Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study

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Abstract. The European APD Outcome Study (EAPOS) is a 2-yr, prospective, multicenter study of the feasibility and clinical outcomes of automated peritoneal dialysis (APD) in anuric patients. A total of 177 patients were enrolled with a median age of 54 yr (range, 21 to 91 yr). Previous median total time on dialysis was 38 mo (range, 1.6 to 259 mo), and 36% of patients had previously been on hemodialysis for >90 d. Diabetes and cardiovascular disease were present in 17% and 46% of patients, respectively. The APD prescription was adjusted at physician discretion to aim for creatinine clearance (Ccrea) ≥60 L/wk per 1.73 m^2 and ultrafiltration (UF) ≥750 ml/24 h during the first 6 mo. Baseline solute transport status (D/P) was determined by peritoneal equilibration test. At 1 yr, 78% and 74% achieved Ccrea and UF targets, respectively; median drained dialysate volume was 16.2 L/24 h with 50% of patients using icodextrin. Baseline D/P was not related to UF achieved at 1 yr. At 2 yr, patient survival was 78% and technique survival was 62%. Baseline predictors of poor survival were age (>65 yr; $P = 0.006$), nutritional status (Subjective Global Assessment grade C; $P = 0.009$), diabetic status ($P = 0.008$), and UF (<750 ml/24 h; $P = 0.047$). Time-averaged analyses showed that age, Subjective Global Assessment grade C and diabetic status predicted patient survival with UF the next most significant variable (risk ratio, 0.5/L per d; $P = 0.097$). Baseline Ccrea, time-averaged Ccrea, and baseline D/P had no effect on patient or technique survival. This study shows that anuric patients can successfully use APD. Baseline UF, not Ccrea or membrane permeability, is associated with patient survival.

Survival on dialysis is determined by removal of nitrogenous waste products, correction of electrolyte and acid-base imbalance, and fluid removal to maintain normal body fluid status. Patients feel unwell if inadequately dialyzed; they eat less, become malnourished, and are therefore at increased risk of infection. Inadequate fluid removal causes hypervolemia with the resulting hypertension, fluid overload, and cardiac complications. Most studies determining adequacy of dialysis as related to survival have concentrated on the impact of small solute clearance. For peritoneal dialysis, clinical practice guidelines such as DOQI (1) and UK Renal Association (2) are mainly based on the results of the CANUSA study (3). The patients in this study were on continuous ambulatory peritoneal dialysis (CAPD) and had significant residual renal function, so small solute clearances achieved represented a combination of dialysis and renal clearance. The CANUSA study confirmed data from other studies (4,5) suggesting that patients on CAPD with high membrane permeability had increased mortality, possibly because of poor ultrafiltration (UF) and consequent fluid overload.

Reanalysis of data from the CANUSA study suggests that peritoneal and renal clearances are not equivalent (6). The current guidelines are therefore speculative for anuric patients on PD. Indeed, anuric patients are a difficult group to dialyze effectively using CAPD (7). Not only may membrane permeability increase with time on PD with a consequent decrease in achieved UF (8), but also it is difficult to increase dialysis small solute clearance using CAPD because of the practical difficulties in increasing exchange volume and/or number. Automated peritoneal dialysis (APD) is a possible alternative for dialyzing anuric patients. The nighttime component of APD enables more frequent exchanges with reduced cycle length, thereby enhancing UF. Solute clearance can be increased by using higher volume exchanges and by adding daytime exchanges (9), and UF can be increased by the use of icodextrin for the long-day dwell (10). Even so, there is still doubt as to

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whether adequate clearances and successful clinical outcomes can be achieved, particularly in patients with large body surface area (11).

There are some data about the outcomes of anuric patients on PD, mostly CAPD, as very few patients in any of the studies were on APD. The largest prospective study of PD in anuric patients is from Hong Kong (12); all patients were on CAPD, and mean creatinine clearance (Ccrea) was low at 43.7 L/wk per 1.73 m^2. Two-year patient and technique survival in this study was 68.8% and 61.4%, respectively. Anuric patients were included in another study from Hong Kong with a 2-yr patient survival of 80% (13). Both of these studies suggest that outcome may be related to baseline Kt/V, as does retrospective data from Toronto (14). Another retrospective study suggested that Kt/V may be related to hospitalization rates but not mortality in 142 anuric patients (15). In contrast, the relationship between small solute clearance and survival was not confirmed by the ADEMEX study (16), a large, randomized, prospective study with 965 patients, more than half of whom were anuric at baseline.

The European APD Outcome Study (EAPOS) is a 2-yr prospective, observational, multicenter study of anuric patients receiving APD. The aim of the study was to determine the factors that affect patient and technique survival and thereby to arrive at guidelines for the treatment of such patients. Unlike previous studies, dialysis prescription was altered throughout the study, aiming to achieve both small solute clearance (Ccrea >60 L/wk per 1.73 m^2) and UF (>750 ml/24 h) targets. The baseline characteristics of the patients recruited into this study have been reported elsewhere (17).

Materials and Methods

Patient Selection

Between January 1999 and April 2000, 177 anuric patients on APD from 26 European centers in 13 countries were recruited into the study. Anuria was defined as 24-h urine output <100 ml and/or residual renal function (measured as mean of 24-h urea and Ccrea) <1 ml/min normalized to body surface area (1.73 m^2). Patients were recruited from the prevalent chronic dialysis population in each center. The only exclusion criterion was a predicted survival of <6 mo. The study had local ethical committee clearance at all sites, and all patients gave informed consent. Support of EAPOS was provided by Baxter Healthcare Corporation through sponsorship of investigator meetings, maintenance of a database, and statistical support.

Study Design

The aim of the study was to determine the impact on technique and patient survival of achieving the predetermined targets of a total Ccrea of 60 L/wk per 1.73 m^2 and a UF rate of 750 ml/24 h. Before initiation of the study, the investigator group established guidelines for the starting APD prescription for anuric patients (Table 1). These guidelines were based on a combination of personal clinical experience of the investigators, modeling using PD Adequest, and a considerable amount of discussion. Individual centers determined the appropriate APD prescription to achieve these targets. At the baseline assessment and at 2 monthly intervals thereafter, patients who did not achieve either or both of these targets were identified at each center by the central data collection office. The dialysis prescription of each of these patients was then examined and, when possible, modified to attempt to improve Ccrea (by increasing the volume of fluid cycled overnight or by adding in daytime exchanges) and/or UF (by increasing dextrose concentration of one or more exchanges or using icodextrin for the long-day dwell). The aim was to optimize the APD prescription over the first 6 mo of the study. In addition, targets were set for BP and biochemical and hematologic parameters as defined by the UK Renal Association (18). Recruitment to EAPOS was completed in April 2000, and the final patient completed the study in April 2002.

Potential patients were screened by individual centers and then enrolled into the study. At baseline, a full medical history and examination was noted to determine comorbidity; all patients had a peritoneal equilibration test (PET), measurement of dialysis adequacy (Ccrea and UF), and assessment of nutritional status by using Subjective Global Assessment (SGA) (19). Blood was taken for estimation of hemoglobin, serum venous bicarbonate, total calcium, phosphate, and intact parathyroid hormone in the local laboratory. Patients were seen every 2 mo for routine clinical assessment. Formal study visits took place every 6 mo. When Ccrea and/or UF targets were not achieved at baseline, measurements of adequacy were repeated after 2 mo to assess the effect of the prescription change. This process was repeated at 4 mo. Patients whose dialysis adequacy remained below target levels remained in the study. After this 6-mo period of optimization of dialysis, adequacy measurements were repeated at 6 monthly intervals in all patients. The PET was repeated at 12 and 24 mo.

Table 1. Guidelines for initial APD prescription in anuric patients[a]

Solute transport	Low	Low average	High average	High
BSA <1.71 m^2	CAPD	3 × 2.5 L (9–10 h) night 2 × 2 L day	4 × 2 L—8 h night 2 × 2 L day	4 × 2.5 L—8 h night 2 × 2 L
BSA 1.71–2.0 m^2	CAPD or HD APD 3 × 2 L (9–10 h) night 2 × 2 L day	3 × 2.5 L (9–10 h) night 2 × 2.5 L day	4 × 2.5—8 h night 2 × 2.5 L day	4 × 2.5 L or 5 × 2 L—8 h night 2 × 2.5 L day
BSA ≥2.0 m^2	CAPD or HD	CAPD or HD APD 3 × 3 L (9–10 h) night 2 × 3 L day	4 × 3 L—8 h night 2 × 2.5 L day	4–5 × 2.5 L—8 h night 2 × 2.5 L day

[a] APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; BSA, body surface area; HD, hemodialysis. Solute transport determined by peritoneal equilibration test.

Peritoneal Dialysis Measurements

Solute Clearance. Weekly Ccrea was calculated from creatinine concentration in plasma, urine, and dialysate; 24-h urine volume, and 24-h dialysate volume using PD-Adequest (Baxter Healthcare Corporation, Brussels, Belgium). Residual renal function was measured as mean of urea and Ccrea.

UF Rate. UF rate was calculated as the difference between the volume of total dialysate infused (including both nighttime and daytime fluid) and the volume drained over 24 h for the same period as the solute collection.

PET. The PET was performed as described previously, and the recognized classification (20) was used to subdivide patients on the basis of the results.

Comorbidity. The number of comorbidities was counted for each patient to calculate the Stoke index of comorbidity (21). This index was recently validated by an analysis of outcomes from the NECOSAD study (22).

Data Management

Peritoneal, urine, and dialysate concentrations of creatinine and all other blood tests were measured in each local laboratory. Results of these and all other demographic data were collated in the central EAPOS office (Baxter Healthcare Corporation) where the PET results and Ccrea were calculated. Individual centers were notified of patients who did not achieve the Ccrea and/or UF targets at a visit so that adjustments could be made in the APD regimen.

Statistical Analysis

Baseline and Longitudinal Data. Parametric data are presented as mean values with their SD, and nonparametric data are presented as median values with their range. Between-group comparisons were performed using the Mann-Whitney *U* test, and longitudinal changes in variables were analyzed using paired and unpaired ANOVA.

Univariate Survival Analysis. For comparing survivals according to baseline characteristics, patient, combined patient/technique, and pure technique survival were calculated using life table analysis using log rank statistics. Patients were censored at the point of transplantation or if lost to follow-up. An important feature of this study is that all patients were followed for the full 24 mo unless they reached an end point (death, technique failure, or transplantation). For calculating pure technique survival, patients were censored at death and transplantation.

Multivariate Survival Analysis. Cox proportional hazards regression was used in three stages. First, baseline characteristics were added sequentially to a model that included age, body surface area, gender, comorbidity grade (categories 0, 1 to 2, and >2) and SGA (treated as three categories, A, B, and C). Second, as this was a study with planned interventions for UF and Ccrea, these variables, including total and peritoneal Ccrea, were treated as time-dependent covariates. As reanalysis of the CANUSA study (6) showed benefit from even small differences in urine volume, residual Ccrea was included as a separate time-dependent covariate. Finally, a forward step-wise Cox regression model was constructed in which only covariates with a $P < 0.5$ are included in their order of importance according to their likelihood score (χ^2) (23,24).

Results

Baseline Demographics

Of the 204 consecutive anuric patients screened by participating centers, 177 were included in the study. Age, peritoneal solute transport, and gender ratio were not different between included and nonincluded patients. Of the 27 patients who were not included, 14 (52%) were because of withdrawal of the center between screening and enrollment. Other reasons included patient choice, therapy switch, or unsuitability for APD mainly as a result of comorbidity. Included patients had a lower median cumulative comorbidity score (0.82) than nonincluded patients (1.37; $P = 0.046$), accounted for by more diabetes and peripheral vascular disease in the nonincluded patients. Of the included patients, 119 (67%) were completely anuric. Fifty-eight patients had some urine output (median urine volume, 96 ml/24 h; Ccrea, 0.4 ml/min per 1.73 m^2 or 4.03 L/wk per 1.73 m^2).

Baseline demographics of patients enrolled in the study are shown in Table 2. The duration of total dialysis time before recruitment into EAPOS was long (median, 37.8 mo). Of note, 64 (36%) of the patients had previously received hemodialysis for some period of their dialysis history. Fifteen percent of patients had diabetes, and 42% had cardiovascular disease at baseline. Mean D/P creatinine on PET at baseline was 0.74 ± 0.12; the distribution of patients according to transport status is shown in Table 1, with no patients being in the low transport group. Only seven patients were severely malnourished at baseline as defined by SGA grade C.

Dialysis Adequacy and Prescription

Dialysis prescriptions varied widely, as each center determined these individually. At baseline, patients received dialysis for a median of 9.0 h overnight (range, 7 to 12), using a median overnight dialysate volume of 11.0 L (range, 6 to 28.75). The median daytime dialysate volume was 4.0 L (range, 0 to 9.0), with almost all patients using a daytime dwell and many an extra daytime exchange. There also were variations in the nighttime APD regimen, with 26 patients using tidal dialysis.

Details of dialysis volume, Ccrea, and UF over the course of the study are given in Table 3. At baseline, median total was

Table 2. Baseline demographics[a]

N (M:F)	177 (102:75)
Age (median [range])	54 (21–91) yr
White, Asian	*n* = 142, 21
BSA (m^2)	1.75 ± 0.22
Body weight (kg)	76.9 ± 15.2
Total dialysis time (median [range])	37.8 (1.6–259) mo
Previously on HD	*n* = 64 (36%)
Diabetic	*n* = 27 (15%)
Cardiovascular disease	*n* = 75 (42%)
Nutrition	A *n* = 77 (46%)
SGA	B *n* = 81 (49%)
	C *n* = 7 (4%)
Membrane permeability (PET)	LA *n* = 44 (26%)
	HA *n* = 80 (46%)
	H *n* = 49 (28%)

PET, peritoneal equilibration test; LA, low average; HA, high average; h, high.

Table 3. Renal and total creatinine clearance, dialysis volume, and ultrafiltration parameters throughout the study[a]

Months in study	0	6	12	18	24
n	177	135	100	75	57
Urine volume (ml/d)[b]	0	0	0	0	0
	0–70	0–0	0–0	0–0	0–0
Residual Ccrea (L/wk per 1.73 m^2)[b]	0	0	0	0	0
	0–1.58	0–0	0–0	0–0	0–0
Mean (SD) residual Ccrea (L/wk per 1.73 m^2) in patients with residual renal function at baseline	1.92	1.40	0.69	0.46	0.59
	(4.80)	(4.02)	(2.31)	(1.94)	(2.27)
Drained dialysate volume (L/d)[b]	15.7[c]	16.2	16.2	16.9	16.7
	(13.8–18.6)	(14.6–20.1)	(14.9–19.7)	(14.7–20.5)	(14.8–20.2)
Total Ccrea (L/wk per 1.73 m^2)[b]	63.4[c]	65.5	69.1	68.6	68.8
	(55.2–71.1)	(58.8–70.9)	(60.6–75.7)	(60.2–76.6)	(61.6–68.8)
Net UF (L/d)[b]	1.09	1.17	1.02	1.08	0.95
	(0.75–1.65)	(0.676–1.62)	(0.72–1.47)	(0.63–1.4)	(0.69–1.22)
No. using icodextrin	82 (46%)	60 (44%)	50 (50%)	42 (56%)	34 (60%)

[a] Ccrea, creatinine clearance; UF, ultrafiltration.
[b] Median and interquartile range.
[c] Less than subsequent months of study, $P < 0.05$, ANOVA.

63.4 L/wk per 1.73 m^2, UF rate was 1.09 L/d, drained dialysate volume was 15.7 L/d, and 45% of the patients were using icodextrin during their daytime dwell. For the 64 patients with Ccrea below target at baseline, a significant increase in prescribed volume (14.2 L/d to 15.1 L/d; $P < 0.001$) resulted in a mean increase in Ccrea from 49.7 to 57.5 L/wk per 1.73 m^2 by 6 mo ($P < 0.001$). In contrast, patients with Ccrea above target at baseline had no change in dialysis dose, and Ccrea was unchanged during the first 6 mo (70.9 *versus* 70.1 L/1.73 m^2; $P = 0.34$). The increase in dialysis dose below target is reflected by the increase in dialysate volume at 6 mo (Table 3). This is also reflected in the higher percentage of patients reaching the target, as shown in Table 4.

Baseline daily UF volumes were below the 750 ml target in

Table 4. Quality assessment (% patients achieving targets)[a]

	Months				
	0	6	12	18	24
Systolic BP	(*n* = 176)	(*n* = 130)	(*n* = 100)	(*n* = 75)	(*n* = 57)
age <60 <140 mmHg	(*n* = 110) 66%	(*n* = 86) 66%	(*n* = 71) 71%	(*n* = 54) 62%	(*n* = 41) 68%
age >60 <160 mmHg	(*n* = 66) 92%	(*n* = 44) 88%	(*n* = 29) 86%	(*n* = 21) 81%	(*n* = 16) 100%
Diastolic BP <90 mmHg	(*n* = 176) 80%	(*n* = 130) 84%	(*n* = 100) 84%	(*n* = 75) 83%	(*n* = 57) 88%
Ccrea ≥60 L/wk	(*n* = 167) 60.7%	(*n* = 112) 73%	(*n* = 88) 78.3%	(*n* = 59) 76.6%	(*n* = 50) 82.4%
UF ≥750 ml/24 h	(*n* = 174) 75.3%	(*n* = 125) 73.4%	(*n* = 95) 73.7%	(*n* = 65) 67.2%	(*n* = 55) 72.7%
Bicarbonate ≥20 mmol/L	(*n* = 161) 97%	(*n* = 120) 98%	(*n* = 73) 100%	(*n* = 57) 98%	(*n* = 49) 91.8%
Phosphate ≤1.7 mmol/L	(*n* = 174) 57.5%	(*n* = 135) 63.7%	(*n* = 99) 67.7%	(*n* = 73) 71.2%	(*n* = 56) 77%
PTH ≤195 pg/ml	(*n* = 145) 74%	(*n* = 99) 72%	(*n* = 72) 75%	(*n* = 47) 74%	(*n* = 45) 66%
Hemoglobin ≥10 g/dl	(*n* = 176) 73%	(*n* = 132) 82.6%	(*n* = 99) 81.8%	(*n* = 73) 83.6%	(*n* = 53) 73.4%
Calcium ≥2.0 mmol/L	(*n* = 173) 98%	(*n* = 134) 95%	(*n* = 97) 94%	(*n* = 72) 94%	(*n* = 55) 96%

[a] PTH, parathyroid hormone.

43 patients. Peritoneal transport characteristics of these patients were similar to those of patients above target (0.76 *versus* 0.75; $P = 0.5$). However, UF capacity on baseline PET was significantly worse in patients below target (247 *versus* 350 ml; $P = 0.03$). At 6 mo, this group had a significant increase in mean UF, 512 rising to 872 ml/d ($P = 0.012$), whereas those above target achieved less (1423 *versus* 1243 ml/d; $P = 0.02$), a trend that persisted throughout the study (Figure 1). This increase in the below-target group was associated with an increased prescription of glucose and a higher proportion of patients using icodextrin. The average daily concentration of glucose increased from baseline to 6 mo (1.74 to 1.94%; $P = 0.023$) and again at 12 mo, when it was 2.01% ($P = 0.006$). No significant changes in average glucose prescription occurred in patients who were above target at baseline (1.95 *versus* 1.96% at 6 mo; $P = 0.44$), although it should be noted that these patients used a greater baseline glucose concentration ($P = 0.016$). By 6 mo and thereafter, there was no difference in the average daily glucose prescription between these patient groups.

Patients who were using icodextrin at baseline had significantly worse peritoneal membrane function (solute transport, 0.77 *versus* 0.73; $P = 0.011$) and UF capacity on baseline PET (272 *versus* 373 ml; $P = 0.02$) compared with patients not using icodextrin. The number of patients using icodextrin for the long dwell increased to 50% at 12 mo and 60% at 24 mo. There was evidence of preferential increase in the use of icodextrin in patients below the UF target at baseline (48%) and at 6 mo (58%) during the period of dialysis optimization.

Other Targets

Quality of dialysis management (BP, hemoglobin, calcium, and phosphate control) was measured against the 1997 UK Renal Association standards (16). The results achieved are shown in Table 4. A total of 77% of patients were treated with human recombinant erythropoietin therapy.

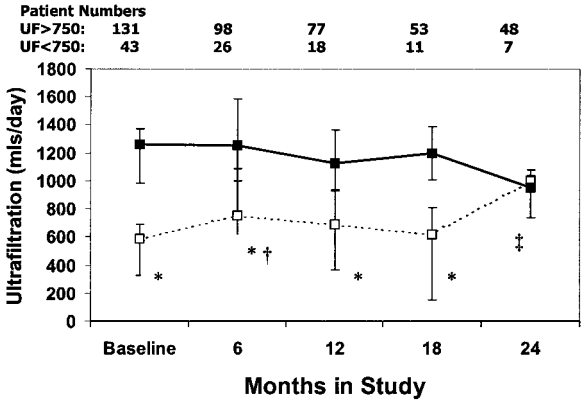

Figure 1. Median (±interquartile range) longitudinal changes in achieved daily ultrafiltration (UF) in patients with >750 ml (group 1; ■) and <750 ml (group 2; □) UF at baseline. (*between-group difference, $P < 0.007$; ‡decrease from baseline in group 1, $P < 0.001$; †increase from baseline in group 2, $P = 0.015$).

Peritonitis Rate

The overall peritonitis rate during the study was 139 episodes in 2621 patient-months, or one episode in 18.8 mo. The causes of peritonitis were coagulase-negative staphylococci (40 patients [29%]), Gram-negative organisms (34 [24.5%]), *Staphylococcus aureus* (12 [9%]), *Streptococcus viridans* group (12 [9%]), fungal (4 [3%]), culture negative (21 [15%]), and unknown (16 [11%ü.

Causes of Dropout

A total of 120 patients dropped out of the study (Table 5). Twenty-four (20.3%) of these patients received a transplant; 31 (26.3%) died, mainly of cardiovascular disease. Infection was the second most common cause of death, with four patients dying of peritonitis. Transfer to hemodialysis occurred in 51 (43.2%) patients; in 22 patients, the cause was peritonitis. Two of the patients who transferred because of peritonitis died within 1 mo of transfer. Other reasons for dropout were partial recovery of residual renal function and loss to follow-up.

Survival Analysis

The 2-yr actuarial patient, pure technique, and combined patient and technique survivals were 78%, 62%, and 49%, respectively (Figure 2). Age (>65 yr; $P = 0.001$), worse SGA grade ($P = 0.0014$), increased comorbidity grade ($P = 0.012$), diabetic status ($P = 0.008$), and UF (<750 ml/d; $P = 0.0048$; Figure 3) at baseline all were associated with significantly worse patient survival on univariate analysis. Gender, body surface area, total peritoneal or residual Ccrea, and peritoneal solute transport status at baseline did not influence patient, technique, or combined patient and technique survival.

The initial multivariate Cox regression model of baseline

Table 5. Causes of dropout

Dropout reasons	*n*
Transplantation	24 (20%)
Death	31 (25.8%)
cardiovascular disease	20
infection	6
others[a]	5
Transfer to hemodialysis	51 (42.5%)
peritonitis	22
UF failure	5
malnutrition	3
inadequate dialysis	5
burnout	2
noncompliance	2
others[b]	9
unknown	3
Partial recovery of residual renal function	3 (2.5%)
Loss to follow-up	11 (9.2%)

[a] Respiratory failure (2), gastrointestinal bleeding (1), lupus encephalopathy (1), and liver failure (1).

[b] Abdominal complications (6), hypotension (1), respiratory failure (1), and malignant hypertension (1).

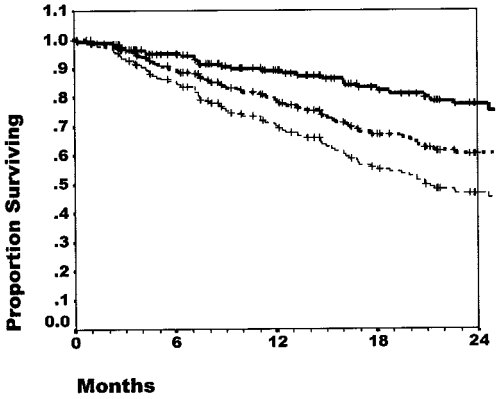

Figure 2. Kaplan Meier plots of 2-yr patient (▤), pure technique (▬ ▬ ▬) and combined patient and technique survival (---).

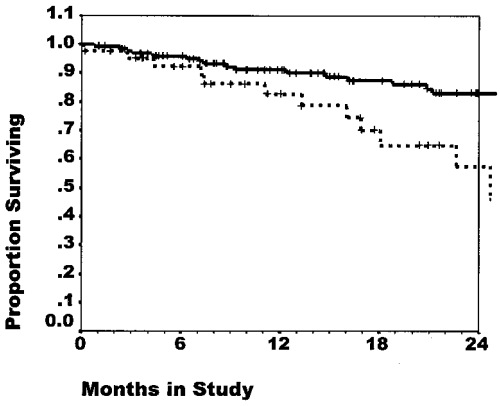

Figure 3. Kaplan Meier patient survival according to baseline UF of >750 ml/d (▤) and <750 ml/d (▬ ▬ ▬); $P = 0.0048$.

characteristics is shown in Table 6. It can be seen that the main independent predictors of patient survival were age, the presence of more than two comorbidities, and severe malnutrition (SGA grade C). As additional covariates were added, diabetic status, which was always present in patients with grade 2 comorbidity, displaced the comorbidity score in the model. Table 7 shows the model including the achieved daily UF at baseline, here treated as a continuous variable. Increased UF was associated with improved survival independent of the above predictors, whereas both membrane transport and previous time on dialysis were not predictors of survival. When baseline total Ccrea was substituted for UF, the model did not predict outcome (relative risk [RR, 0.99/L per wk; $P = 0.76$), whereas other predictors remained essentially the same.

Using the same general approach, models were then constructed treating achieved UF and Ccrea as time-dependent covariates. Two approaches were used: time averaging of the covariate of interest or a method that carries forward the last value to predict survival over each subsequent 6-mo period. Using these approaches, the only time-dependent covariates that came close to significance were the time-averaged UF (RR, 0.5/L per d; $P = 0.097$) and the residual renal Ccrea (RR, 0.86/L per wk; $P = 0.19$). These time-dependent covariates were then used in forward step-wise Cox regression models, summarized in Tables 8 and 9. Time-averaged UF was used in both models; however, the last value at each 6 mo for residual and peritoneal Ccrea was used in the model for Table 8 and the time-averaged total Ccrea was used in the model for Table 9. In each case, age, an SGA grade C, and diabetic status predicted outcome, with UF the next most significant variable.

These analyses suggested an important although not statistically significant role for baseline UF in clinical outcomes that seems to have persisted throughout the study. Therefore, it was important to evaluate the success of the clinical interventions in achieving the predetermined UF targets. The longitudinal changes in achieved UF during the study according to baseline grouping (below and above the 750 ml target) are shown in Figure 1. Among the patients below target at baseline, values for UF were generally lower than those obtained in patients above target at baseline, despite the changes in dialysis prescription, discussed above. The exception was at 24 mo, at which time seven patients with baseline UF <750 ml remained in the study.

Discussion

This study has shown that a large proportion of anuric patients can be maintained successfully on APD, with >70 to 80% of patients achieving a Ccrea of 60 L/wk per 1.73 m^2. The main predictors of survival were age, diabetes, poor nutrition, and UF; survival was not influenced by small solute clearance (either peritoneal or from the very small amount of residual renal function remaining in some patients) or peritoneal solute transport status. It should be borne in mind, however, that the

Table 6. Initial multivariate Cox regression of baseline predictors of patient survival

Variable	DF	Parameter estimate	Standard error	Relative risk	*P* value
Age (yr)	1	0.052	0.016	1.05	0.0014
Baseline BSA (m^2)	1	−0.339	1.207	0.71	0.7787
Comorbidity grade 1–2 (0 = no, 1 = yes)	1	0.182	0.471	1.20	0.6987
Comorbidity grade >2 (0 = no, 1 = yes)	1	1.267	0.648	3.55	0.0507
Gender (0 = M, 1 = F)	1	0.114	0.512	1.12	0.8237
SGA score B (0 = no, 1 = yes)	1	0.573	0.435	1.77	0.1875
SGA score C (0 = no, 1 = yes)	1	2.221	0.719	9.22	0.0020

Table 7. Multivariate Cox regression of baseline predictors of patient survival, including UF, diabetes, and previous time spent on dialysis therapy

Variable	DF	Parameter estimate	Standard error	Relative risk	*P* value
Age (yr)	1	0.048	0.017	1.05	0.0064
Baseline BSA (m^2)	1	−0.182	1.268	0.83	0.8856
Baseline UF L/d	1	−0.79	0.399	0.45	0.0469
Comorbidity grade 1–2 (0 = no, 1 = yes)	1	0.023	0.512	1.02	0.9628
Comorbidity grade >2 (0 = no, 1 = yes)	1	0.54	0.811	1.72	0.5035
Diabetes (0 = no, 1 = yes)	1	1.02	0.592	2.80	0.0823
Gender (0 = M, 1 = F)	1	0.179	0.531	1.20	0.7356
PET D/P <0.65 (0 = no, 1 = yes)	1	0.144	0.611	1.16	0.8134
PET D/P >0.81 (0 = no, 1 = yes)	1	0.399	0.483	1.49	0.4081
Previous months on dialysis	1	−0.00004	0.004	1.00	0.9916
SGA grade B (0 = no, 1 = yes)	1	0.280	0.469	1.32	0.5511
SGA grade C (0 = no, 1 = yes)	1	2.103	0.808	8.19	0.0093

Table 8. Summary of step-wise Cox regression models using time-dependent UF and last value for Ccrea

Step	Variable	Score (χ^2)	Score *P* value	DF	Parameter estimate	Standard error	Relative risk	*P* value
1	Age (yr)	15.88	<0.0001	1	0.058	0.016	1.06	0.0004
2	SGA score C (0 = no, 1 = yes)	7.87	0.005	1	1.83	0.713	6.30	0.0099
3	Diabetes (0 = no, 1 = yes)	4.86	0.027	1	0.936	0.491	2.55	0.0569
4	Time-averaged UF(t) L/d	2.90	0.088	1	−0.56	0.407	0.57	0.1675
5	Residual Ccrea(t) L/wk per 1.73^2	1.47	0.223	1	−0.13	0.112	0.88	0.2472
6	SGA score B (0 = no, 1 = yes)	0.52	0.468	1	0.327	0.453	1.39	0.4702

Table 9. Summary of stepwise Cox regression models using time-dependent UF and Ccrea

(b) Step	Variable	Score (χ^2)	Score *P* value	DF	Parameter estimate	Standard error	Relative risk	*P* value
1	Age (yr)	17.47	0.00003	1	0.057	0.016	1.06	0.0004
2	SGA score C (0 = no, 1 = yes)	7.16	0.007	1	1.941	0.703	6.97	0.0058
3	Diabetes (0 = no, 1 = yes)	5.16	0.023	1	1.015	0.487	2.76	0.037
4	Time-averaged UF(t) L/d	2.01	0.156	1	−0.544	0.413	0.58	0.187
5	SGA score B (0 = no, 1 = yes)	0.83	0.361	1	0.416	0.453	1.52	0.358
6	Time-averaged total Ccrea(t) L/wk per 1.73^2	0.49	0.483	1	0.009	0.013	1.01	0.483

number of end points determines the power of an observational study. Thirty-one deaths occurred in the study, which typically would be enough to identify three to four covariates as predictors of outcome. It may well be, therefore, that this study did not have sufficient power to identify other factors.

The 2-yr patient survival of 78% and technique survival of 62% in this study are identical to those reported from the NECOSAD study (hemodialysis and PD) (22). Patients in EAPOS were representative of the European general dialysis population, with a similar age range and prevalence of diabetes and cardiovascular comorbidity to the NECOSAD study (22). A possible criticism of EAPOS is that by recruiting from a predominantly prevalent patient cohort, the patients who were selected were survivors. In fact, their survival was similar to that of the incident PD patients of the NECOSAD study (25), which along with other studies (26) have shown that survival of incident and prevalent patients are identical.

The results from EAPOS differ from those of the only other prospective study of anuric patients on PD (12), in which outcome was determined by small solute clearance. Mean Ccrea in that study was only 43.7 L/wk per 1.73 m^2. Patient survival (68.8% at 2 yr) was lower than that of EAPOS but was similar to that of the ADEMEX study in which approximately half of the patients were anuric (16). ADEMEX was a large,

prospective, controlled trial of 965 patients on CAPD who were randomized to two different target levels of peritoneal Ccrea. Achieved peritoneal Ccrea were different in the two groups (33rd to 67th percentile values, 42.5 to 49.1 L/wk per 1.73 m^2 and 53.4 to 60.5 L/wk per 1.73 m^2); however, 2-yr patient survival was similar in both groups (68.3 and 69.3%, respectively), again suggesting that survival is independent of small solute clearance. These results, though, are in contrast to other prospective and retrospective studies (3,27,28) that show increasing mortality with declining total Ccrea. In each of these studies, the decline in total Ccrea was related to loss of residual renal function as no change was made to the dialysis prescription.

Although it is difficult to compare results from different studies, it could be suggested that there is a minimum level of small solute clearance that has to be achieved to avoid morbidity directly related to uremia. Indeed, in the ADEMEX study, uremia-related deaths did occur in the low clearance group. However, once this threshold has been reached, a further increase in small solute clearance has no survival advantage, at least in the range achievable with current APD techniques. The results from EAPOS will certainly add to the debate about the need to focus on small solute clearance in PD management guidelines (29–33).

EAPOS was designed to be a real-life observational study. The only exclusion criterion was a life expectancy of <6 mo. There was no age limit, and patients who would not change their dialysis regimen to meet targets remained in the study. To be included in the study, a patient's residual renal function had to be <1 ml/min per 1.73 m^2; therefore, although some patients had some urine output at baseline, none did by the end of the study. The majority of patients were completely anuric throughout the study. Although it was possible that the presence of even a minimal amount of urine output could have had an impact on study outcomes, this was not shown by the various analyses of residual renal function at baseline or as a time-related variable.

Peritoneal membrane transport status at baseline had no effect on outcome, unlike in previous studies of patients on CAPD (4,5,34). High transport status in CAPD results in poor UF with consequent fluid overload. With APD, there is little fluid reabsorption across the peritoneum as cycle length is short. Potential fluid reabsorption during the long-day dwell was avoided by the use of icodextrin (35). This suggests that these treatment effects could ameliorate the detrimental effect on UF inherent in high transport status.

No patients with low transport status were enrolled in the study, in part because of the guidelines for prescribing APD in the study, which specified that CAPD patients with low transport status who became anuric would not be transferred to APD. One can only speculate that APD patients with preexisting low transport status may have already transferred to hemodialysis because of inadequate dialysis as a result of progressive decline in residual renal function or that their peritoneal membranes became more permeable with time on dialysis as has been shown in a number of studies (34).

Although it seems that the dropout rate in this study was high, the 2-yr technique survival of 62% is similar to that of other multicenter studies (12,25). The main cause of transfer to hemodialysis was peritonitis (12% of all patients, 43% of transfers). Although this rate of technique failure seems to be more than expected, it is in agreement with other studies of long-term PD reported by Davies *et al.* (34), in which peritonitis accounted for 13 to 54% of technique failure. A peritonitis rate of one episode in 18.8 patient-months may seem to be high, but this rate has been reported by others (36) and does fall within the UK Renal Association guidelines (2). It has been suggested that the outcome of peritonitis is adversely affected by length of time on PD (37), but the cure rate in this study was 81%, which compares favorably to the UK Renal Association standard of 80%.

A striking finding from this study is the association between poor UF and reduced survival. Baseline UF rate, unlike Ccrea, was shown to be a significant predictor of survival by both univariate and multivariate analyses. An important feature of the study design was a preestablished plan to manage patients' dialysis prescriptions to prospectively determined targets for UF and Ccrea. There is clear evidence from the longitudinal analysis of these parameters, particularly during the first 6 mo of treatment optimization, that clinicians took appropriate steps to reach targets. Greater success was achieved in reaching the target for Ccrea than for UF, and at least part of the apparent improvement in the latter was due to informative censoring, as the dropout rate as a result of death in this group was significant.

To account for treatment changes, Cox modeling was also undertaken in which UF and Ccrea were treated as time-dependent covariates. Although not statistically significant, higher time-averaged UF continued to be associated with better survival. This, combined with the consistently poor UF achieved by patients who were below target at baseline and their poor UF capacity on the baseline PET, suggests a persistent problem of fluid removal in these patients. Many aspects of membrane function contribute to the achieved UF. The best documented is solute transport, which reduces UF by increasing the rate of glucose absorption and thus decreasing the osmotic gradient. However, solute transport accounts only for approximately 15% of the variance in achieved UF, other factors being fluid reabsorption and those determining osmotic conductance of the membrane—literally the amount of UF obtained for a given osmotic gradient. Factors that affect the osmotic conductance will include the hydraulic conductance of the membrane, membrane area, and the efficiency of various pore systems that determine the reflection coefficient for glucose. By using APD and icodextrin, the intention is to eradicate the bad effect of high transport on UF, as seems to have happened in this study. However, all of the other factors remain and indeed now assume relatively more importance as this study shows. These factors are difficult to measure individually but are lumped together as the UF capacity of the membrane—measured in the PET. Thus, the lower UF capacity in the patients below target is very significant and explains why these patients failed to achieve targets despite equivalent glucose use by 6 mo.

The reason that these patients did so poorly cannot be determined with certainty from this study, as fluid status in an individual patient is determined as much by fluid intake as by UF achieved (38). However, prolonged abnormal fluid status is one possible mechanism for poor survival, perhaps contributing to cardiovascular death. Equally, if these patients were euvolemic, then very low intakes of both fluid and salt would be required. Typically, <750 ml of UF in APD is associated with <50 mmol of sodium removal, as a result of sieving in short exchanges. Whatever the explanation, this study suggests that clinicians need to pay close attention to APD patients who consistently achieve low UF volumes. This observation is in keeping with those from other recent studies, such as Ates *et al.* (39), which suggested that the impact of loss of residual renal function on survival was due to its effect on salt and water removal and not the loss of small solute clearance.

In conclusion, the survival of anuric patients on APD is similar to other patients on PD. Furthermore, the poor prognosis of CAPD patients with high peritoneal solute transport does not apply to patients on APD. By using APD, it is possible to achieve sufficient small solute clearance and UF to treat successfully even anuric patients. This is important not just for patients who are already on PD but also for patients who are on hemodialysis, particularly those who no longer have vascular access. Finally, this study demonstrates the important role of UF in contrast to small solute clearance as an outcome parameter in patients on PD.

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