Dialysis vintage and cardiovascular injury as factors influencing long-term survival in peritoneal dialysis and hemodialysis

Krzysztof Hoppe¹, A–D, F, Krzysztof Schwermer¹, A–C, F, Anna Olewicz-Gawlik³, B, C, E, Patrycja Klyszz², B, C, Anna Kawka², B, C, F, Ewa Baum³, B, C, F, Dorota Sikorska², B, C, Katarzyna Ścigacz³, B, D, Magdalena Roszak⁴, C, Bengt Lindholm⁵, E, F, Krzysztof Pawlaczyk¹, 5, A, C, E, F, Andrzej Oko¹, E, F

¹ Department of Nephrology, Transplantology and Internal Diseases, Poznan University of Medical Sciences, Poland
² Department of Pathophysiology, Poznan University of Medical Sciences, Poland
³ Department of Philosophy and Bioethics, Poznan University of Medical Sciences, Poland
⁴ Department of Biostatistics, Poznan University of Medical Sciences, Poland
⁵ Karolinska Institutet, Clinical Science, Intervention and Technology, Stockholm, Sweden

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Background. Cardiovascular (CV) incidents are the major cause of mortality in maintenance dialysis (MD) patients undergoing peritoneal dialysis (PD) or hemodialysis (HD). CV injury indicators may be useful to investigate the dialysis modality influence on survival.

Objectives. The aim of this study was to compare selected laboratory and echocardiographic (ECHO) markers of CV injury in terms of dialysis vintage (DV), CV-related mortality and all-cause mortality.

Material and methods. The study involved 301 patients on HD (n = 301) and PD (n = 58), who were divided into subgroups according to DV. The subjects’ medical histories included diabetes mellitus (DM), myocardial infarction (MI), stroke, CV deaths and deaths from non-CV causes. Their CV parameters were measured with ECHO for the left ventricle ejection fraction (EF), posterior wall (LWV) and interventricular septum (IVS). Serum analyses of cardiac troponin T (TnT) and N-terminal pro-brain natriuretic peptide (BNP) were also carried out.

Results. In the subgroup with a DV of 4 years, the PD and HD patients were of a similar age, and had similar mortality and morbidity rates and CV markers, except for thicker IVS in the HD patients.

Conclusions. Focusing on the data analysis based on mortality, and both laboratory and echocardiographic markers of cardiovascular injury, PD seems to be a more favorable method of dialysis. The advantage of PD was noted in subjects with a DV < 2 years. HD showed no outcome benefit over PD in longer DV.

Key words: hemodialysis, mortality, peritoneal dialysis, echocardiography, troponin T
There is a lack of objective guidelines for initiating renal replacement therapy (RRT) with peritoneal dialysis (PD) or hemodialysis (HD) in patients with end-stage renal disease (ESRD) who develop uremic complications before receiving kidney transplantation. In routine practice, the choice of which dialysis modality to initiate is often based on the physicians’ inclination, the patient’s preferences, and any contraindications to one therapy or the other. Clinical trials that randomize the dialysis modality initiated are currently lacking, since RRT qualification guidelines are based on social and ethical aspects. Exploring the outcomes in current dialysis patient populations may therefore be worthwhile. Studies of that kind could analyze the effect of dialysis over different time periods, called the “dialysis vintage”, as well as look for trends in patient survival, and could thus define mortality risk markers for different dialysis vintage periods. As a result of the highly subjective criteria for dialysis initiation, populations undergoing maintenance HD or PD are significantly heterogeneous in terms of age, gender, ESRD background and comorbidities. This means there is a need for reliable markers to objectively compare the safety of the different dialysis modalities. Recent epidemiological data confirm that cardiovascular (CV) incidents are the major contributors to the high mortality rate in the ESRD population.

Consequently, CV injury markers may be useful predictors in determining the effect of the 2 dialysis modalities on the recipient’s survival. Previous studies have provided evidence emphasizing the value of serum cardiac troponin T (cTnT) as a predictor of CV incidents and mortality. N-terminal pro-brain natriuretic peptide (NT-proBNP) has been found to be another useful prognostic marker associated with mortality in dialysis patients. The correlation between ESRD and development of CV disease (CVD) is well known. Renal failure affects both the structure and the function of the myocardium, which can be detected using echocardiography. It would be beneficial to conduct a study comparing different CV variables and observing potential CV injury in patients on HD and PD.

The aim of the current study was to compare selected markers of CV injury in terms of their impact on morbidity and mortality within 2 cohorts of Polish patients undergoing maintenance dialysis with HD and PD respectively. After separating the dialysis patients into subgroups according to dialysis vintage, the outcomes of each group were analyzed.

Material and methods

A total of 359 Polish patients undergoing chronic dialysis during the period from 2010 to 2014 were followed-up for 24 months. They comprised 301 patients on thrice-weekly in-center HD (Group H) and 58 on home PD (Group P). The exclusion criteria were a lack of written consent, RRT vintage lower than 6 weeks and age below 18 years old. Subjects with a history of dialysis modality conversion before qualification to the study were also excluded. The patients in this study provided informed written consent, and the Poznan University of Medical Sciences Ethics Committee approved the study.

The patients’ history included the ESRD background, diabetes mellitus (DM), myocardial infarction (MI) during follow-up, stroke during follow-up and end-point (death, renal transplantation, conversion to another type of dialysis or termination of dialysis). The cause of death was specified as CV (including sudden cardiac arrest, acute MI, venous thromboembolism and consequences of heart failure) or non-CV. Each of the 2 dialysis modality groups were divided into 3 subgroups depending on the dialysis vintage: a) HD and PD patients in subgroups HA and PA received dialysis for < 104 weeks (< 2 years); b) patients included in subgroups HB and PB remained on dialysis treatment with HD and PD respectively for 104–208 weeks (2–4 years); and c) subgroups HC and PC included patients whose dialysis vintage on HD and PD respectively exceeded 208 weeks (> 4 years).

A number of procedures were performed on each patient at the beginning of observation (for HD patients before the midweek dialysis session). Blood samples were obtained before dialysis to analyze CV injury markers cTnT (using the Elecsys®/cobas e® cTnT fourth-generation assay, Roche Diagnostics, Basel, Switzerland) and NT-proBNP. Transthoracic echocardiography was performed following current guidelines to assess left ventricle parameters: ejection fraction, posterior wall (LVW) and interventricular septum (IVS) thickness. The statistical analysis was carried out using STATISTICA 12.5 software (StatSoft, Tulsa, USA). All correlations were calculated using the Spearman correlation coefficient. The comparisons of the HD and PD group variables were performed using either the Mann-Whitney or the t-test, depending on normality. A survival analysis was conducted using Kaplan-Meier curves. Logistic regression was used for a multivariable analysis of markers affecting mortality.

Results

Characteristics of the HD and PD study participants

A summary of patient characteristics is shown in Table 1. The 301 HD patients studied were significantly older than the 58 PD patients (64 ± 15 vs 56 ± 17 years; p < 0.001), and they were more often men (63% vs 48%; p < 0.05). The mean dialysis vintage was longer for HD patients than for PD patients (264 ± 216 vs 135 ± 96 weeks; p < 0.001). Globally there was no significant difference in the incidence of DM, MI or stroke. The gross mortality, expressed as a percentage, was higher for HD than for PD...
patients (29.6% vs 10.3%; \( p < 0.001 \)), while CV mortality was comparable for HD and PD (Table 2). The rate of transplantation was higher in PD than HD patients (15.5% vs 7.6%; \( p < 0.05 \)). The mean concentrations of cardiac markers were substantially higher in HD than PD patients: For NT-proBNP it was 12192 ± 12873 vs 6571 ± 10203 pg/mL \( (p < 0.001) \); for cTnT it was 75.5 ± 84.4 vs 71.8 ± 99.1 ng/mL \( (p < 0.05) \). Echocardiography demonstrated that both the mean IVS \( (14.1 ± 2.8 \text{ vs } 12.2 ± 2.1 \text{ mm}; \ p < 0.001) \) and the LVW \( (13.4 ± 2.3 \text{ vs } 12.0 ± 2.3 \text{ mm}; \ p < 0.01) \) were thicker in HD than PD patients, while the 2 groups did not differ with regard to EF. Selected correlations are presented in Table 3.

The Kaplan-Meier curves illustrate that DM was a main factor shortening survival time, both in patients on HD (Fig. 1a; \( p < 0.05) \) and those on PD (Fig. 1b; \( p < 0.05) \). Age > 65 years appeared to be a negative prognostic factor only for the HD patients (Fig. 1c; \( p < 0.01 \)), not for PD patients (Fig. 1d).

There are numerous risk factors and potential predictors of dialysis recipients’ mortality and their influence is not independent. For precise assessment of each parameter’s influence in vivo, it is necessary to combine them in models. Multivariable logistic regression analysis was introduced to create models including statistically significant identify markers affecting all-cause and CV mortal-
and age > 65 years were connected with a higher risk of death (Table 4; p < 0.001). None of the models including markers of CV injury other than cTnT as variables appeared significant.

### A. Dialysis vintage < 2 years: Subgroup HA vs subgroup PA

In the study group, 13.6% of the HD patients and 48.3% of the PD patients had been on dialysis for less than 24 months (p < 0.001). As shown in Table 5, the

Table 5. Comparison of subgroups on hemodialysis (HA) and peritoneal dialysis (PA) for < 104 weeks (< 2 years)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HA</th>
<th>PA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.5 ± 18.5</td>
<td>50.9 ± 17.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Patients, n</td>
<td>41</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Males/females, n</td>
<td>26/15</td>
<td>12/16</td>
<td>0.15</td>
</tr>
<tr>
<td>Dialysis vintage, weeks</td>
<td>66.4 ± 26.6</td>
<td>57.0 ± 26.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Comorbidity and deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM, n</td>
<td>15</td>
<td>7</td>
<td>0.22</td>
</tr>
<tr>
<td>MI, n</td>
<td>8</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke, n</td>
<td>2</td>
<td>1</td>
<td>0.76</td>
</tr>
<tr>
<td>All-cause deaths, n</td>
<td>28</td>
<td>1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiovascular-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deaths, n</td>
<td>15</td>
<td>1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Tx, n</td>
<td>6</td>
<td>7</td>
<td>0.29</td>
</tr>
<tr>
<td>Predictors investigated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>13967 ± 13449</td>
<td>4464 ± 7643</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>cTnT, ng/mL</td>
<td>70.1 ± 56.0</td>
<td>405 ± 500</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>12.7 ± 6.8</td>
<td>12.1 ± 2.5</td>
<td>0.73</td>
</tr>
<tr>
<td>LVW, mm</td>
<td>13.3 ± 3.2</td>
<td>11.8 ± 2.7</td>
<td>0.37</td>
</tr>
<tr>
<td>EF, %</td>
<td>61.0 ± 9.5</td>
<td>55.3 ± 11.4</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation; BNP – N-terminal pro-brain natriuretic peptide; cTnT – cardiac troponin T; DM – diabetes mellitus; DN – diabetic nephropathy; EF – ejection fraction of left ventricle; GN – glomerulonephritis; HT – hypertension; IVS – interventricular septum; LVW – left ventricle posterior wall; MI – myocardial infarction; Tx – kidney transplantation.
HA patients were significantly older than the PA patients (65.5 ± 18.5 vs 50.9 ± 17.1 years; p < 0.01) while the gender distribution in the 2 subgroups was comparable. There was no significant difference noted in the mean dialysis vintage, the presence of DM or the incidence of stroke. A substantially higher incidence of MI (8 vs 1; p < 0.05) and higher mortality rate (28 [15 CV] vs 1; p < 0.001) were recorded in group HA in comparison to group PA. In the HA group, 6 patients received kidney transplants, and kidney function improved in 2 subjects with no further dialysis requirement. In the PA group, 7 patients underwent transplantation, while 2 converted to HD. The mean serum concentrations of CV markers were higher in the HA group compared to the PA group: For NT-proBNP they were 13967 ± 13449 vs 4464 ± 7643 pg/mL (p < 0.01), and for cTnT they were 70.07 ± 55.98 vs 40.54 ± 49.95 ng/mL (p < 0.001). The mean values of echocardiographic parameters did not differ between these 2 subgroups.

B. Dialysis vintage 2–4 years: Subgroup HB vs subgroup PB

A similar proportion of HD and PD patients had a dialysis vintage of 2–4 years. The mean age, gender distribution and dialysis vintage were similar in the HB and PB subgroups (Table 6). Additionally, the incidence of MI, stroke, DM and mortality rate did not differ significantly in the HB and PB groups. In the HB group, 10 patients received kidney transplants, and 1 patient was switched to PD. In the PB group, 1 patient underwent a transplant and 5 required the conversion to HD. No differences were observed between these 2 subgroups with regard to the mean serum values of CV markers NT-proBNP and cTnT or echocardiographic indicators IVS, LVW, EF.

C. Dialysis vintage > 4 years: Subgroup HC vs subgroup PC

Among the patients with a dialysis vintage of > 4 years, there was a higher proportion of HD than PD patients (49.5% vs 22.4%; p < 0.001). The mean age and gender distribution in the HC and PC subgroups were comparable (Table 7). The mean dialysis vintage was slightly higher in the HC subgroup than in the PC subgroup (404 ± 232 vs 286 ± 45 weeks; p = 0.06). There was no significant difference in the incidence of MI, stroke or the presence of DM. The death rate was also comparable in these 2 subgroups. Within the HC subgroup, 7 patients received kidney transplants, while 1 patient was transferred to another HD center and was lost to further follow-up. One PC patient received a transplant and 3 required conversion to HD. The mean concentrations of NT-proBNP and cTnT were comparable in subgroups HC and PC. Among the echo-
cardiographic parameters analyzed, only IVS differed significantly: It was thicker in subgroup HC (14.71 ± 2.75 vs 12.22 ± 1.56 mm; p < 0.01).

Discussion

In the current study, characteristics of HD and PD patients treated over different periods of time (dialysis vintage) were compared within each vintage group. Although the HD population studied was significantly older than the PD patients, it did not present a higher incidence of DM, MI or stroke. A natural, increasing proportion of HD patients with a longer dialysis vintage was observed, possibly due to the time-dependent limitation of the peritoneum as a dialytic membrane resulting in a need for conversion from PD to HD.16,17 Another explanation for the increasing proportion of HD patients with a longer dialysis vintage is the higher incidence of renal transplantation in PD patients.

A higher mortality rate was observed on HD as compared to PD, but this was limited to patients on dialysis for less than 2 years. There are numerous causes that could be responsible for the higher early mortality observed among HD patients. The first possible cause is the significantly lower mean age of the patients undergoing PD. As expected, age and death rate were correlated (Table 3), and the influence of age on death rate was illustrated by Kaplan-Meier curves (Fig. 1c). This result is due to this study’s aim of comparing patients in terms of dialysis vintage. PD is often more likely in younger ESRD patients because it offers them more independence as compared to HD. Another probable explanation is that the start of therapy may be related to psychosocial and economic factors associated with HD and PD: Patients who choose PD seem to be more active, have lower rate of comorbidities and benefit from having better family support.19,20

Although CV-related mortality compared to total all-cause mortality was in fact higher in PD, overall mortality rates – both CV-related and all-cause mortality – were higher in HD. Signs of non-specific CV injury, reflected by both laboratory markers (cTnT, NT-proBNP) and echocardiographic indicators (IVS, LVW) were more prominent in HD than in PD patients. Furthermore, increases in both cTnT and NT-proBNP showed a positive correlation with the mortality rate in HD patients, while in PD patients only cTnT correlated with mortality. Increases in both cTnT and NT-proBNP were, however, connected with LV wall hypertrophy in the HD population. Interestingly, the laboratory CV injury markers analyzed appeared to be predictors of overall all-cause mortality, but not specifically of CV-related mortality. These results indicate that dialysis and ESRD may induce specific CV injuries that lead to increased mortality which are not reflected in myocardial hypertrophy or in EF decrease. It can only be suggested that these 2 echocardiographic findings may illustrate a mechanism of myocardial adaptation to an increased CV burden, rather than a direct cause of poor outcomes.

The results outlined above appear to show that PD has an advantage in terms of patient outcomes. However, due to the lack of randomized trials comparing HD and PD in the ESRD population, an objective comparison of both modalities is difficult.6 As a possible alternate solution, propensity score-stratified (PS) models that serve as an equivalent of randomization have been proposed. A study by Liem et al. confronted a PS model with a multivariable-adjusted (MV) model in survival estimation.21 The same variables were included in both models. With the PS model, covariate balance between the groups was achieved. On the other hand, the features from the PS model were entered into the MV model as covariates. Eventually, the hazard ratios for mortality in both models appeared to be identical: 0.99 vs 0.97 respectively for the MV and PS models.21 In the current study, a MV logistic regression model was introduced to estimate the influence of the variables analyzed on the differences between the subgroups undergoing HD or PD in order to assess their influence on the disproportionate outcomes. A strong disadvantage of both the PS and MV models is their low utility for small sample sizes as in the current study. Furthermore, due to the low mortality rate in the PD study group, a significant logistic regression MV model could not be created for this population. In the HD population, an increase in cTnT, dialysis vintage < 104 weeks and age > 65 years were associated with increased overall and CV mortality.

Previous studies – either prospective, often performed in small groups and lacking the statistical power of large cohort analyses, or retrospective, which rely on a large number of patient samples in national or dialysis center registries – have not delivered definitive proof of one modality being superior over the other.23–28 Research based on PD and HD groups adjusted for demographic factors and comorbidities has commonly warned of increased global mortality in PD populations.22,25,26 Nevertheless, after the year 2000, improvements in dialysis methods and supportive therapies appear to have resulted in a more substantial decrease of mortality rates among PD patients compared to HD patients.7,20,27,29,31,32 Hence, in order to determine the advantages of each modality, there must be an up-to-date analysis of overall outcomes taking influential factors into account. Differences between HD and PD long-term survival have been reported to depend on the dialysis vintage. Previous studies have announced different cutoff points that are favorable for PD as an initial dialysis modality.7,24,26,30,33 The results of the current study...
showed a significantly better prognosis for both survival and the probability of renal transplantation in patients on maintenance PD for less than 24 months. A favorable outcome for HD was not observed either in the medium term or in the longest dialysis vintage group.

Most recent studies reveal a survival advantage for PD patients younger than 65 years old, non-diabetics and those with only one comorbidity.\textsuperscript{20,30,34,35} According to the current results and those of other research groups, initiating dialysis with PD seems to be more favorable in general. The exception is that a longer dialysis vintage reduces the advantage of PD.\textsuperscript{20,30,32,34,35} Nonetheless, without selecting specific patient characteristics, no survival benefit was proved for any of the HD vintage subgroups. A prospective comparison of survival among patients converted from PD – after the favorable vintage of up to 2 years – to HD would be required. A crucial variable that was not considered by this study is a patient’s quality of life on the preferred dialysis modality. Its influence on survival is immeasurable using non-randomized comparative analyses of the advantages of HD and PD.

This prospective observational study comparing the effectiveness of dialysis modalities carries several limitations. First, due to limitations arising from the ESRD population, it does not have the quality of a randomized trial. Patients who had initiated RRT in a different modality were excluded; however, patients with an unplanned switch to HD were qualified. Moreover, the analysis did not take into account comorbidities other than those mentioned, or changes in a patient’s health status over time. Another source of bias emerged from demographic differences between the populations compared. Nevertheless, the patients’ demographic and psychosocial variations play a major role in modality selection; therefore, a comparison of heterogeneous populations of ESRD patients on different dialysis modalities seems reasonable.

To evaluate the influence of demographic variables on survival, a multivariable analysis was performed; however, its value is limited by the relatively low number of patients in the PD group and – as a result – its low mortality rate. The data presented in the study do not include vascular access in HD patients or PD regimens.

A definite advantage of this study is that it represents a contemporary prospective multifactorial comparison of a fairly large Polish cohort of patients undergoing maintenance dialysis. The qualification criteria excluded patients who had converted from one dialysis modality to another, to eliminate this source of bias. Focusing on the frequency of CV-related mortality in the ESRD population, the patients on each modality were divided into subgroups according to their dialysis vintage, and as described above analyzed in terms of selected co-morbidities, CV incidents, CV-related mortality and all-cause mortality. Laboratory markers and echocardiographic indicators of CV injury were evaluated as potential predictors of a poor prognosis.

In summary, in terms of mortality, as well as laboratory markers and echocardiographic indicators of cardiovascular injury, PD seems a more favorable method of dialysis. Nevertheless, PD recipients were younger and had more often received early pre-dialysis nephrological care. The influence of these factors on the parameters measured cannot be precisely calculated. Therefore, the advantage of PD cannot be clearly confirmed. Moreover, this advantage of PD was observed only in patients on dialysis for less than 2 years. With longer dialysis vintages, the laboratory and clinical advantages of PD were no longer present. However, even with longer dialysis vintages, HD showed no benefit with regard to outcomes. In addition to individual preferences of patients, PD seems to be the dialysis method of choice for candidates anticipating early kidney transplantation. Nevertheless, a more reliable analysis of the benefits of each modality would require an evaluation of the patients’ quality of life.

References


