ORIGINAL RESEARCH ARTICLE

Peritoneal dialysis as therapeutic option in heart failure patients

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Abstract

Aims   Each episode of acute decompensated heart failure (HF) incrementally adds to mortality. Peritoneal dialysis (PD) offers an alternative therapeutic option in refractory HF and reduces the incidence of decompensation episodes. The objective of this study was to determine the efficacy of PD, in terms of functional status, surrogate endpoints, rate of hospitalizations, and mortality.

Methods and results   This study is based on the registry of the German Society of Nephrology, involving 159 patients receiving PD treatment due to refractory HF between January 2010 and December 2014. Body weight was reduced by PD (82.2 ± 14.9 to 78.4 ± 14.8 kg, $P < 0.001$), and significant improvements in New York Heart Association functional class (3.38 ± 0.55 to 2.85 ± 0.49, $P < 0.001$) were found already after 3 months. Left ventricular ejection fraction did not change (31.5 ± 13.8 to 34.0 ± 15.7%, $P = 0.175$). C-reactive protein improved with PD treatment (33.7 ± 52.6 to 17.1 ± 26.3 mg/L, $P = 0.004$). Blood urea nitrogen/creatinine ratio decreased significantly (148.7 ± 68.3 to 106.7 ± 44.8 mg/dL, $P < 0.001$). Hospitalization rates decreased significantly (total number 2.86 ± 1.88 to 1.90 ± 1.78, $P = 0.001$, and 39.2 ± 30.7 to 27.1 ± 25.2 days, $P = 0.004$). One year mortality was 39.6% in end-stage HF patients treated with PD.

Conclusions   Peritoneal dialysis offers an additional therapeutic option in end-stage HF and is associated with improved New York Heart Association classification and reduced hospitalization. Although PD treatment was associated with various benefits, further studies are necessary to identify which patients benefit the most from PD.

Introduction

Congestive heart failure (CHF) is one of the fastest growing morbidities in industrial countries and the most common cause of hospital admission in elderly patients. In this patient cohort, CHF is accompanied by chronic kidney disease in up to 63% of patients[1] and is associated with a very poor outcome.[1–8] Pathophysiological mechanisms of this cardiorenal syndrome are arterial underfilling and renal venous congestion, which hinder adequate volume control by 'excretory renal insufficiency', resulting in repeated hydropic decompensations.[3,5,9–17] Although highly suggestive within this context, there is no evidence favouring ultrafiltration (UF) over conservative treatment with loop diuretics as first-line therapy in patients with acute or chronic HF.[18,19] However, UF may be considered in patients with refractory congestion who failed to respond to diuretic-based strategies.[2] Whereas the UNLOAD-HF[20] and the AVOID-HF trials[21] showed some beneficial effects of UF, the CARESS-HF trial not only failed to demonstrate the superiority of UF but was also associated

with an increased number of adverse events. Peritoneal dialysis (PD), another therapeutic option that is frequently used in patients with refractory CHF,[22] is associated with improved haemodynamic stability and lower costs and is able to drain ascites, which might at least theoretically improve outcome.

The aim of this study was therefore to provide more 'real-life' information about outcome and treatment parameter patients (according to European Society of Cardiology 2012[2]) treated with PD, employing the national registry of the German Society of Nephrology (DGfN).

Methods

For this prospective, multicentre, and national observational study, data from the registry of the DGfN were evaluated.

Between January 2010 and December 2014, a total of 159 patients with symptomatic end-stage CHF were enrolled in ambulatory PD therapy after interdisciplinary assessment on the following conditions:

(i) individually optimized pharmacological therapy according to the recommendation of the European Society of Cardiology[2];

(ii) diuretic resistance defined as refractory hypervolaemia despite optimal sequential diuretic therapy [loop diuretics, thiazides, or, if possible, mineralocorticoid receptor antagonists (MRAs)] as recommended by national authorities[2,23];

(iii) device therapy as indicated by current guidelines[2];

(iv) recurrent hospitalizations due to cardiac decompensation, at least two times within the last 6 months; and

(v) patients not eligible for heart transplantation.

Before initiating PD, specific renal pathologies, for example, glomerulonephritis, were excluded, and conservative HF therapy was optimized. Echocardiography was performed before initiating PD. Exclusion criteria for this study were inotropic support and contraindication for PD. Renal function, as estimated by glomerular filtration rate, was calculated using the Modification of Diet in Renal Disease equation.

After implantation of a peritoneal dialysis catheter and careful instruction, patients performed PD by continuous ambulatory PD, automated PD, or intermittent PD. Scheduled study visits were recorded at initiation of PD, after 3 and 6 months, and every 6 months thereafter. All visits included assessment of patient history, physical examination, body weight, echocardiography, laboratory measurements, and medication. The main objective was hospitalizations.

All patients provided written informed consent, and the study was approved by the local ethics committee (vote number S-106/2011).

Statistical analysis included the Kolmogorov–Smirnov test, Wilcoxon signed-rank test, or Student's *t*-test for paired variables, Levene's test, Pearson's correlation, and Kaplan–Meier estimator and log-rank test. Level of significance was $\alpha = 5\%$. Statistical analysis was performed using SPSS version 24 (IBM Corp., Armonk, NY, USA) and Excel version 2011 (Microsoft Copr., Redmond, WA, USA).

Results

Patient characteristics and treatment modalities are summarized in *Table 1*. Study population comprised a cohort of $n = 159$ patients with a mean follow-up time of 13.3 ± 15.0 months (66 months at longest).

Seventy-four patients underwent cardiac catheterization (46.5%), and 66 patients received an implantable cardioverter–defibrillator (41.6%) before PD was started. Eighteen patients (11.3%) needed precursory intermittent haemodialysis, primarily due to acute hypervolaemia or hyperkalaemia (mean duration of haemodialysis 12.4 ± 3.24 h/week or 3 times a week with average period of 4.15 ± 1.08 h, respectively; average blood flow 230.6 ± 67.1 mL/min).

Within the first 3 months, a slight increase of IPD was observed (*Figure 1*). Average $Kt\,V$ was $2.2 \pm 1.2.14$. Patients required intermittent haemodialysis at different time points after beginning of PD.

Laboratory results are demonstrated in *Table 2*. N-terminal pro-brain natriuretic peptide (NT-proBNP) revealed a negative absolute and relative personal change with PD treatment (-606 ng/L, relative change -3%).

Follow-up results of clinical variables after beginning of PD are shown in *Table 3*. There were no significant differences regarding peritoneal UF, body weight, and urine volume (*Figure 2*).

Regarding medication, use of MRA (35.8 vs. 35.7%) remained unchanged, while use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) decreased (51.6 vs. 40.2%) during the first year after starting PD. Meanwhile, use of beta-blockers increased during this period (59.7–73.1%).

Twenty-four patients (15.1%) were treated with erythropoiesis stimulation agents (ESAs) pre-PD. This number increased to 32.8% at 12 months ($n = 19$, patients at risk 58). In patients without ESAs or being on stable dosages of ESAs, we initially detected a significant increase of haemoglobin after 3 months (from 11.5 ± 1.89 to 12.0 ± 1.79 mg/dL, $P = 0.024$). But again, results were not of significance at the end of the observation period (11.6 ± 2.17 mg/dL, $P = 0.724$).

In total, number as well as days of hospitalization significantly decreased over the first year of PD from 2.86 ± 1.88 to 1.90 ± 1.78 ($P = 0.001$) and 39.2 ± 30.7 to

**Table 1** Baseline patient characteristics (medical and demographic data)

	n	(%)
	159	(100)
Sex		
Male	133	(83.7)
Female	26	(16.3)
Age (years)	72.8 ± 12.1	(100)
Aetiology of CHF		
Ischaemic cardiomyopathy	58	(36.5)
Dilated cardiomyopathy	50	(31.5)
Pulmonary hypertension and right ventricular dysfunction	7	(4.40)
Hypertensive heart disease	3	(1.89)
Pericarditis constrictiva	2	(1.26)
Congenital heart defect	2	(1.26)
Not specified	37	(23.3)
Valvular heart disease		
Tricuspid regurgitation		
I	12	(7.55)
II	27	(17.0)
III	17	(10.7)
Mitral regurgitation		
I	18	(11.3)
II	33	(20.8)
III	10	(6.29)
Medication		
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	82	(51.6)
Beta-blockers	95	(59.7)
Spironolacton	57	(35.8)
Erythropoietin	24	(15.1)
NYHA functional class		
II	7	(4.40)
II–III	5	(3.14)
III	41	(25.8)
III–IV	38	(23.9)
IV	41	(25.8)
Not specified	27	(17.0)
PD regime at beginning		
APD	54	(34.0)
CAPD	79	(49.7)
IPD	5	(3.14)
Not specified	21	(13.2)
Haemodialysis prior to PD	18	(11.3)

APD, automatic peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; IPD, intermittent peritoneal dialysis; NYHA, New York Heart Association; PD, peritoneal dialysis.
Data are presented as mean ± standard deviation or n.

27.1 ± 25.2 days (P = 0.004), respectively (*Figure 3*). In a linear regression model, there was no significant correlation between left ventricular ejection fraction (LVEF) and number (R = −0.14, P = 0.319) as well as days of hospitalizations (R = 0.296, P = 0.155) after 1 year.

Within 3 months, New York Heart Association (NYHA) significantly improved from 3.38 ± 0.55 to 2.85 ± 0.49 (P < 0.001) and remained at this level. In patients with worsening HF (n = 23), defined as reduction in ejection fraction (EF) ≥ 5%,[24] a significant decrease in number of hospitalizations over 1 year was observed (3.00 ± 1.30 to 1.77 ± 1.93, P = 0.036) (*Figure 4*). There was a negative correlation between difference in NYHA classification and days of

Figure 1 Peritoneal dialysis regime over the first year. APD, automatic peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; IPD, intermittent peritoneal dialysis.
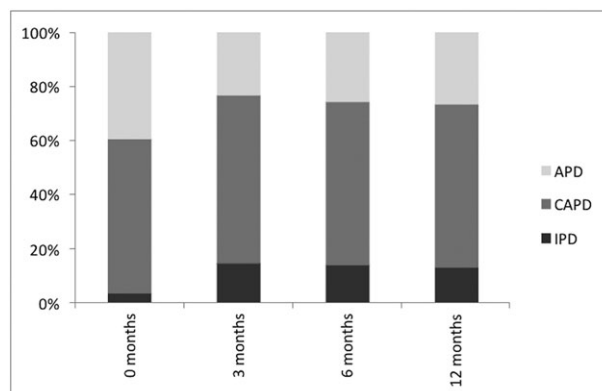
hospitalizations at 12 months (R = −0.281, P = 0.008). While overall LVEF did not change with PD treatment (31.5 ± 13.8% at baseline to 34.0 ± 15.7%, P = 0.175).

Mortality during the first 2 years after starting PD is shown in *Figure 5*. Average time until death was 437.6 ± 428.5 days. Seven patients recompensated and, therefore, intermittently stopped PD treatment. In addition, 13 patients changed medical centres for different reasons, and 36 were lost to follow-up. One year mortality was 39.6% (n = 44), while 2 year mortality was found to be 59.1% (n = 65). In addition, mortality of ischaemic cardiomyopathy vs. dilated cardiomyopathy patients did not differ significantly in 1 and 2 year survival (log-rank = 0.142 and 0.242, respectively).

Discussion

This is a prospective observational multicentre study, based on the national registry data of the DGfN, to evaluate the efficacy of PD in patients with refractory CHF.

First of all, our study confirms previous observations that even in end-stage CHF patients, PD significantly reduced both number and days of hospitalization for all causes. It has to be emphasized that hospitalizations were also reduced in patients with declining EF, which is of importance because as repeated decompensations are followed by an incremental worsening of prognosis.[25]

In general, conservative therapeutic options are rare for end-stage CHF patients with refractory to pharmacological treatment alone. Therefore, in diuretic-resistant CHF, current guidelines are directed at symptom relief and co-morbidity conditions, with UF or haemofiltration recommended as beneficial options. Nevertheless, to date, no further specifications concerning patient selection, treatment modality, or outcome measures can be given.[26] Moreover, evidence of

Table 2 Laboratory variables at baseline and during follow-up after starting PD

| | Pre-PD | Post-PD | | | | | | |
		3 months	P	6 months	P	12 months	P	Last follow-up	P
NT-proBNP (pg/mL)	3857 (IQR 2017–6303)	2553 (IQR 1343–5001)	0.931	2527 (IQR 1125–4874)	0.904	1829 (IQR 958–3904)	0.388	2747 (IQR 977–5743)	0.770
Albumin (g/L)	38.5 ± 5.74	37.4 ± 6.18	0.048	37.8 ± 7.11	0.201	39.4 ± 4.94	0.988	37.2 ± 7.01	0.031
Creatinine (mg/dL)	3.06 ± 2.75	3.11 ± 2.43	0.939	3.46 ± 2.54	0.575	3.35 ± 2.64	0.020	3.89 ± 2.79	0.014>
MDRD eGFR (mL/min/1.73 m²)	24.0 ± 11.3	28.5 ± 18.1	0.345	26.2 ± 15.5	0.669	25.9 ± 14.7	0.831	21.4 ± 14.0	0.019
BUN (mg/dL)	148.7 ± 68.3	105.9 ± 75.4	<0.001	102.5 ± 41.9	<0.001	96.8 ± 39.6	<0.001	106.7 ± 44.8	<0.001
CRP (mg/L)	33.7 ± 52.6	12.6 ± 25.1	0.001	13.2 ± 35.7	0.013	7.70 ± 7.65	0.002	17.1 ± 26.3	0.004
Sodium (mmol/L)	136.4 ± 4.77	137.9 ± 6.46	0.131	137.4 ± 4.96	0.111	137.9 ± 4.45	0.160	136.9 ± 5.55	0.635
Potassium (mmol/L)	4.31 ± 0.73	4.21 ± 0.66	0.013	4.27 ± 0.58	0.070	4.22 ± 0.55	0.106	4.37 ± 0.72	0.391
Phosphate (mmol/L)	1.57 ± 1.05	1.54 ± 0.81	0.299	1.57 ± 0.73	0.473	1.53 ± 0.85	0.834	1.70 ± 1.27	0.909
Haemoglobin (mg/dL)	11.2 ± 1.74	11.8 ± 1.82	0.004	11.7 ± 2.20	0.003	12.4 ± 1.85	<0.001	11.5 ± 2.17	0.219

BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IQR, inter-quartile range; MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; PD, peritoneal dialysis.
Median, standard deviation, and Student's *t*-test for paired variables. Mean, IQR, and Wilcoxon signed-rank text for not normally contributed paired variables.

Table 3 Clinical variables at baseline and after starting PD

| | Pre-PD | Post-PD | | | | | | |
		3 months	P	6 months	P	12 months	P	Last follow-up	P
NYHA	3.38 ± 0.55	2.85 ± 0.49	<0.001	2.76 ± 0.68	<0.001	2.57 ± 0.73	<0.001	2.73 ± 0.68	<0.001
Systolic BP (mmHg)	110.9 ± 19.9	113.5 ± 18.9	0.605	111.8 ± 19.3	0.542	114.1 ± 22.2	0.524	110.6 ± 21.2	0.428
Diastolic BP (mmHg)	67.7 ± 12.1	65.5 ± 10.9	0.003	66.6 ± 12.6	0.112	67.7 ± 15.9	0.226	65.4 ± 13.5	0.009
EF (%)	31.5 ± 13.8	31.9 ± 12.6	0.409	32.6 ± 11.5	0.093	33.9 ± 14.9	0.486	34.0 ± 15.7	0.175
Urine (mL)	1283.0 ± 956.6	1380.5 ± 799.9	0.095	1333.6 ± 868.9	0.237	1258.4 ± 685.2	0.279	1077.7 ± 686.6	0.804
pUF (mL)	NA	1125.8 ± 1229.7	NA	1175.0 ± 1398.4	0.907	1025.3 ± 838.5	0.558	1078.3 ± 687.4	0.289
Body Weight (kg)	82.2 ± 14.9	78.4 ± 14.8	<0.001	78.5 ± 13.8	<0.001	79.0 ± 15.2	0.015	78.7 ± 15.8	<0.001

BP, blood pressure; EF, ejection fraction; NA, not applicable; NYHA, New York Heart Association; PD, peritoneal dialysis; pUF, peritoneal ultrafiltration.
Median, standard deviation, and Student's *t*-test for paired variables. Mean and Wilcoxon signed-rank test for not normally contributed paired variables. Data are presented as mean ± standard deviation.

Figure 2 Comparison of body weight (A), relative change of body weight over time (B), urine volume (C), and peritoneal ultrafiltration (D) after starting peritoneal dialysis (PD). $^*P < 0.05$; $^{***}P < 0.001$.
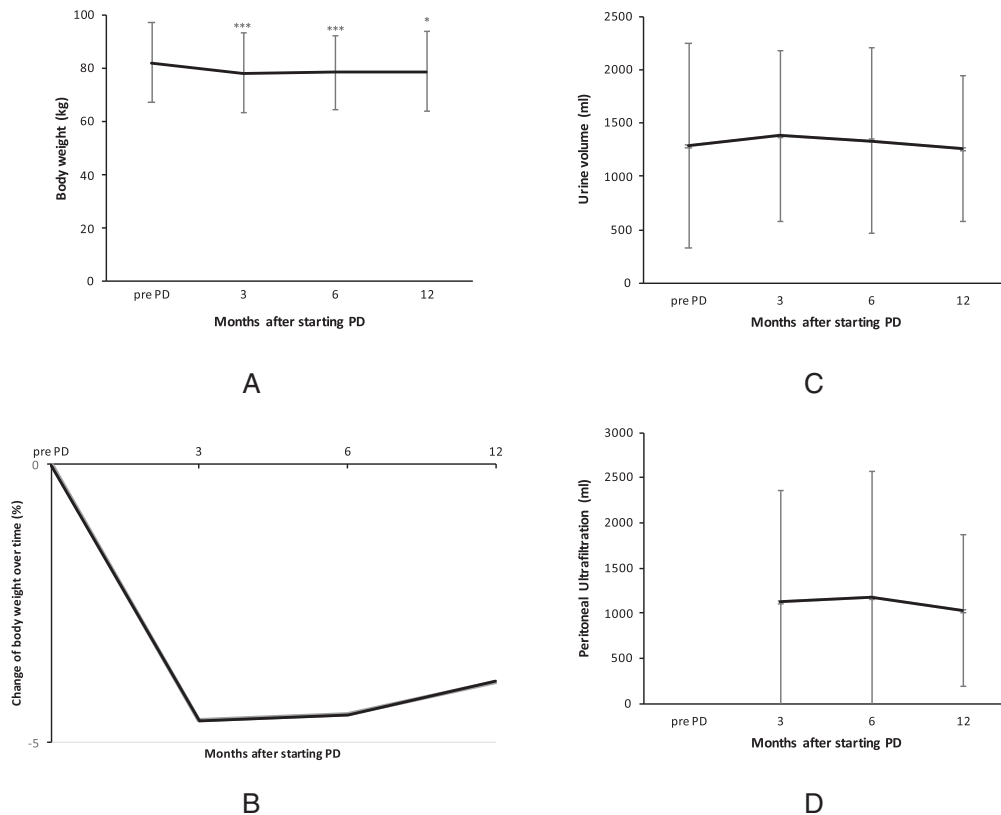
extracorporeal UF in CHF is conflicting.[18,19,27] Although extracorporeal UF might be an efficient method of treating decompensated HF on an acute basis, it may not be feasible to employ this treatment modality on a chronic basis for the growing number of patients with end-stage HF. For this reason, in a recent recommendation, the German Societies of Cardiology and Nephrology suggested PD treatment of patients with chronic refractory cardiorenal syndrome.[23]

Against this background, PD as a treatment modality carries some potential advantages.[23] PD offers, at least theoretically, the opportunity of a gentle and continuous UF that, in particular, relieves the increased renal venous[28,29] as well as intra-abdominal pressure and elegantly drains ascites, thus potentially re-establishing glomerular filtration and increasing diuresis. This was reflected by the relatively stable serum creatinine within the first months of PD treatment, which is in contrast to the study published by Bart *et al.*, using an extracorporeal device.[18,19]

In our patient cohort, an overall significant weight loss was observed. On the one hand, weight loss can be considered a surrogate for better volume management due to additional UF accompanied with remained urine output. On the other hand, it can reflect development of muscle loss and malnutrition, as PD patients lose several grammes of protein in the dialysate every day. Nevertheless, albumin levels remained

within the normal range, which is of importance because albumin is regarded as a strong predictor of survival. Despite weight loss and improved dyspnoea, serial overall NT-proBNP values remained unchanged throughout the study. However, the between-person variation of NT-proBNP is known to be large and markedly greater than the within-person variation.[30] Indeed, the relative NT-proBNP levels decreased, indicating the positive effects of PD treatment in HF patients.

The finding of a weight loss accompanied by significantly lowered C-reactive protein and blood urea nitrogen (BUN) with only slight glomerular filtration rate changes probably reflects a sustained loss of oedema, especially from intra-abdominal compartments, that otherwise would trigger translocation of lipopolysaccharide and hinder the resorption of nutritional compounds, finally ending up with profound cachexia as described by Cicoira *et al.*[31] A low BUN with a better nutritional status is associated with a better prognosis.[32–34] PD treatment decreased the BUN/creatinine ratio, which is consistent with the described reduced mortality.

HF therapy in patients with chronic kidney disease is frequently limited by life-threatening hyperkalaemia; therefore, patients were less likely to receive ACE inhibitors or ARBs.[35] Of note, patients on PD therapy often display a mild hypokalaemia. Although well known, no data are available whether this is also true in patients with cardiorenal
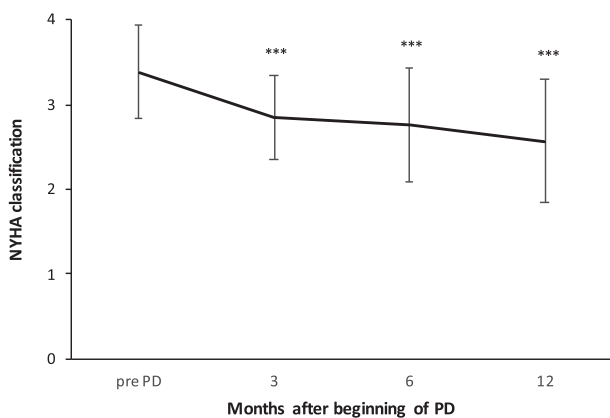
influence prognosis in this special patient cohort has to be demonstrated in further studies.

Applying the Charlson Comorbidity Index, reflecting 1 year mortality of patients with co-morbid states, we would have expected a mortality rate of 80% in our cohort, while historical collectives displayed mortality rates ranging from 45 to 75%[36,37] with conventional treatment. Various studies on PD reported 1 year mortality rates between 18 and 44%.[38–40] As 43% of our patients were hospitalized, a maximum of two times in the previous year, and 25% of the annual in-hospital days were less than 3 weeks, this might even strengthen the generalizability of the findings to a patient population frequently not assessed for PD. However, it limits the mortality comparisons with historical controls. Wang *et al.*[41] confirmed an increased mortality in patients with HF with PD treatment, and furthermore, in a previous study, our group described similar mortality rates of 33% in HF patients undergoing PD and 23% in a propensity score-matched HF cohort.[42] Against this background and given that HF cohorts may vary considerably in co-morbidity load, our finding of 1 year mortality of 39.6% in end-stage HF patients treated with PD indeed insinuates a strong survival benefit.

Even from an economic point of view, PD may prove beneficial as it contributes to lower healthcare costs by reducing hospital days.[43]

Our observations accord with former results, as NYHA classification did significantly improve with PD,[44] which is in line with previous results of Courivaud *et al.*[40] and implies that the impact of PD might differ regarding the change/improvement in EF, depending on the baseline EF. Nevertheless, recent studies found that LVEF does not add significant prognostic information to relevant demographic and biochemical variables in patients with advanced chronic kidney disease. It seems that the determination of global longitudinal strain rates indeed allows a significantly better prognostication than EF with respect to cardiovascular death.[45] Substantiating this thesis, the subgroup analysis of 1 and 2 year mortality did not reveal any difference between dilated cardiomyopathy and ischaemic cardiomyopathy patients.

There are a few limitations to be taken into consideration. Although, to the best of our knowledge, this study encompasses the largest PD patient population treated for HF, it is still a relatively small patient cohort to allow for any exclusion of a potential bias, considering the highly heterogeneous presentation of cardiorenal patients from 18 different centres. As a frequent problem of register data is incomplete data entry or follow-up, some patients have to be excluded for statistics. There was no standardized quality of life assessment, so there might be concerns that the morbidity of hospital admission can be counterbalanced by the complexity of doing PD at home for these patients. However, our previous study can invalidate this objection by demonstrating an improved quality of life with PD.[42] In addition, there could be a bias as patients

syndrome treated with PD and whether PD offers the chance for an increased dosage of renin–angiotensin–aldosterone system blockers as well as MRAs.[23] In our patient cohort, use of ACE/ARBs decreased and use of MRAs remained stable. Whether higher MRA and ACE/ARB doses might

Figure 5 Kaplan–Meier survival curve. Cumulative survival 2 years after starting peritoneal dialysis.
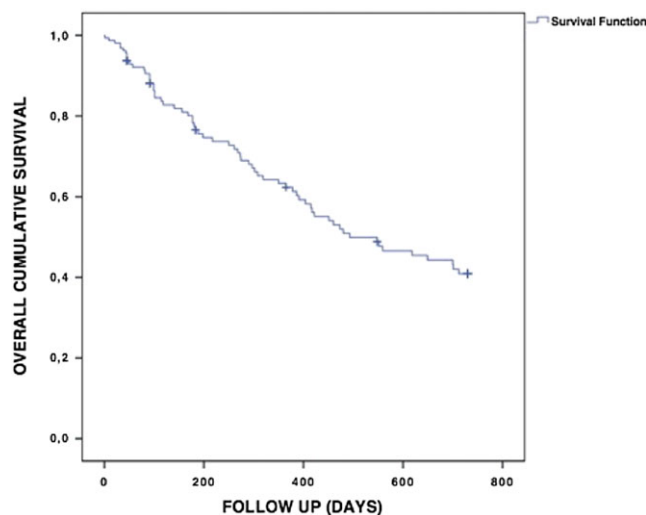
that were not started on PD were excluded while patients who received PD were closely monitored. Finally, the majority of our patients were male and of White Caucasian origin, which may hamper the translation of our findings to other populations from different ethnic backgrounds.

In conclusion, there are beneficial effects of PD as non-classical palliative therapy in CHF patients. Our data underline the need for larger controlled studies to identify factors for patient selection, employing PD as an adjunct therapy to modern pharmacological and device therapies and to broaden the view in guidelines on the most important risk factor in patients with HF–renal failure.

Conflict of interest

C.B., L.F., L.G., L.P.K., M.M.K., K.M., A.R., V.S., and M.Z. declare that they have no conflicts of interest. B.S. reports a conference/travel grant from St Jude Medical—HeartWare and a travel grant as well as personal fees from Berlin Heart GmbH, outside the submitted work. R.W. has received personal fees from Baxter Germany and Fresenius Germany. H.A.K. reports personal fees from AstraZeneca, personal fees from Daiichi Sankyo, personal fees from NovoNordisk, personal fees from Novartis, personal fees from Roche Diagnostics, personal fees from Bayer Vital, outside the submitted work.

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