Survival and Development of Cardiovascular Disease by Modality of Treatment in Patients with End-Stage Renal Disease

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Abstract. Patients undergoing dialysis are at high risk for cardiovascular disease (CVD). The aim of this study was to evaluate the influence of hemodialysis (HD) versus peritoneal dialysis (PD) on survival and the risk of developing de novo CVD. Of the 4191 patients with end-stage renal disease (ESRD) who started renal replacement treatment (RRT) in Lombardy between 1994 and 1997, 4064 (who were on dialysis 30 d after the start of RRT) were considered for survival analysis: 2772 were on HD (mean age 60.9 yr; 21.2% diabetic) and 1292 on PD (mean age 63.6 yr; 16% diabetic). The 3120 patients who were free of CVD at the start of RRT were included in the analysis of the risk of developing de novo CVD. HD and PD were compared by use of a Cox-regression proportional hazard model, stratified by diabetic status; the explanatory covariates were age and gender. The death rate was 13.3 per 100 patient-years (13.0 on HD and 13.9 on PD); 197 (6.3%) of the 3120 patients included in the CVD analysis developed de novo CVD (128 on HD and 69 on PD). After adjustment for age, gender, and established CVD and stratification by diabetic status, there was no significant between-treatment difference in 4-yr survival (relative risk [RR], 0.91; 95% confidence interval [CI], 0.79 to 1.06). The risk of de novo CVD did not differ significantly by treatment modality (RR, 1.06; 95% CI, 0.79 to 1.43). The risk of mortality and de novo CVD for new patients with ESRD assigned to HD or PD was similar in Lombardy in the period 1994 through 1997.

Cardiovascular disease (CVD), whether due to ischemic heart disease or to congestive heart failure, is the major cause of death in patients on renal replacement therapy (RRT) (1–3). According to two of the largest end-stage renal disease (ESRD) registries, the United States Renal Data System, and the European Registry of patients on renal replacement therapy (RRT), the estimated risk for cardiac events such as myocardial infarction is 3.5 to 50 times higher among patients on RRT than among the general population (4,5).

There are various reasons for such negative cardiovascular outcomes. Many of the well-documented risk factors for CVD in the general population (age, smoking, hypertension, diabetes, dyslipidemia, physical inactivity, etc.) are also present in patients with ESRD and have also been acting for many years before the beginning of RRT. The number of new elderly, diabetic, and hypertensive patients with ESRD is continuously increasing and is reflected in the high proportion of patients starting RRT who have established CVD.

In addition to general cardiovascular risk factors, patients with ESRD have uremia-specific risk factors that can be responsible for the onset or progression of CVD: volume overload with consequent hypertension, anemia, deranged calcium-phosphate metabolism, specific uremic toxin accumulation (advanced glycation end-products, asymmetric dimethyl arginine, and homocysteine), and chronic inflammatory processes. All of these risk factors can finally lead to left ventricular impairment via myocardial hypertrophy and/or ischemia, which may predispose to cardiac dilatation and pump dysfunction.

The modality of treatment itself—hemodialysis (HD) versus peritoneal dialysis (PD)—could also have a different effect on general and specific cardiovascular risk factors and may differentially influence the risk of developing de novo CVD. HD and PD are very different RRT modalities. Patients on PD are exposed to a high glucose intake and its possible metabolic side effects, such as obesity, hyperglycemia-diabetes or hyperlipidemia, which predispose to ischemic heart disease, and chronic overhydration with the consequent risk of long-term hypertension, which predisposes to left ventricular hypertrophy. This is consistent with the finding by Cocchi et al. (6) that a high proportion (73%) of their patients undergoing PD were hypertensive. It is worth noting that a 10-mm Hg increase in systolic BP in patients undergoing PD has been found to be associated with a relative death risk of 1.42 (7). On the other hand, patients on HD are exposed to considerable hemodynamic stresses due to intra- and interdialytic changes in cardiac filling and fluctuations in BP, acid-base balance, and serum electrolyte levels, which predispose to heart failure as well as arrhythmias. HD and PD are also different in terms of the overall clearance of traditional markers, such as urea and creatinine (lower on PD) and the rate of loss of residual renal function.
(higher on HD). Both treatment modalities play a role in triggering chronic systemic inflammatory responses, which are related to wasting, hypoalbuminemia, and atherosclerosis (8): HD because of the bio-incompatibility of the materials and dialysate impurity and PD because of its association with frequent infections and glucose-derived oxidation end products. All of these elements mean that the impact of HD versus PD on cardiovascular outcomes (ischemic heart disease or congestive heart failure) is still an open and intriguing issue. The aim of this study was to compare the influence of HD and PD on overall mortality and the risk of developing de novo CVD.

Materials and Methods

Patients and Data Collection

The data used in this analysis came from the Lombardy Dialysis and Transplant Registry, which included 4191 patients who started RRT for ESRD between January 1, 1994, and December 31, 1997, in the region’s 44 dialysis units. The Registry was begun in 1982 under the aegis of the Lombardy Regional Section of the Italian Society of Nephrology and the Regional Health Department, and the data are collected at the end of each year (100% center response rate). A detailed study concerning the 1983 to 1992 dialysis and transplantation results in Lombardy has been published elsewhere (9). The patients were classified as diabetic on the basis of the presence of diabetes at the beginning of RRT.

Of the 4191 patients, the 4064 still on dialysis 30 d after the start of RRT were included in the survival analysis; the 3120 patients who were free of CVD at the start of RRT were also included in an analysis of the risk of developing de novo CVD.

Patient Classification. The patients were classified as having CVD if they had:

- Ischemic heart disease, as defined by either of the following conditions:
  1. Coronary artery disease, as documented by coronary angiography or, even if no coronary angiography was performed, any of the following clinico-instrumental findings of coronary insufficiency: angina pectoris associated with ischemic electrocardiographic (ECG) changes, ischemic ECG changes during a stress test, or ischemic scintigraphic changes during a stress test (in the few centers where this method was available).
  2. Myocardial infarction, as documented by ECG changes and/or a pathologic increase in myocardial necrosis markers after an episode of angina pectoris or heart failure (acute myocardial infarction) or as documented by any of the following signs of previous myocardial infarction: Q-waves at ECG, akinetic areas at echocardiography, or necrotic areas at myocardial scintigraphy. The definitions of coronary artery disease and myocardial infarction were conventionally considered to be mutually exclusive.

- Congestive heart failure (and/or overhydration), as documented by any sign of a failure to pump at a rate commensurate with the requirements of metabolizing tissues. This definition included any of the following conditions: more than one episode of pulmonary edema while the patients were at their normal dry body weight in the judgement of the attending nephrologist, an echocardiographic finding of systolic dysfunction, or the finding of cardiomegaly regardless of the imaging technique (chest x-ray or echocardiography).

The definitions of CVD for each patient in the Lombardy Registry database were made by the attending nephrologist and reflect the final result of periodic global patient evaluations (including clinical and instrumental findings) rather than strict and predefined inclusion/exclusion criteria.

Statistical Analyses

The univariate descriptive survival analyses were based on the Kaplan-Meier technique, with events being defined as death for any cause or the development of de novo CVD (with or without death). The patients were classified as being on HD or PD on the basis of the treatment they were receiving 1 mo after the start of RRT, and patient survival was tracked under the assumption of that treatment modality. Patient survival was censored at the time of the first occurrence of any of the following conditions: a change in dialysis treatment modality, kidney transplantation, the recovery of renal function, or moving away from Lombardy; they were otherwise censored at the final observation date (December 31, 1997). All of the events that occurred during the first month after a change in dialysis method were related to the previous treatment.

To evaluate the risk of developing de novo CVD, only the patients without any evidence of CVD at the time of beginning RRT were selected. The development of ischemic heart disease or chronic heart failure or the occurrence of death due to cardiac causes (including those occurring within 24 h of the onset of cardiac symptoms or sudden deaths with a diagnosis of cardiac death at autopsy) were used as end points. Patients were censored for all causes of death other than those due to CVD.

Cox–proportional hazard regression models were used to compare survival (end point, death) and the risk of developing de novo CVD in the patients undergoing PD and HD. The models were adjusted for the effect of age and gender. Because previous studies have shown that hazard rates in diabetic and nondiabetic patients are not proportional (10), the models were stratified on the basis of diabetic status (11). The patients were censored as for the descriptive analysis. The proportionality of the covariates was evaluated by use of log–log plots.

All of the statistical analyses were made with the use of the SPSS version 10.0 software package (SPSS Inc., Chicago, IL). The contribution of the covariates toward explaining the dependent variable was assessed by means of a two-tailed likelihood ratio test, with \( P < 0.05 \) considered significant.

Results

Patient Characteristics

The mean age \((\pm SD)\) of the patients admitted to dialysis was 61.8 \(\pm 15.6\) yr (59.9 \(\pm 15.6\) in 1994 and 62.5 \(\pm 15.4\) in 1997). There was an excess of men (60.5%) without any significant change between 1994 and 1997. At the time of the onset of ESRD, 964 patients (23.3%) had at least one concomitant cardiac disease: 417 (9.9%) had coronary artery disease, 346 (8.3%) a history of myocardial infarction, and 370 (8.8%) chronic heart failure. During the 4-yr follow-up period, the percentage of patients beginning RRT with coronary artery disease (9.4% in 1994 and 10.2% in 1997) or documented myocardial infarction (8.6% in 1994 and 8.9% in 1997) remained relatively stable, whereas the percentage of those with chronic heart failure increased from 6.3% to 11.1%.

Of the 4191 patients considered in the study, 127 (96 on HD and 31 on PD) were not included in the analysis because they had been on dialysis <30 d by December 31, 1997; 99 started...
dialysis in December 1997 (72 on HD and 27 on PD); 18 died before the end of the 30-d period (16 on HD and 2 on PD); 2 had undergone transplantation (both previously on HD); 7 had moved away from Lombardy (5 on HD and 2 on PD), and 1 (on HD) was lost to follow-up during the first month of RRT. Consequently, 4064 patients were still on dialysis 30 d after the initiation of RRT (2772 on HD and 1292 on PD). Of the patients undergoing HD, 91.4% were on a thrice-weekly schedule (mean session duration, 230 ± 27 min), 8% on a twice-weekly schedule (mean session duration, 236 ± 34), and 0.6% underwent dialysis more than three times per week (mean session duration, 189 ± 36 min). Table 1 shows the mean age and gender of the patients and the frequencies of diabetes, coronary artery disease, myocardial infarction, and heart failure by modality of treatment. The patients on HD were significantly younger (by 2.7 yr) than those on PD, whereas the difference in the proportion of males was of borderline significance. The percentage of diabetic patients was significantly greater in the HD group (21.2% versus 16.0%; \( P < 0.0001 \)). The proportion of patients with coronary artery disease or heart failure was not statistically different between the two groups, but there was a higher percentage of patients who had suffered a previous myocardial infarction in the PD group (9.5% versus 7.6%, \( P = 0.05 \)). The mean follow-up period was 20 mo (median 17.6 mo, with 25th and 75th percentiles of, respectively, 7.6 and 29.9 mo), for a total number of patient-years of 6764.

**Patient Survival**

Nine hundred patients (22.1%) died during the follow-up period (594 on HD and 306 on PD); the death rate was 13.3 per 100 patient-years (13.0 on HD and 13.9 on PD). CVD was the main cause of mortality, accounting for about 42% of the deaths: 293 patients (32.5%) died as a result of cardiac causes (190 [21.1%] on HD and 103 [11.4%] on PD) and 85 (9.45%) due to vascular causes (61 [6.78%] on HD and 24 [2.67%] on PD). These statistics do not consider changes in treatment: 17.0% of the patients originally on PD switched to HD, and 3.1% of the patients on HD switched to PD.

After censoring at the time of the change of treatment, the cumulative survival of the patients on HD was 85.4% after 1 yr, 75.7% after 2 yr, and 67.0% after 3 yr of follow-up; the corresponding figures for the patients on PD were, respectively, 87.2%, 74.7%, and 58.2% (Figure 1). The crude mortality rate from the first to the fourth year of follow-up decreased from 14.6 to 10.8 deaths per 100 patient-years. After adjustment for age and diabetic status (reference, the cohort at the beginning of ESRD), all-cause mortality increased from 14.6 to 17.3 deaths per 100 patient-years. The pattern of cardiac mortality was similar (Figure 2): crude mortality decreased from 4.6 to 3.6 deaths per 100 patient-years, whereas adjusted mortality increased from 4.9 to 5.1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Peritoneal Dialysis</th>
<th>Hemodialysis</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>63.6 ± 15.3</td>
<td>60.9 ± 15.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (% males)</td>
<td>58.3</td>
<td>61.0</td>
<td>0.056</td>
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<tr>
<td>Diabetes (%)</td>
<td>16.0</td>
<td>21.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>10.7</td>
<td>9.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>9.5</td>
<td>7.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Chronic heart failure (%)</td>
<td>10.0</td>
<td>8.3</td>
<td>0.085</td>
</tr>
</tbody>
</table>

**Table 1.** Mean age, gender, and proportion of diabetic patients and patients with coronary artery disease, myocardial infarction, and heart failure at baseline, by modality of treatment

![Figure 1. Kaplan-Meier cumulative survival by modality of treatment.](image1.png)

![Figure 2. Crude and adjusted mortality rates due to cardiac causes by follow-up.](image2.png)
After stratification by diabetic status and considering the influence of age, gender, and established CVD, no significant difference in 4-yr survival was found between the patients undergoing HD and PD (relative risk [RR], 0.91; 95% confidence interval [CI], 0.79 to 1.06) (Table 2). This result was confirmed when the nondiabetic patients and diabetic patients were considered separately, by using HD as the reference treatment; the RR after 1 mo of treatment was 0.90 for the nondiabetic patients (95% CI, 0.76 to 1.06) and 1.00 for the diabetic patients (95% CI, 0.73 to 1.35). The proportionality of the covariates was ensured by use of the log–log plot, which did not show any significant deviation from linearity.

Of the 3120 patients without coronary artery disease, myocardial infarction, or heart failure at the time of admission to RRT (2158 on HD and 962 on PD), 197 (6.3%: 128 on HD and 69 on PD) subsequently developed one of these conditions; 20 patients developed coronary artery disease (10.1%: 13 on HD and 7 on PD), 118 patients developed myocardial infarction (59.9%: 77 on HD and 41 on PD), and 59 patients developed congestive heart failure (29.9%: 38 on HD and 69 on PD). This was fatal for 142 of them (91 on HD and 51 on PD). The rate of de novo cardiovascular events was 4.42 per 100 patient-years (4.18 for HD and 4.94 for PD). Table 3 and Figure 3 show the results of the Cox–proportional hazards model (main effect) estimate of the relative risk of developing de novo CVD. After adjustment for age and gender and stratification by diabetic status, the RR associated with PD was not significantly different from that associated with HD (RR, 1.06; 95% CI, 0.79 to 1.43). This result was confirmed when the nondiabetic and diabetic patients were considered separately by using HD as the reference treatment: the RR after 1 mo of treatment was 1.06 for the nondiabetic patients (95% CI, 0.75 to 1.51) and 1.13 for the diabetic patients (95% CI, 0.64 to 1.97).

Furthermore, the risks of developing de novo ischemic heart disease or de novo congestive heart failure were separately evaluated as a function of the dialysis modality after correcting for age and gender and stratifying by diabetic status; neither model revealed any significant relationship with the treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
<th>Relative death rate mean (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Per yr</td>
<td>1.056 (1.049–1.063)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
<td>1.026 (0.892–1.180)</td>
<td>0.717</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>No ischemic heart disease</td>
<td>1.154 (0.949–1.403)</td>
<td>0.152</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>No ischemic heart disease</td>
<td>1.364 (1.100–1.692)</td>
<td>0.005</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>Absent</td>
<td>1.726 (1.423–2.094)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>Hemodialysis</td>
<td>0.912 (0.788–1.055)</td>
<td>0.215</td>
</tr>
</tbody>
</table>

\( ^a \) CI, confidence interval.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
<th>Relative death rate Mean (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Per yr</td>
<td>1.045 (1.033–1.058)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
<td>1.003 (0.756–1.331)</td>
<td>0.982</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>Hemodialysis</td>
<td>1.062 (0.790–1.429)</td>
<td>0.688</td>
</tr>
</tbody>
</table>

Figure 3. Kaplan-Meier cumulative survival by modality of treatment (event, onset of de novo CVD) in the group of patients without cardiovascular disease when admitted to renal replacement therapy.
modality. The RR of de novo ischemic heart disease was 1.00 (95% CI, 0.61 to 1.64; \( P = 0.988 \)), and that of de novo congestive heart failure was 1.07 (95% CI, 0.66 to 1.72; \( P = 0.796 \)). The proportionality of the covariates was ensured by use of the log – log plot, which did not show any significant deviation from linearity.

**Discussion**

The relative survival rates of patients treated with HD or PD have been intensively investigated ever since PD was first introduced, but the results of the studies based on single-center, multicenter, or registry databases have been discordant. In an attempt to resolve these discrepancies, a meta-analysis has recently been performed (12) that used the data from 82 published nonregistry studies, 55 published registry studies, and 2 registry reports (ranging from 1980 to 1997), but the results were inconclusive because survival and mortality outcomes varied with the data sources and formats.

The analysis of Lombardy patients admitted to RRT between 1994 and 1997, which was adjusted for age, gender, and established CVD and stratified by diabetic status, did not reveal any significant difference in survival between PD and extracorporeal treatment. A previous Lombardy registry report indicated a significant 34% greater risk of death for patients undergoing PD (9) but referred to the outcomes of patients undergoing PD (9) but referred to the outcomes of patients undergoing treatment. A previous Lombardy registry report indicated a significant 34% greater risk of death for patients undergoing PD (9) but referred to the outcomes of patients undergoing PD (9) but referred to the outcomes of patients admitted in the period 1983 to 1992. It is interesting to note that a study of a Canadian cohort of 433 patients admitted to RRT over a similar period (1982 to 1991) also found that mortality after 2 yr of follow-up was significantly higher in the patients treated with PD (13). However, our currently presented results are in line with those of more recent comparative studies (14–16). Greater attention has been given to the adequacy of peritoneal dialysis since the publication of the preliminary results of the CANUSA and Maiorca studies (17,18), which demonstrated the effect of the dialysis dose on the survival of patients undergoing PD; and it is also worth noting that an Italian study found no difference in survival between HD and PD after adjustment for urea clearance, which thus suggests that the two modalities can have a similar outcome provided that the dialysis dose is kept at an optimal level (19). It is therefore possible that the absence of any statistical difference in survival found by us and other authors of recent studies (14–16) is not related to shorter follow-up times but to the application in everyday clinical practice of the suggestions from the CANUSA and Maiorca studies (17,18).

As in other Western countries, we found that CVD was the main cause of mortality in our Lombardy cohort, accounting for about 42% of deaths (32.5% due to cardiac causes and 9.45% due to vascular causes). We compared the risk of developing de novo CVD in HD- and PD-treated patients who showed no signs of CVD at the time they began RRT and, after adjusting for age and gender and stratifying by diabetic status, found no statistical difference between the two modalities. Given that theoretical considerations suggest that patients undergoing HD may be more prone to left ventricular dysfunction and heart failure than patients undergoing PD and that patients undergoing PD may be more prone to ischemic heart disease, we separately analyzed the risk of developing de novo congestive heart failure and the risk of developing de novo ischemic heart disease as a function of dialysis modality and once again found no difference between the patients undergoing PD and HD. At least on the basis of the average follow-up of 20 mo, it therefore seems that the modality of treatment does not lead to any difference in the risk of developing de novo CVD.

Because patients temporarily starting RRT on one dialysis modality (e.g., HD) may be switched to their planned maintenance dialysis modality soon after 1 mo of RRT (e.g., PD), we also performed the analysis by categorizing the patients as being on HD or on PD on the basis of their modality of treatment 3 and 6 mo after starting RRT. The results were the same (data not shown): mortality and the risk of developing de novo CVD (congestive heart failure or ischemic heart disease) were not different between treatment modalities.

CVD plays a critical role in the clinical history of patients with ESRD, because cardiac alterations begin early during the course of chronic renal failure and are highly prevalent when patients start RRT. Given the association between echocardiographic abnormalities and higher subsequent mortality rates in patients undergoing dialysis, it is particularly striking that only 16% of the Canadian cohort of patients starting dialysis had a normal echocardiogram (20). In the Lombardy Registry cohort of patients starting RRT between 1994 and 1997, 9.9% had preexisting coronary artery disease, 8.3% had experienced a previous myocardial infarction, and 8.8% were affected by congestive heart failure. Like the Canadian studies (21), we have previously shown that the presence of CVD at the time of beginning RRT has a negative impact on patient survival (22).

The increasing incidence of patients with ESRD is secondary to the greater acceptance of older and sicker patients, who are more subject to CVD mortality. It has been suggested that the growing incidence of patients with ESRD in Western countries is due to the longer survival of patients with other chronic diseases, particularly heart disease (23), given that these patients now have a greater probability of surviving until the onset of renal failure (the so-called competing risk) (24). However, given the overall burden of CVD in patients undergoing dialysis, it is plausible that the uremic state per se and, possibly, dialysis treatment are significant factors for the development or progression of CVD. In relation to this, a previous study showed an 8% cumulative incidence of de novo ischemic heart disease among patients undergoing PD after 1 yr, which increased to 15% at the end of the second year (25); a study of patients undergoing HD showed a 12% cumulative incidence at the end of the first year and 18% at the end of the second year (26). The influence of treatment modality (HD versus PD) on the development of de novo CVD was previously compared in the Canadian cohort of 433 patients, with no difference being found (13). We made the same comparison in 3120 patients in our regional registry cohort: the results in this large number of patients from a homogeneous geographic area strengthen the view that treatment modality does not have a predominant effect on at least the medium-term development of clinically overt CVD, although we cannot exclude the pos-
sibility that a longer follow-up may detect real differences between the two treatments over the long term.

There is a possibility that the results of observational population studies may be affected by treatment selection bias. Analysis of the characteristics of the patients beginning to RRT in Lombardy during the calendar years 1994 through 1997 showed that patients with diabetes mellitus were more likely to be administered HD, and those with a previous myocardial infarction or chronic heart failure were more likely to be administered PD. Another criterion for the selection of PD is age, because the mean age of the Lombardy Registry patients administered PD has always been greater than that of those administered HD; in the 1983 incident cohort, the difference in age was about 7 yr (9), whereas, in the current evaluation, it was only 1.6 yr. Although the analysis was adjusted for known gross confounding factors (correction for age and gender and stratification by diabetic status), there may be an imbalance in other confounding factors that are unknown or unavailable in our registry (such as serum albumin and residual renal function), and this may flaw the comparison of HD and PD outcomes.

Furthermore, we are well aware of the difficulties of objectively defining CVD in a large registry database such as ours. In particular, the definition of congestive heart failure and, consequently, its use as an outcome, may be problematic in the practical setting because it is not always possible to distinguish pulmonary edema from overhydration versus heart failure in registry reports. The definition of ischemic heart disease also has limitations due to heterogeneity, because patients with asymptomatic coronary artery disease diagnosed by a stress test were included, but not all of the cohort underwent a screening stress test. However, the effect of this subgroup was negligible, because patients with coronary artery disease were a minority in our cohort of patients affected by ischemic heart disease (of the 138 patients who developed ischemic heart disease during the follow-up, 20 were affected by coronary artery disease and 118 by myocardial infarction). Moreover, it was the practice in Lombardy during the 1994 to 1997 period to screen asymptomatic patients for coronary artery disease, by use of a stress test, only in selected cases at the request of the referring renal transplantation center. The CVD conditions of the patients were defined by their attending nephrologist in the different dialysis centers on the basis of global clinical evaluations rather than on the basis of the predefined strict inclusion/exclusion criteria that are possible only in the case of clinical trials. However, we believe that the definitions are sufficiently homogeneous insofar as the data were collected from dialysis centers located in the same geographical area, in which nephrologists share the same professional education and clinical experience. Furthermore, given that the risk of developing de novo CVD as a function of dialysis modality has previously only been investigated in a cohort of 433 patients (13), we think that the interest of the information derived from our study of 4191 patients undergoing dialysis coming from a region with 9 million inhabitants at least partially compensates for the degree of imprecision inevitable in any observational survey of a renal registry.

Ideally, a prospective randomized controlled clinical trial would be necessary to compare outcomes (such as mortality and the de novo development of CVD) in patients undergoing PD and HD while excluding the risk that the analysis may be affected by unmeasured confounding factors or any imprecision in inclusion/exclusion criteria. However, randomizing dialysis treatments (which are currently chosen in agreement with the patients, taking into account their personal and family needs) would raise a large number of ethical issues, and the lack of patient consent and ethical concerns could make treatment assignments unrepresentative and flaw the results (27). In conclusion, our observational analysis of Lombardy Registry patients admitted to RRT between 1994 and 1997 showed no difference between HD and PD in the risk of mortality or developing de novo CVD.

Appendix: Participating Researchers and Centers

D. Marchesi and T. Bertani (Bergamo); P. Faranna (Trescore Balneario); G. Alongi and M. Lorenz (Zingonia); P. Ondei and L. Rusconi (Ponte S. Pietro); M. Massazza and M. Borghi (Treviso); A. Strada and R. Maiorca (Brescia); S. Bove and F. Brandi (Brescia Umberto I); A. Testori (Desenzano); M. Bognoli and M. Uberti (Leno); R. Broccoli (Esine); F. Cossandi and S. De Marinis (Chiari); M. Fraticelli and R. Rossi (Como); B. Rivetti and F. Pechlini (Cremone); V. Oghiari and M. Milette (Crema); G. Pontoriero, L. Del Vecchio and F. Locatelli (Lecco); F. Malberti and E. Imbsciati (Lodi); P. Botti and R. Tarchini (Mantova); A. Perezo and G. Civati (Milano-Niguarda); G. C. Ambrosio and C. Ponticelli (Milano-Croff); L. Luciani and G. D’Amico (Milano-S. Carlo); S. Bertoli and G. Barbiano di Belgioioso (Milano-Sacco); D. Spotti and G. Bianchi (Milano-San Raffaele); A. Baretta and D. Brancaccio (Milano-S. Paolo); A. Edefonti and F. Sereni (Milano-ICP); M. Beccari and G. Sorgato (Milano-FBF); M. Viganò and B. Redaelli (Monza); A. Manfredi and R. Marangoni (Bollate); F. Conte and A. Sessa (Vimercate); O. Braccini and S. Sforzini (Cernusco SN); M. Sarugulia and F. Vallino (Cinisello Balbano); G. Bonforte and M. Surian (Desio); G. Renzetti and A. Colombo (Legnano); E. Orazi and C. Grassi (Melegnano); G. Pisano and C. Novi (Magenta); M. Doria and A. Frontini (S. Donato Milanese); A. Dal Canton (Pavia-S. Matteo); G. Villa and A. Salvadeo (Pavia-CI. Lavoro); M. Nai and R. Bellazzi (Vigezano); W. Bazzini and C. Barbieri (Voghera); F. Samà and L. Pedrini (Sondrio); O. Amatruda and L. Gastaldi (Varese); A. Limido and P. Cantu (Gallarate); P. Scala and C. Grossi (Tradate); and L. Brambilla Pisoni and A. Giangrande (Busto Ariszio).

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