A Comparison of Cause of Death Between Patients Treated With Hemodialysis and Peritoneal Dialysis

Wendy E. Bloembergen, Friedrich K. Port, Elizabeth A. Mauger, and Robert A. Wolfe

Source of Data and Study Population

A detailed description of the source of data and the study population can be found in our companion article (1), which compares all-cause mortality between PD and HD. For this comparison of cause-specific mortality, U.S. Renal Data System (USRDS) data on cause of death were also obtained. The Health Care Financing Administration (HCFA) requires the primary cause of death to be reported by the patient's renal physician for each death occurring in the U.S. ESRD.
population. This occurs by means of a Death Notification Form (HCFA-2746), which lists 22 cause of death categories (e.g., acute myocardial infarction, sepsis, etc.). The USRDS database includes these data as well as a "missing" cause of death category for those patients who, by means of the Social Security System and/or hospital discharge records, are known to have died but for whom no Death Notification Form was received. These 23 cause-of-death categories were collapsed into 8 categories for the purpose of this analysis: acute myocardial infarction, "other cardiac causes" (including "other cardiac" and "pericarditis" categories from original Death Notification Form), cerebrovascular disease, infection, malignancy, withdrawal from dialysis, other known cause, and unknown/missing causes (Table 1). Because revisions to the cause-of-death categories on the Death Notification Form were made in 1990, this study uses data only through 1989.

Data Analysis

The total number of patient deaths and years at risk for the three cohorts of patients prevalent at the start of years 1987, 1988, and 1989 were available in aggregated form, similar to the analysis of all-cause mortality. Cause-specific death rates (DR) were computed as the total number of deaths due to an individual cause divided by the total number of patient years at risk for the three cohorts and expressed as deaths per 100 patient years at risk. The cause of death was unknown or missing in 18% of deaths during 1987 to 1989. To ensure that a difference in DR due to a specific cause was not simply the result of a difference in the proportion of patients within a subgroup with cause of death missing/unknown, both the number of deaths (N = 7,653) and the corresponding patient years (31,901 patient years) for the missing/unknown category were excluded from the analyses.

DR for each of the cause-of-death categories were compared between PD and HD by the use of Poisson regression, which allowed adjustment for age, gender, race, cause of ESRD, and time on ESRD therapy (< 1 yr or > 1 yr). The calculated relative risks (relative death rates, RR) represent the adjusted likelihood of death due to an individual cause in PD-treated as compared with HD-treated patients. Interaction terms were then included in a regression model to determine if the RR for each cause of death varied by each of the demographic characteristics (e.g., gender, race). If an interaction was found to be significant a PD/HD RR was calculated for each subgroup (e.g., for males only). To determine if there was a significant difference in cause-specific mortality between PD and HD within each subgroup (e.g., for males only), the calculated RR was compared with an RR of 1.00 and a P value was determined. Statistical analysis were performed with the PROC LOGISTIC procedure of SAS v6.07 (Cary, NC).

The level of significance was determined and is presented. Because of the large sample size, many results fall within the realm of what is traditionally referred to as "highly statistically significant." However, in assessing the clinical relevance, the strength of the associations found (i.e., deviation of RR from 1.0) must be primarily considered.

To account for the multiple comparisons, we used the Bonferroni procedure to compute adjusted P values. Because there were seven categories of cause of death, a P value of less than 0.007 (0.05 divided by 7) was required to conclude that a significant difference existed between DR among PD- and HD-treated patients for each cause of death. Similarly, to conclude that there was a significant interaction of modality by age, gender, race, cause of ESRD, or time on dialysis, a P value less than 0.01 (0.05 divided by five interactions tested) was required for a particular cause. Because the Bonferroni correction provides a conservative statistical criterion, true differences may be missed. The data are therefore presented with the unadjusted level of confidence noted. Items that are significant with the Bonferroni correction are indicated. If an interaction was present, the PD/HD RR was calculated for each subgroup, and the RR value that deviated from 1.00 by less than 0.05 (i.e., RR = 0.95 to 1.05) was judged to be clinically not important even if P values indicated significance.

RESULTS

In this study population of prevalent dialysis patients, there were 42,372 deaths occurring over 170,700 patient at risk. Demographics of the study population have been reported in our preceding article. As is also reported in our companion article, the overall (all-cause) DR was 19% higher for PD-treated (25.3 of 100 patient years) compared with HD-treated (21.3/100 patient years) patients (RR = 1.19; P < 0.001) when adjusted for age, race, gender, diabetic versus nondiabetic ESRD, and time of dialysis. This represents a difference of four deaths per 100 patient years. Comparisons of adjusted DR (per 100 patient years) for each cause of death were therefore performed and revealed a significantly increased mortal-

<table>
<thead>
<tr>
<th>Collapsed Category</th>
<th>Includes:</th>
</tr>
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<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Other Cardiac Causes</td>
<td>Other cardiac causes</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>Cerebrovascular</td>
</tr>
<tr>
<td>Infection</td>
<td>Septicemia</td>
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<tr>
<td></td>
<td>Pulmonary infection</td>
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<tr>
<td></td>
<td>Infection, other</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Withdrawal from Dialysis</td>
<td>Withdrawal from dialysis</td>
</tr>
<tr>
<td>Other</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>Vascular access hemorrhage</td>
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<tr>
<td>Hemorrhage, other</td>
<td></td>
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<tr>
<td>Suicide</td>
<td></td>
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<tr>
<td>Hyperkalemia</td>
<td></td>
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<tr>
<td>Air embolism</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Accident, treatment related</td>
<td></td>
</tr>
<tr>
<td>Accident, not treatment related</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Unknown/Missing</td>
<td>Unknown cause</td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
</tr>
</tbody>
</table>

* DR < 0.1 per 100 patient years at risk, overall and in all subgroups.
HD/PD Cause of Death

...ability risk for PD compared with HD for each cause category except malignancy (Figure 1). Specifically, patients treated with PD have a higher risk of death due to infection (RR = 1.42; \(P < 0.001\)), acute myocardial infarction (RR = 1.31; \(P < 0.001\)), withdrawal from dialysis (RR = 1.21; \(P < 0.001\)), cerebrovascular disease (RR = 1.2; \(P = 0.002\)), "other cardiac causes" (RR = 1.08; \(P = 0.004\)), and "other causes" (RR = 1.19; \(P < 0.001\)) and a significantly lower risk of death due to malignancy (RR = 0.66; \(P = <0.001\)). Figure 1 also reveals the adjusted DR risk difference (PD – HD) for each cause of death. This is the number of excess deaths per 100 patient years for PD compared with HD for each cause of death. As seen, the greatest number of excess deaths for PD is due to infection, accounting for 1.4 (35%) of the 4 excess deaths per 100 patients years. Myocardial infarction constituted approximately 24% of the excess deaths. Cardiac causes other than acute myocardial infarction accounted for approximately 16%, and withdrawal and cerebrovascular disease each contributed approximately 8%.

Further analyses were performed to determine if these observed PD/HD rate ratios for individual causes of death varied by age, race, gender, cause of ESRD (diabetic or nondiabetic), or length of time on dialysis (< 1 yr or > 1 yr). The significance levels for all interactions tested are presented in Table 2. Many interactions were observed; however only those significant with Bonferroni correction applied \((P < 0.007)\) will be discussed:

**Acute Myocardial Infarction**

The increased risk of death due to acute myocardial infarction seen in PD-treated patients was accentuated in patients with diabetes as a cause of ESRD. The PD/HD RR was 1.51 \((P < 0.001)\) in diabetic patients and 1.20 \((P < 0.001)\) in nondiabetics (Figure 2). These RR were significantly different \((P = 0.003)\) from each other.

**"Other Cardiac Causes"**

The increased risk of death due to "other cardiac causes" seen in PD was found only in patients with diabetes as a cause of ESRD \((RR = 1.21; P < 0.001)\) and not in patients with other causes of ESRD \((RR = 1.02; P < 0.51)\) (Figure 3). This RR also varied significantly by age \((P = 0.002)\), with a crossing of the risks at age 55 (PD = HD).

**Infection**

The increased risk of death for PD-treated compared with HD treated patients as the result of infection was significantly accentuated \((P = 0.006)\) in females \((RR = 1.58; P < 0.001)\) compared with males \((RR = 1.28; P < 0.001)\) (Figure 4).

**Withdrawal**

Although the DR due to withdrawal from dialysis was higher in PD- compared with HD-treated patients, this difference was only noted in patients with diabetic nephropathy \((RR = 1.54; P < 0.001)\) and not in patients with other causes of ESRD \((RR = 1.07; P = 0.312)\) (Figure 5a). In addition, this difference was greatest in young patients and became smaller and less significant with increasing age (Figure 5b).

**Cerebrovascular Disease**

The RR of death due to cerebrovascular disease in PD and HD varied significantly with age. Although DR were higher in PD-treated patients overall, there was a crossing of risks at age 52 (PD = HD) and DR appeared to be higher in HD-treated patients below that age. However, the DR were not significantly different at any given age.

**Malignancy**

The increased risk of death for HD-treated compared with PD-treated patients as the result of malignancy did not vary significantly by age, race, gender, cause of ESRD, or time on dialysis.

**DISCUSSION**

This large national study of prevalent U.S. dialysis patients has found mortality risk to be higher for PD-compared with HD-treated patients for each cause-of-death category except malignancy. A higher degree of...
TABLE 2. P values for significant differences among PD/HD RR for categories of demographic characteristics

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Demographic Characteristics</th>
<th>Race</th>
<th>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Gender</th>
<th>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration of ESRD</th>
<th>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Age</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>0.068</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.049</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.056</td>
<td>0.253</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>0.040</td>
<td>0.069</td>
<td>0.006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.142</td>
<td>0.056</td>
<td>0.056</td>
<td>0.004&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td>0.934</td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.103</td>
<td>0.006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.343</td>
<td>0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.753</td>
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<tr>
<td>Other cardiac</td>
<td></td>
<td>0.388</td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.397</td>
<td>0.050</td>
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<td>0.004&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Withdrawal</td>
<td></td>
<td>0.920</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.027</td>
<td>0.050</td>
<td>0.004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.050</td>
<td>0.004&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cerebrovascular</td>
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<td>0.970</td>
<td>0.114</td>
<td>0.020</td>
<td>0.511</td>
<td>0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.704</td>
<td>0.400</td>
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<tr>
<td>Malignancy</td>
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<td>0.747</td>
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<td>0.593</td>
<td>0.704</td>
<td>0.040</td>
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<sup>a</sup> RR varies significantly at 0.05 level among categories of characteristic (Bonferroni correction).

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specific preexisting comorbid conditions among PD compared with HD patients may explain these results; therefore, it would be desirable to adjust for comorbidity. However, such data are not available for this study. Furthermore, results of the USRDS Case-Mix Severity Study (15) have suggested that there is no or little difference in the presence (albeit not the severity) of specific comorbid conditions that would be likely to contribute to the specific causes of death between PD- and HD-treated patients. Differential dose of dialysis, compliance, or medical care between PD- and HD-treated patients may also contribute to the differences noted in cause-specific mortality. On the other hand, the substantial technical differences between HD and PD, including obvious differences in access, process site (extracorporeal versus intracorporeal), requirement for systemic anticoagulation, membrane, weekly removal patterns, and rates of the various uremic toxins (16), may be contributing to these noted differences in cause-specific mortality in PD and HD.

Infection

Infection was found to be a major contributor to the excess deaths in PD-treated patients. Patients treated with PD were over 40% more likely to die of an infection than were patients treated with HD, and infection accounted for 35% of the excess deaths in PD patients (1.4 of 4.0 deaths per 100 patient years). This study of comparative DR confirms previous reports (7,10), which have shown the percentage of deaths due to be higher in PD- than in HD-treated patients. To our knowledge, there are no data to suggest that, at baseline (pretherapy), patients treated with PD are more likely to have or be susceptible to an infection. A number of comparative studies that documented the presence of infection at baseline found no apparent difference in PD- and HD-treated patients (9,10). It is...
advances in connection technology have been accounting of peritonitis have been reported previously (4,7,10), peritonitis patients have a high risk of infection, most commonly, of death, the excess mortality in PD patients is related greater than in HD patients, because PD patients have (P...cantly different among males compared with females (P = 0.006, also significant at the P < 0.05 level with Bonferroni correction). DR are for patients with average characteristics of the study population. *Significantly different from 1.0, by criteria outlined in Methods. CAPD, continuous ambulatory PD.
	herefore reasonable to speculate that, with this cause of death, the excess mortality in PD patients is related to the therapy itself. There is no question that PD patients have a high risk of infection, most commonly, peritonitis (17). This study suggests that this does not simply interfere with quality of life but may also implications on survival. Deaths occurring as a result of peritonitis have been reported previously (4,7,10), accounting for as many as 13% of deaths among PD patients (7).

Several technical factors may contribute to an increased risk of infection in PD-treated patients. The peritoneal access clearly contributes to infection because advances in connection technology have been shown to reduce peritonitis rates substantially (18–20). A number of studies have shown a deleterious effect of the PD fluid itself on the function of phagocytes (21–23) and/or other immunologic defense mechanisms (24–26), in part because of the low pH and lactate concentration (27,28) as well as its glucose content (29). In addition, the obligatory dialysate protein loss that occurs with PD (30) may also increase the risk of infection. In the general population, there is a well-established relationship between nutrition and immunity. Although the evidence that the nutritional status of continuous ambulatory PD patients correlates with a risk of peritonitis or systemic infection is conflicting (31,32), there is convincing evidence among HD patients that low albumin levels increase the risk of infection (33). If this relationship is also true among PD-treated patients, the risk of infection and subsequent deaths due to infection may be greater than in HD patients, because PD patients have been shown to have lower serum protein levels than HD-treated patients (2,8,16,34). As in HD patients (35,36), low albumin has been shown to be associated with greater morbidity (32,37) and mortality (38–40) in PD patients. Data from the USRDS Case-Mix Severity Study would suggest that the strength of the relationship of low serum albumin and all-cause mortality is similar among PD- and HD-treated patients (39). Last, it is conceivable that small-molecular-weight toxins, of which clearance is less in PD relative to HD, are toxic to the immune system, thus contributing to the greater risk of death due to infections.

The finding that this PD/HD risk of death due to infection is markedly and significantly greater in females than males has not been previously described. There are no obvious explanations for this finding. Our result is apparently because of both a lower infection DR among female HD patients and a higher rate among female PD patients than among male patients.

**Acute Myocardial Infarction**

Patients treated with PD were 30% more likely to die of a myocardial infarction than were those treated with HD. Approximately one of the four excess deaths per 100 patient years noted in the PD-treated patients was attributable to this cause of death. Maiorca et al. (9,10) have also shown a higher percentage of deaths due to myocardial infarction in PD-treated patients, although other studies have shown no difference (7) or a greater percentage of deaths due to cardiovascular causes among HD patients (4). These studies did not compare the subgroup of deaths due to acute myocardial infarction as a separate cause.

It has been suggested that PD is the preferred dialysis modality for patients with coronary artery disease (40–42) because it is continuous, avoids the vascular instability frequently seen with HD, avoids the cardiac effects of an arteriovenous fistula, and allows better control of left ventricular preload. However, in the USRDS Case-Mix Severity Study (15), coronary artery disease was not present in a higher fraction of incident PD- as compared with HD-treated patients although patients with more severe coronary artery disease might have been selected to PD. In terms of the traditional risk factors of coronary artery disease (age, male gender, diabetes, hypertension, hyperlipidemia, and smoking), this study adjusts for differences in age, gender and diabetes. The Case-Mix Study (15) did not find differences in baseline blood pressure or smoking history, and to our knowledge, there are no comparative data regarding differences in family history of cardiac disease between PD- and HD-treated groups.

Although selection remains a potential explanation, some investigators have suggested that treatment with PD itself may increase the risk of coronary artery disease. Previous studies have shown more atherogenic lipid profiles in PD-treated patients (8,43,44). Some have speculated that this may be a result of the excess glucose absorption or protein losses associated...
with PD (16,43). The excess relative mortality risk of PD-compared with HD-treated patients was much higher in patients with diabetes as the cause of ESRD compared with nondiabetics, which would be consistent with these proposed mechanisms.

Cardiac Causes Other Than Acute Myocardial Infarction

Although patients treated with PD were only 8% more likely to die of other cardiac causes than HD-treated patients, the high percentage of deaths due to this cause yields a relatively large number of excess deaths attributable to this cause. It accounted for 0.02 of the 4 excess deaths per 100 patient years (16%) in the PD-treated group. The excess was shown to occur only among patients with diabetic ESRD. Although a number of cardiac causes of death are included in this category, it likely consists primarily of deaths due to congestive heart failure. In a large U.S. study of incident HD patients, 41% had a diagnosis of congestive heart failure (36). Possible etiologic factors may include volume overload, chronic hypertension, anemia, arteriovenous fistula, and ischemic cardiomyopathy (45). Despite the general conception that these problems are more easily managed on PD, the USRDS Case-Mix Study (15) found no difference in the presence of congestive heart failure between incident HD and PD patients. Furthermore, this study suggests that deaths as the result of this category are more common in the PD-treated group. Perhaps compliance is worse in PD as compared with HD patients, offsetting any theoretical advantages of PD. Alternatively, if cardiac toxins are present in uremia, the findings of this study may suggest that these are of small molecular weight and receive less clearance with PD as compared with HD.

Withdrawal From Dialysis

Among diabetics only, there was a high additional risk (54%) of withdrawal from dialysis in PD-com pared with HD-treated patients, confirming the results of a study of Michigan patients by Nelson et al. (46). However, in contrast to that study, we did not observe the opposite (increased risk among HD) among nondiabetics (Figure 5). Roberts and Kjellstrand (47) found withdrawal from dialysis to be three times more common as a cause of death in home as compared with center dialysis and suggest that this may be related to the stress of performing the dialysis procedure. They advocate a realistic introduction to home therapy, better training, a greater realization of the problems inherent in this modality, and better psychiatric support as measures to decrease deaths due to this cause. On the other hand, self-care may simply imply greater self-determination. From a physical perspective, one might also speculate that the protein loss occurring in PD contributes to cachexia and malnutrition, which ultimately leads to withdrawal from dialysis.

Cerebrovascular Disease

The USRDS Case-Mix Study found that HD-treated patients were 50% more likely to have a history of cerebrovascular disease than were PD-treated patients at ESRD incidence. Despite this finding in incident patients, this study of predominantly prevalent patients has found that patients treated with PD were 20% more likely to die of cerebrovascular disease than were patients treated with HD. This is consistent with results obtained by Maiorca et al. in two studies (9,10) in which cerebrovascular disease accounted for a higher percentage of deaths in the PD- as compared with the HD-treated patients. Because of the relatively
low frequency of cerebrovascular disease deaths in general, deaths as the result of this cause accounted for only approximately 8% of the excess of deaths in PD-treated patients.

Malignancy

Patients treated with PD were 34% less likely (PD/HD RR = 0.66) to die of a malignancy than were patients with HD. Some previous studies have also shown a greater percentage of deaths due to malignancy in HD- compared with PD-treated patients (3,10) although the opposite was observed in other studies (7,9). The USRDS Case-Mix Study (15) found more neoplasms/metastases present in incident HD-compared with PD-treated patients in a univariate analysis; however when adjusted for age and diabetes, there was no statistically significant difference. Although selection and preexisting neoplasms remain a consideration, it is conceivable that aspects of the HD procedure such as the blood-dialysis membrane interaction, the exposure to synthetic graft and tubing plasticizers, products of the sterilization process, and the dialysate or the relatively smaller removal of middle molecules may cause/promote carcinogenesis (48).

The availability of this large national data set allows the detection of clinically important differences in cause-specific mortality between PD- and HD-treated patients overall or within specific subgroups. A limitation of this comparison of cause-specific mortality is that the cause of death is reported by renal physicians in a manner that has not been standardized. Despite the listing of 22 causes of death on the ESRD Death Notification Form, different physicians may use different criteria/definitions for each cause. This raises the issue of misclassification. However, study results would be compromised only if there was a selective difference in misclassification between the groups compared. Analysis of a data base of this size has substantial advantages in terms of statistical power, counterbalancing this potential limitation.

CONCLUSIONS

This study of prevalent U.S. dialysis patients has found the risk of death for each cause-of-death category except malignancy to be higher among PD- as compared with HD-treated patients, thereby expanding the understanding of the excess mortality observed in PD-treated patients. We have offered several hypotheses as to how the technical features of PD or their consequences may contribute to the observed differences in cause-specific mortality. However, differences noted in causes of death could also result from the selection of patients more likely to die of a specific cause to a particular modality. Differential dose of dialysis, compliance, or medical care may also contribute to the differences noted in causes of death between HD- and PD-treated patients. Further epide-

miologic and clinical studies are required to evaluate the potential role of these factors.

ACKNOWLEDGMENTS

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