, hemodialysis; ITT, intent-to-treat; PD, peritoneal dialysis; RR, relative risk.

attempts to improve on the studies of Ganesh et al.² and Stack et al.³ by including age as an effect modifier (interaction) in the analysis. Justification for stratifying by age as well as DM and co-morbidity is based not only on historical precedence but also on a careful preliminary analysis of the data and on a subsequent model goodness-of-fit test.⁴ Further strengths of the Vonesh et al. study⁴ are the inclusion of more recent cohorts of patients, a longer period of follow-up (3 versus 2 years), and a sample size sufficiently large enough to provide adequate statistical power for the various subgroup analyses. Its major weakness, like the other three studies, may be its reliance on the use of administrative data and any under reporting of data (e.g., co-morbidities) commonly associated with Medical Evidence Form 2728 and other administrative data. Indeed, 45% of the patients studied by Vonesh et al.⁴ had no co-morbidity reported on their Medical Evidence Form 2728. When compared with clinical data obtained from the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study,²¹ there is evidence that data from Medical Evidence Form 2728 under reports the level of co-morbidity, which should be taken into account when evaluating the strengths and weaknesses of registry studies.

Despite limitations of all four US registry studies, the fact that these studies share the same limitations allows us to perform a side-by-side comparison of results in the hope of determining where there is synergism and where there is not. Table 4, for example, compares the percentage of patients associated with lower (PD < HD), neutral (PD = HD), or higher (PD > HD) risks of death on PD versus HD for each of the four US registry studies. The optimistic view for PD put forth by the Collins et al. study¹ can be readily explained by its lack of adjustment for baseline differences between PD and HD in the level of co-morbidity and other clinical and laboratory characteristics. Discrepancies between the Ganesh et al.² and Stack et al.³ studies compared with the study by Vonesh et al.⁴ are less clear but they are probably due, in part, to the latter's inclusion of more recent cohorts of patients, its inclusion of age as a stratifying factor, and to its use of a

general level of co-morbidity (none versus 1 or more) as a stratifying factor rather than a specific co-morbid condition. With respect to the inclusion of more recent patients, Vonesh *et al.*⁴ showed that among PD patients, the risk of death declined by 6% for patients initiating dialysis during 1998–2000 versus 1995–1997 while the risk of death among HD patients remained the same over the same time span. To examine the impact of these temporal trends, we estimated an overall adjusted RR over a 3-year period of follow-up using a proportional hazards model similar to that used by Ganesh *et al.*² and Stack *et al.*³ The average RRs and 95% simultaneous CI are shown in Table 5 along with results reported by Ganesh *et al.*² and Stack *et al.*³ Whether we include or exclude patients with missing laboratory data, we obtain results for the 1995–1997 cohort of patients that are very similar to those reported by Ganesh *et al.*² and Stack *et al.*³ Specifically, for those patients who initiated dialysis during 1995–1997, PD was associated with a higher average risk of death compared to HD (RR(PD:HD) = 1.07, 95% CI 1.04–1.09, $P < 0.001$). However, for those patients who initiated dialysis during 1998–2000, there was no overall difference in mortality between PD and HD (RR(PD:HD) = 1.01, 95% CI 0.98–1.04, $P = \text{NS}$). Of course, one should be careful when interpreting these overall RRs, as they do not reflect the lower risk of death associated with PD for non-DM and younger DM and, conversely, the lower risk of death associated with HD for older DM patients.

We also examined the impact of stratifying patients by a specific co-morbid condition on the RR of death. Specifically, we replicated the analysis of Stack *et al.*³ and stratified

patients according to the presence or absence of CHF. The results (Table 6) strongly mirror the results of Stack *et al.*³ when confined to patients with co-morbidity. The difference, however, rests with those patients that have no reported co-morbidity – an important subgroup not considered by Ganesh *et al.*² and Stack *et al.*³ For example, 27% of the patients studied were classified as non-DM with no reported co-morbidity including no CHF. Within this subgroup, PD was clearly associated with better survival compared to HD or stated differently; HD was clearly associated with an increased risk of death compared to PD. These additional analyses demonstrate that there is a level of synergism between the Ganesh *et al.*,² Stack *et al.*,³ and Vonesh *et al.*⁴ studies when similar methods are applied to a similar cohort of patients. However, by including more recent patients and by further stratifying patients according to age, the study by Vonesh *et al.*⁴ results in a more neutral position with respect to differences in outcomes between PD and HD.

Non-US registry studies

We now consider evidence from non-US registry studies, specifically published results based on data from the Canadian Organ Replacement Registry⁵ and combined data from the Danish Terminal Uremia Register and the Danish National Patient Register (LPR).⁶ In the publication of the Canadian Organ Replacement Registry study of Schaubel *et al.*,⁵ comparisons of PD and HD survival were carried out on 14 483 incident Canadian patients who began dialysis between 1990 and 1995 with follow-up through 31 December 1995. Both as-treated and ITT proportional hazards models

Table 4 | Percentage of patients associated with a lower (PD < HD), neutral (PD = HD), or higher (PD > HD) risk of death on PD versus HD according to recent US registry studies

Study	Stratification (effect modifiers)	Average RR		
		PD < HD ($P < 0.05$)	PD = HD ($P = \text{NS}$)	PD > HD ($P < 0.05$)
Collins <i>et al.</i> ¹	DM, age, gender	69	14	18
Ganesh <i>et al.</i> ²	DM, CAD	—	43	57
Stack <i>et al.</i> ³	DM, CHF	—	41	59
Vonesh <i>et al.</i> ⁴	DM, age, comorbidity	27 ^a	28 ^a	45 ^a

CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HD, hemodialysis; PD, peritoneal dialysis; RR, relative risk.

^aAveraged across age groups to allow comparison to results from Ganesh *et al.* and Stack *et al.*

Table 5 | Overall adjusted RRs and associated 95% CI from Ganesh *et al.*² and Stack *et al.*³ versus stratified analysis by cohort period based on data from Vonesh *et al.*⁴

Study	Cohort years	Excludes patients with missing data ^a		Includes patients with missing data ^b	
		N	ITT RR (PD:HD)	N	ITT RR (PD:HD)
Ganesh <i>et al.</i> ² and Stack <i>et al.</i> ³	1995–1997	107 922	1.11 (1.07–1.16)*	—	—
Vonesh <i>et al.</i> ⁴	1995–1997	123 036	1.09 (1.06–1.12)*	185 704	1.07 (1.04–1.09)*
	1998–2000	150 082	1.03 (0.99–1.07) ^{NS}	213 236	1.01 (0.98–1.04) ^{NS}
	1995–2000	273 118	1.07 (1.05–1.09)*	398 940	1.04 (1.03–1.06)*

CI, confidence interval; HD, hemodialysis; ITT, intent-to treat; PD, peritoneal dialysis; RR, relative risk.

NS, not significant ($P > 0.05$); * $P < 0.001$ compared to an RR of 1.00.

^aPatients with missing laboratory values are excluded as per Ganesh *et al.*² and Stack *et al.*³

^bPatients with missing laboratory values are included with missing values categorized as not available as per Vonesh *et al.*⁴

Table 6 | Average RRs and associated 95% CI from Stack et al.³ and Vonesh et al.⁴

Study	Subgroup	Co-morbid conditions	Non-DM		DM	
			% Pts ^a	RR (PD:HD)	% Pts	RR (PD:HD)
Stack et al. ³	No CHF	—	41	0.97 (0.91–1.04) ^{NS}	26	1.11 (1.02–1.21)*
	CHF	—	15	1.24 (1.14–1.35) ^{***}	18	1.30 (1.20–1.41) ^{***}
Vonesh et al. ⁴	No CHF	None	27	0.88 (0.83–0.92) ^{***}	18	1.08 (1.03–1.14) ^{***}
	No CHF	1 or More	15	0.98 (0.92–1.04) ^{NS}	10	1.18 (1.10–1.26) ^{***}
	CHF	1 or More	13	1.08 (1.01–1.15) ^{**}	17	1.24 (1.18–1.31) ^{***}

CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; HD, hemodialysis; PD, peritoneal dialysis; RR, relative risk.

NS, not significant ($P > 0.05$); * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared to an RR of 1.00.

^aBased on the number of patients studied (Stack et al.: $N=107\ 922$; Vonesh et al.: $N=398\ 940$).

were used to compare patient survival adjusting for case-mix differences in both demographic (age, gender), and clinical (cause of ESRD, co-morbidity) characteristics. Co-morbidity was measured by the presence or absence of five cardiovascular conditions (angina, acute myocardial infarction, pulmonary edema, cerebrovascular disease and peripheral vascular disease), chronic obstructive lung disease, malignancy, and other illnesses (e.g., HIV). Subgroup analyses were carried out according to diabetic status (DM and non-DM) and age (< 65 years and ≥ 65 years).

In similar fashion, the study by Heaf et al.⁶ compared PD and HD survival among 4921 incident patients (HD = 3281 (67%); PD = 1640 (33%)) from the Danish Terminal Uremia Register who began dialysis between 1 January 1990 and 31 December 1999. Survival comparisons were adjusted for case-mix differences in demographic (age, gender) and clinical (cause of ESRD, co-morbidity) characteristics. A comprehensive attempt was made to adjust for baseline differences in co-morbidity with 18 co-morbid conditions based on WHO ICD discharge data incorporated in the analyses. As with the Canadian Organ Replacement Registry study,⁵ both as-treated and ITT analyses were carried out using both proportional and non-proportional hazards models. Likewise, subgroup analyses were carried out stratifying patients according to diabetic status (DM and non-DM) and age (< 55 years, ≥ 55 years).

Results from both as-treated and ITT analyses from these two non-US registry studies^{5,6} are summarized in Table 7. For comparison purposes, we included results from the study of Vonesh et al.⁴ obtained by pooling across the levels of co-morbidity (from Table 5 of Vonesh et al.⁴) and also by computing the RR across all patients from an overall proportional hazards model. With respect to non-DM and younger DM patients, the US (Table 7), Canadian,⁵ and Danish⁶ registry studies are all in agreement with regard to PD having equivalent or better adjusted survival compared to HD (both as-treated and ITT). Discordant results, however, occur among older DM patients. In the US (Table 7) HD is associated with improved survival for DM patients over the age of 45 (both as-treated and ITT) whereas in Canada and Denmark, no such advantage is seen for HD. This may reflect the relatively smaller percentage of DM patients as the primary cause of ESRD in these two countries (Canada: 25%; Denmark: 19%) compared to the US (45%).

Prospective cohort studies

Finally, we examine results from three recent national prospective cohort studies; the Netherlands Cooperative Study on the Adequacy of Dialysis Study,⁷ the CHOICE Study,⁸ and a study of incident Canadian patients by Murphy et al.⁹ The strengths of these three studies lie with the prospective nature of the study design and in the detailed clinical and laboratory information each study was able to collect. Indeed, all three studies utilized more elaborate methods for scoring disease severity compared with the simple presence or absence index used in the registry studies. These studies are also less likely to under-report co-morbidity as demonstrated in the CHOICE study.²¹ Perhaps because of increased costs and other factors, a major weakness with all three studies is the relatively small number of patients that were enrolled. Consequently, these studies are not powered to detect meaningful differences within select subgroups of patients.

The Netherlands Cooperative Study on the Adequacy of Dialysis study followed a cohort of 1222 incident-only patients (HD = 742 (61%); PD = 480 (39%)) from January 1997 to September 2002. As with three of the four registry studies, comparison of PD and HD patient survival was carried out using both as-treated and ITT analyses with allowances for proportional and non-proportional hazards. Case-mix adjustments were carried out for demographic (age, gender), clinical (cause of ESRD, Davies co-morbidity index, CVD, subjective global assessment of nutrition, glomerular filtration rate) and laboratory (albumin, hemoglobin) characteristics. Time-dependent estimates of RRs, as summarized in Table 8, indicate no difference in overall survival between PD and HD during the first 2 years of follow-up, but after 2 years HD was associated with lower mortality rates. The results in Table 8 are not dissimilar from the Canadian and Danish registries over the first 2 years of follow-up. However, whereas the Canadian⁵ and Danish⁶ registry studies show no difference between the PD and HD adjusted mortality rates after 2 years, the Netherlands Cooperative Study on the Adequacy of Dialysis study does show PD to be associated with an increased risk of death after 2 years.

The CHOICE study enrolled 1041 incident-only patients (HD = 767 (74%); PD = 274 (26%)) from 81 dialysis clinics in 19 US states.⁸ Enrollment covered the period from October

Table 7 | Average RRs and associated 95% CI from Schaubel *et al.*,⁵ Heaf *et al.*⁶ and Vonesh *et al.*⁴

Study	Patient group	RR (PD:HD)	
		As-treated	ITT
Schaubel <i>et al.</i> ⁵	All patients	0.73 (0.69–0.77)*	0.93 (0.87–0.99)*
	Non-DM, < 65 years	0.53 (0.46–0.60)*	0.84 (0.73–0.96)*
	Non-DM, ≥ 65 years	0.75 (0.65–0.86)*	0.95 (0.86–1.05) ^{NS}
	DM, < 65 years	0.76 (0.65–0.83)*	0.90 (0.82–1.10) ^{NS}
Heaf <i>et al.</i> ⁶	DM, ≥ 65 years	0.88 (0.75–1.04) ^{NS}	1.04 (0.87–1.24) ^{NS}
	All patients	0.65 (0.57–0.74)***	0.86 (0.78–0.95)**
	Non-DM, < 55 years	0.41 (0.24–0.68)***	0.83 (0.59–1.15) ^{NS}
	Non-DM, ≥ 55 years	0.65 (0.55–0.76)***	0.84 (0.74–0.95)**
Vonesh <i>et al.</i> ⁴	DM, < 55 years	0.74 (0.50–1.10) ^{NS}	0.91 (0.70–1.19) ^{NS}
	DM, ≥ 55 years	0.72 (0.53–0.99)*	1.04 (0.75–1.43) ^{NS}
	All patients	0.99 (0.97–1.01) ^{NS}	1.04 (1.03–1.06)***
	Non-DM, < 45 years	0.67 (0.58–0.78)***	0.82 (0.72–0.92)***
	Non-DM, 45–64 years	0.86 (0.80–0.93)***	0.94 (0.88–1.01) ^{NS}
	Non-DM, ≥ 65 years	0.95 (0.91–1.00)*	0.98 (0.94–1.03) ^{NS}
	DM, < 45 years	0.71 (0.62–0.82)***	0.85 (0.76–0.96)***
	DM, 45–64 years	1.12 (1.06–1.19)***	1.17 (1.11–1.23)***
DM, ≥ 65 years	1.20 (1.14–1.26)***	1.22 (1.16–1.27)***	

CI, confidence interval; DM, diabetes mellitus; HD, hemodialysis; ITT, intent-to treat; PD, peritoneal dialysis; RR, relative risk. NS, not significant ($P > 0.05$); * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared to an RR of 1.00.

Table 8 | Summary of ITT RR estimates [RR (PD:HD)] from the NECOSAD study⁷

Patient group	Months on dialysis			
	3–12	12–24	24–36	36–48
All patients	0.76 ^{NS}	0.94 ^{NS}	1.82***	2.38***
Non-DM, < 60 years	1.30 ^{NS}		1.30 ^{NS}	
Non-DM, ≥ 60 years	0.97 ^{NS}		2.44***	
DM, < 60 years	0.16***		2.43 ^{NS}	
DM, ≥ 60 years	0.78 ^{NS}		1.52 ^{NS}	

CI, confidence interval; DM, diabetes mellitus; HD, hemodialysis; ITT, intent-to treat; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; PD, peritoneal dialysis; RR, relative risk. NS, not significant ($P > 0.05$); *** $P < 0.05$.

1995 to June 1998 and follow-up for survival analysis was up to 7 years. Comparison of PD and HD survival was carried out using Cox proportional and non-proportional hazards models adjusting for case-mix differences in demographic characteristics (age, gender, race, education level, marital status, employment status, distance from clinic), clinical characteristics (cause of ESRD, Index of Coexistent Disease, CVD, body mass index, glomerular filtration rate, late referral), and a number of laboratory values (albumin, creatinine, Hgb, calcium × phosphate product, cholesterol, C-reactive protein).

Estimated RRs are summarized in Table 9, according to select subgroups of patients adjusting for differences in demographic, clinical, and laboratory characteristics. For comparative purposes, results for the same subgroup analyses are also presented based on data from the 398 980 incident US Medicare patients described by Vonesh *et al.*⁴ When an overall analysis is carried out adjusting for demographic and clinical characteristics including co-morbidity, results from the CHOICE study agree with results from the similarly conducted analysis of the US Medicare population in that

neither analysis found an overall difference in the adjusted mortality rates between PD and HD (Table 9). This may reflect that although there is some under-reporting of co-morbidity associated with Medical Evidence Form 2728, the level of under-reporting may not be that severe. In the CHOICE study, for example, 51% of PD patients had an index of coexistent disease score ≤ 1 (none to mild) versus 30% of HD patients.⁸ By comparison, in the study of US Medicare patients, 56% of PD patients had no reported co-morbidity on Medical Evidence Form 2728 versus 43% of HD patients.⁴ Interestingly, when one includes laboratory values in the overall adjustment, both sets of analyses find PD to be significantly associated with a higher risk of death (CHOICE: RR(PD:HD) = 1.61, 95% CI 1.13–2.30; US Medicare: RR(PD:HD) = 1.04, 95% CI 1.03–1.06). However, inclusion of laboratory values increases the RR by 19% in the CHOICE study versus only 3% in the US Medicare study. This may well reflect the inclusion of additional laboratory values in the CHOICE study and/or the use of an older cohort of patients that reflect the medical practice patterns of the 1995–1997 US Medicare cohort (see, eg., Table 5). Alternatively, in treating each laboratory value as a continuous covariate, the CHOICE study implicitly assumes a specific parametric form for the RR associated with each laboratory value and this may or may not affect the remaining RR estimates. In contrast, the analysis by Vonesh *et al.*⁴ is based on classifying laboratory values into discrete categories resulting in semi-non-parametric estimates of RRs.⁴

Of greater concern is the clear divergence in results seen in the various subgroup analyses between the CHOICE study and the US Medicare data. It is clear from Table 9 that results from the CHOICE study⁸ are completely discordant with results from similarly conducted subgroup analyses based on the US Medicare data.⁴ This may well be due to the extremely

Table 9 | Average RRs and associated 95% CI from CHOICE⁸ and US Medicare data from Vonesh et al.⁴

Patient group	CHOICE ⁸		US Medicare ⁴	
	N	RR (PD:HD)	N	RR (PD:HD)
All patients ^a	1041	1.35 (0.97–1.87) ^{NS}	398 940	1.01 (0.99–1.02) ^{NS}
All patients ^b	1041	1.61 (1.13–2.30)**	398 940	1.04 (1.03–1.06)**
Non-DM	480	2.78 (1.35–5.68)**	220 914	0.96 (0.93–0.99)**
DM	561	1.23 (0.79–1.94) ^{NS}	178 026	1.16 (1.13–1.20)**
< 65 years	664	1.67 (1.01–2.75)**	196 533	1.04 (0.99–1.07) ^{NS}
≥ 65 years	377	1.66 (0.93–2.97) ^{NS}	202 407	1.09 (1.05–1.12)**

CHOICE, Choices for Healthy Outcomes in Caring for ESRD; CI, confidence interval; RR, relative risk.

NS, not significant ($P > 0.05$), ** $P < 0.05$ compared to an RR of 1.00.

^aAdjusted for demographic and clinical (including co-morbidity) characteristics alone.

^bAdjusted for demographic, clinical (including co-morbidity) and laboratory characteristics.

low statistical power available for subgroup analyses in the CHOICE study compared with the US Medicare data. Alternatively, these results may reflect a more serious problem related to potential center selection bias. In the CHOICE study, 90% of patients were recruited from a single provider and only 37 of 81 centers offered both PD and HD as an option for their patients. Perhaps because of this, PD patients were over-sampled with a total of 86 (31%) of the 274 PD patients coming from a single center. This implies that there was an average of five PD patients or fewer per center of those remaining 36 centers that offered both PD and HD. It is not clear how this compares with the national average, but it may well explain the discrepancies in the subgroup analyses between the CHOICE study and the US Medicare population.

Finally, the Canadian cohort study of Murphy *et al.*⁹ enrolled 822 incident-only patients (HD = 540 (66%); PD = 282 (34%)) from 11 dialysis clinics in Canada. Enrollment covered the period from March 1993 to November 1994 and follow-up for survival was through 1 January 1998. An ITT comparison of PD and HD survival was carried out using a Cox proportional hazards model, while a Poisson regression model was used for a time-dependent as-treated analysis in which patient years at risk and outcomes are attributed to the modality patients were on. Both analyses adjust for case-mix differences in demographic characteristics (age, gender, race) and clinical characteristics (diabetes, cardiac failure, myocardial infarction, peripheral vascular disease, malignancy, a total comorbidity score that includes level of disease severity, and late referral). Using a 90-day rule analogous to that of the USRDS, no significant difference in survival between PD and HD was observed for either an ITT analysis or an as-treated analysis (ITT: RR(PD:HD) = 1.00, 95% CI 0.78–1.28; as-treated: RR(PD:HD) = 0.84, 95% CI 0.66–1.08). No subgroup analyses were performed in this study probably because the numbers of patients were too small to warrant subgroup comparisons. The results are qualitatively very similar to results from the Canadian Organ Replacement Registry registry.⁵ The lack of significance in the as-treated analysis may be attributed to a more refined adjustment for baseline comorbidity that includes the degree of severity.

DISCUSSION

In this paper, we have tried to provide a comprehensive review of nine recent studies comparing mortality outcomes between PD and HD. While we excluded a number of other important studies in this review, it was never our intention that this be a comprehensive review of all major studies. Rather, our intention was to illustrate the critical thinking necessary when reading and interpreting the numerous outcome studies comparing mortality risk for PD and HD. While there inevitably will be controversy over results, we believe that by paying careful attention to detail and applying a critical eye to differences in patient populations and methodology, one often can obtain a glimmer of truth with regard to trends in results despite appearances to the contrary.

By carefully summarizing results from nine different studies and conducting some additional comparative analyses, we believe we have identified some key results that are well established. These include: (1) compared to HD, PD is associated with equivalent or better survival among non-DM patients and younger DM patients in the US, Canada, and Denmark; (2) the RR of death for PD versus HD varies with time on therapy; PD has an equal or lower mortality rate during the first 1–2 years and thereafter results vary by subgroup; (3) in the US, HD is associated with better survival among DM patients over age 45 whereas in Canada and Denmark, no such difference is observed; (4) the RR of death does vary according to the type of analysis, as-treated versus intent-to-treat; (5) there appears to be a temporal trend of improved outcomes associated with PD in the US that exceeds that associated with HD; and (6) DM, age, and co-morbidity all significantly modify the effect of treatment modality on patient survival. These last two points deserve further clarification.

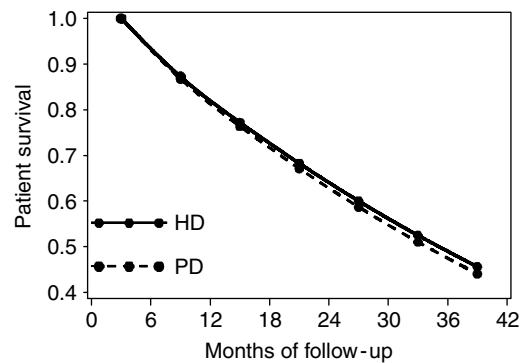
As reported in Chapter 6 of the 2005 USRDS Annual Data Report,²² there was a 7% relative improvement in adjusted 5-year survival for US Medicare patients who initiated HD between 1994 and 1998 compared to those who began dialysis between 1989 and 1993. In contrast, there was a 14% relative improvement in adjusted 5-year survival for patients on PD over the same time frame. Our analyses comparing adjusted overall RRs for the two cohort periods 1995–1997

and 1998–2000 lend further support to this trend. With different temporal trends in survival between the two modalities, it is important that we refer to the most recent data available when advising today's patients about the survival advantages/disadvantages associated with these two modalities.

Finally, three factors, DM, age, and co-morbidity, have repeatedly been found to modify the effect of treatment modality on patient outcomes. Future studies need to account for such effect modifiers if one is to get a more accurate representation of the relative merits and risks associated with both PD and HD. Large-scale registries provide sufficient statistical power to enable one to investigate such interactions using subgroup analyses. While there is still substantial merit in investigating the effects of modality on patient outcomes in single-center or multicenter prospective studies, one should be aware that such studies might well lack the kind of statistical power needed to detect important differences in outcomes between the two therapies, particularly within key subgroups of patients. Indeed, subgroup comparisons that are statistically underpowered may yield results that are inconsistent with and even contrary to evidence from much larger studies. This appears to be the case when one compares results from the registries to results from the Netherlands Cooperative Study on the Adequacy of Dialysis and CHOICE studies. On the other hand, large registry-based studies, while offering adequate statistical power for subgroup analyses, may be overpowered for overall differences between modalities. To illustrate, the overall RR of death for PD versus HD was estimated to be 1.04 (95% CI: 1.03–1.06) for US Medicare patients initiating dialysis between 1995 and 2000, a statistically significant difference ($P < 0.001$) that is powered by the nearly 400 000 patients studied. Although statistically different from 1.00, this average RR of 1.04 translates into an adjusted 3-year survival difference of 45.6% for HD versus 44.0% for PD and a difference in adjusted median life expectancy of just over 1 month (Figure 1). Although estimates of an overall adjusted RR of death suggest that patients on PD and HD have similar overall survival, a better representation of the RRs associated with PD and HD is achieved through subgroup analyses. By examining differences in adjusted survival curves for various subgroups (e.g., Vonesh *et al.*⁴), physicians and patients alike will be better informed with regard to choosing a modality appropriate for the patient.

MATERIALS AND METHODS

In this paper, we examine results from nine recently published studies comparing mortality outcomes between HD and PD.^{1–9} These studies are divided into three categories: (1) US registry studies;^{1–4} (2) Non-US registry studies;^{5,6} and (3) prospective cohort studies.^{7–9} We chose these studies because they appear to be quite discordant from one another and hence somewhat controversial. Within each study category, we briefly summarize the results of the individual studies including a brief description of their strengths and weaknesses. A summary of how the two modalities, PD and HD,



Adjusted median life expectancy:

HD: 35.1 months

PD: 33.8 months

Figure 1 | Population-averaged survival curves comparing adjusted PD and HD survival based on an overall proportional hazards regression model for US Medicare patients (1995–2000). Adjusted median life expectancy: HD: 35.1 months; PD: 33.8 months.

compare across studies is also presented. In an attempt to identify synergism between studies, we compare the results of various subgroup analyses reported in the individual studies against results from similarly defined subgroups using data from the largest of the US registry studies.⁴ This data set, comprised of 398 940 incident US Medicare patients, was chosen as a reference point because it provides adequate statistical power for performing various subgroup analyses, an element many of the other studies may be lacking. When appropriate, an estimate of the average RR for a select subgroup (e.g., DM patients over the age of 65) was achieved by taking a weighted geometric average of the RRs defined by the 12 subgroups reported in Vonesh *et al.*⁴ using a variance-weighting strategy.²³ In some cases, a re-analysis of the 398 940 incident US Medicare patients was carried out so that a more direct comparison could be made to results from other studies. A detailed description of the study populations and methods used for each study can be found in the corresponding references.

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REFERENCES

- Collins AJ, Hao W, Xia H *et al.* Mortality risks of peritoneal dialysis and hemodialysis. *Am J Kidney Dis* 1999; **34**: 1065–1074.
- Ganesh SK, Hulbert-Shearon T, Port FK *et al.* Mortality differences by dialysis modality among Incident ESRD patients with and without coronary artery disease. *J Am Soc Nephrol* 2003; **14**: 415–424.
- Stack AG, Molony DA, Rahman NS *et al.* Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int* 2003; **64**: 1071–1079.
- Vonesh EF, Snyder JJ, Foley RN, Collins AJ. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. *Kidney Int* 2004; **66**: 2389–2401.
- Schaubel DE, Morrison HI, Fenton SS. Comparing mortality rates on CAPD/CCPD and hemodialysis. The Canadian experience: fact or fiction? *Perit Dial Int* 1998; **18**: 478–484.
- Heaf JG, Lokkegaard H, Madsen M. Initial survival advantage of peritoneal dialysis relative to haemodialysis. *Nephrol Dial Transplant* 2002; **17**: 112–117.
- Termorshuizen F, Korevaar JC, Dekker FW *et al.* 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. *J Am Soc Nephrol* 2003; **14**: 2851–2860.
8. Jaar BG, Coresh J, Plantinga LC et al. Comparing the risk of death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med* 2005; **143**: 174–183.
 9. Murphy SW, Foley RN, Barrett BJ et al. Comparative mortality of hemodialysis and peritoneal dialysis in Canada. *Kidney Int* 2000; **57**: 1720–1726.
 10. 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* 1992; **3**: 1147–1155.
 11. Held PJ, Port FK, Turenne MN et al. Continuous ambulatory peritoneal dialysis and hemodialysis: comparison of patient mortality with adjustment for co-morbid conditions. *Kidney Int* 1994; **45**: 1163–1169.
 12. Foley RN, Parfrey PS, Harnett JD et al. Mode of dialysis therapy and mortality in end-stage renal disease. *J Am Soc Nephrol* 1998; **9**: 267–276.
 13. Bloembergen WE, Port FK, Mauger EA, Wolfe RA. A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 1995; **6**: 177–183.
 14. Fenton SS, Schaubel DE, Desmeules M et al. Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. *Am J Kidney Dis* 1997; **30**: 334–342.
 15. 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* 1999; **10**: 354–365.
 16. Serkes KD, Blagg CR, Nolph KD et al. Comparison of patient and technique survival in continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis: a multicenter study. *Perit Dial Int* 1990; **10**: 15–19.
 17. Maiorca R, Vonesh E, Cancarini GC et al. A six-year comparison of patient and technique survivals in CAPD and HD. *Kidney Int* 1988; **34**: 518–524.
 18. Maiorca R, Vonesh EF, Cavalli P et al. A multicenter, selection-adjusted comparison of patient and technique survivals on CAPD and hemodialysis. *Perit Dial Int* 1991; **11**: 118–127.
 19. Xue JL, Everson SE, Constantini EG et al. Peritoneal and hemodialysis: II. Mortality risk associated with initial patient characteristics. *Kidney Int* 2002; **61**: 741–746.
 20. Vonesh EF, Schaubel DE, Hao W, Collins AJ. Statistical methods for comparing mortality among ESRD patients: examples of regional/international variations. *Kidney Int* 2000; **57**(Suppl 74): S19–S27.
 21. Longenecker JC, Coresh J, Klag MJ et al. Validation of comorbid conditions on the end-stage renal disease medical evidence report: the CHOICE study. *J Am Soc Nephrol* 2000; **11**: 520–529.
 22. US Renal Data System, USRDS 2005 Annual Data Report. *Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2005.
 23. Kleinbaum DG, Kupper LL, Morgenstern H (eds). *Epidemiologic Research: Principles and Quantitative Methods*. Research Methods Series, New York: Van Nostrand Reinhold, 1982.