Blocking effects of the renin-angiotensin system in long-term peritoneal dialysis patients

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Chapter 3

Treatment with A-II inhibitors and residual renal function in PD patients

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ABSTRACT

Background: Many studies have shown the renoprotective effect of ACE-inhibitors (ACEi) and Angiotensin –II receptor blockers (ARB) in patients with chronic kidney disease stage I-IV. Two randomised controlled trials (RCT) showed a positive effect of AII-inhibitors on rGFR in PD patients. However, these studies were small and performed in a highly selected group of PD patients. Our aim was to confirm the above findings in a larger number of prospectively followed PD patients.

Methods: First we analyzed the time course of residual glomelurar filtration rate (rGFR) decline in 452 incident PD patients who were not anuric at the start of dialysis and had structured follow-up data with measurements at 3, 6, 12, 18, 24, 30 and 36 months after the start of dialysis. rGFR changes over time were analyzed with a linear mixed model for repeated measures. Additionally Cox regression models were used to estimate the risk of anuria development. With a second approach we aimed to repeat the above analyses within a selected group of patients, who theoretically could have been randomized and therefore resemble the population studied in two mentioned RCTs. Also in this group the follow-up was restricted to one year.

Results: 201 patients were treated with ACEi/ARBs and 251 did not take these drugs at the start of PD. Patients from the treated group more often had diabetes and used more antihypertensive medications. The time course of rGFR decline was not different between the two groups over the 3 years of PD treatment ($p = 0.52$). Less than 25% of patients from each group became anuric and there was no difference in time of complete anuria development between the treated and untreated group. In the second approach, 130 patients were included, 37 were treated with ACEi/ARB and 93 were not. Again, no difference was found between the two groups with regard the rate of decline of rGFR and time of anuria development.

Conclusion: Our findings are not in line with the results of previous RCTs. Given all the benefits of ACEi/ARB the medications should not be withheld from PD patients. However their renoprotective effects may often be overruled by other factors influencing the time course of rGFR.

Introduction

The importance of the preservation of residual renal function (RRF) in peritoneal dialysis (PD) patients is obvious. It has a positive influence on PD adequacy and patients' survival [1-3]. Better preserved RRF is associated with less comorbidity [4-6], improved fluid [7] and nutritional status [8]. One of the advocated strategies for RRF preservation in PD patients is blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). The use of these medications is well-known to have a renoprotective effect in patients with CKD of various aetiologies in chronic kidney disease stages I-IV [9-11]. Results of the study of Moist et al. suggested that a beneficial effect of ACEi/ARB on RRF is also present after dialysis initiation [12]. However, another study could not confirm such results [13]. Moreover, two randomized controlled trials (RCT) were performed to study the impact of ACEi/ARB on the rate of decline of residual glomelurar filtration rate (rGFR) in patients receiving PD and both showed a positive effect of these medications [14;15]. The impact of these results for the general PD population is difficult to assess, because only patients without the accepted indications for ACEi/ARB could be randomized.

The aim of our study is to confirm the results found in the RCTs in a large cohort of PD patients with a long prospective follow-up using both intention-to-treat and as treated designs.

Methods

Patients

The patients were selected from the database of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). This is a large prospective multicentre cohort study in which patients with end stage renal disease from 38 dialysis centers in the Netherlands were followed from the initiation of dialysis until transplantation or death. At the start of dialysis all patients were older than 18 years and had never received renal replacement therapy in the past.

All 585 incident patients who had started renal replacement therapy with PD in the period between January 1 1997 and July 1 2007 were considered for the current analyses. In order to study the time course of rGFR the patients who were anuric already at the start of PD therapy were excluded. To be included, patients had to have a measurement of rGFR available at the time point 3 months after the start of dialysis as well as data on the use of ACEi and ARB and other antihypertensive medications (ß-blockers, calcium channels antagonists, diuretics). After the inclusion patients were followed as long as PD therapy continued.

Data collection

Demographical data, as well as data on comorbidity and primary kidney disease, were collected within 1 month prior the start of dialysis treatment. During the follow-up, data on blood pressure, proteinuria, body mass index (BMI), use of antihypertensive medications and residual renal function were collected at 3, 6, 12, 24, 30 and 36 months after the start of dialysis.

Primary kidney disease was classified according to the codes of the European Renal Association - Dialysis and Transplantation Association (ERA-EDTA) – European Renal Association Registry [16]. Comorbidity was scored on the basis of Davies' comorbidity index as having no, intermediate or severe comorbidity based on number of comorbid conditions [17]. Cardiovascular disease was recorded if one of the following conditions was present: angina pectoris, myocardial infarction, congestive heart failure class III-IV, peripheral vascular disease or cerebro-vascular accident.

RRF was expressed as rGFR and was calculated as the mean of 24 hour creatinine and urea clearance, corrected for body surface area (ml/min/1.73m^2). A 24-hour urine collection was done prior to the monitoring visit at the outpatient clinic and a blood sample was drawn at the visit. The rGFR level was set to zero when urine production was $<$200ml/24h. When a patient had a rGFR value of zero at two consecutive time points he was defined as anuric from the first time point that rGFR was zero.

The use of ACEi/ARB as well as other antihypertensive medications was documented "yes" or "no" at every check-up time point (see above). When "yes" was indicated, the patient was considered to have used the medication during the period preceding the check-up.

Analysis of the data

To study the time course of rGFR with regard to the use of ACEi/ARB two different approaches were applied. Firstly, we performed an analysis of the cohort on an intention-to-treat basis. All included patients were assigned to the ACEi/ARB or control group based on the use of the medication during the first 3 months of PD treatment. When a patient used ACEi/ARB during this period regardless of taking these medications before the start of dialysis – this patient was assigned to the treatment group. If ACEi/ARB were not taken at the start of PD and during 3 months after the start, the patient was included in the control group. After that we compared the time courses of rGFR between the groups for the 3 years of follow-up.
With a second approach we aimed to create conditions similar to ones of the two referenced

RCTs. Therefore, we restricted our study to one – year follow-up and included only those patients who theoretically could participate in randomization process. For this purpose we selected those patients who survived for at least 1 year on PD and excluded those with strict indications for ACEi/ARB, like myocardial infarction, congestive heart failure, cerebrovascular accidents. Unlike in the RCTs, we performed our analysis on an "as treated" basis and therefore included only those patients, who had been continuously treated with ACEi/ARBs with those who had not received these medications in the 1st year of PD. The time course of rGFR during the 1st year on PD was compared between the two groups.

Statistics

To compare patients' baseline characteristics we used standard descriptive statistics. Student's t-test was applied to compare continuous variables and the chi-square test was used to compare categorical data. To analyze the effects of ACEi/ARB medication on the decline of RRF we constructed generalized mixed models for repeated measures. The random-effects mixed model with unstructured covariate matrix was applied to study differences in rGFR over time between the two groups. The multivariate model contained rGFR as dependent variable and treatment group as well as the number of measurements (time) as independent variables. The independent variables were first analyzed separately, and then with an interaction. In addition, the model contained mean arterial blood pressure, proteinuria and the use of antihypertensive medications as repeatedly measured variables. We also made adjustments for age, gender, diabetes and cardiovascular disease as recorded at baseline.

In addition we performed a Cox proportional hazards model to evaluate the risk factors for becoming anuric during the first three years of PD therapy with regard to treatment with ACEi/ARBs. The multivariate model contained age, gender, diabetes, cardiovascular disease, as well as rGFR, mean arterial blood pressure and proteinuria at 3 months after the start of PD.

All statistical analyses were performed using SPSS statistical software, version 14.0 (SPSS Inc., Chicago, Illinois, USA). A p-value of 0.05 or less was considered significant.

Results

Intention-to-treat analysis

Patients

Out of the 585 incident PD patients we excluded those who discontinued with PD therapy within the first 3 months (n = 36), were anuric at 3 months after the start of dialysis (n=34) and patients with missing data on rGFR during the first 6 months (n=25). The remaining 490 patients were assigned to the ACEi/ARB or control group. Patients who used these drugs at the start of PD but stopped right after it were excluded, n = 38. The remaining 452 patients were included for the current analysis. Those patients who used these medications at 3 months after the start of PD regardless of taking them prior to the start of dialysis were included in the treated group (n = 201). Those, who used these medications neither at the beginning of dialysis nor up to the first 3 months were assigned to the control group (n = 251).

Compared to the included patients, the excluded ones more often had cardiovascular disease, had lower rGFR and used less ACEi at the start of dialysis. Other baseline characteristics were not different between in- and excluded patients.

Out of the 201 patients from the ACEi/ARB group, only 90 started to use them after the first 3 months of PD.

Baseline characteristics of the studied cohort are summarized in Table 1. A difference in primary kidney disease was present between the two groups. This was due to a higher number of diabetics in the treated group. More of the ACEi/ARB patients used antihypertensive medications at the start of PD. In particular, patients from the treated group used diuretics and calcium channel blockers more often than controls. No other differences between the two groups were found. When comparing controls with the 90 patients who started to use ACEi/ARB only after the 3 months of PD, similar differences were detected (data not shown). With regard to PD modality there was no difference in use of CAPD or APD between the two groups at any time point (data not shown).

Decline of rGFR

To compare the time course of rGFR between the two groups during the first 3 years of PD treatment we applied a generalized linear mixed model for repeated measures as described above. The results of the unadjusted analysis are shown in Figure 1a.

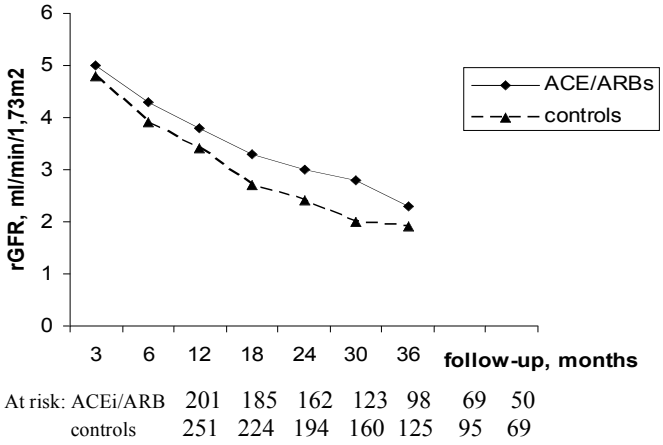
Table 1: Patients' baseline characteristics at 3 months after PD initiation.
Numerical data are given as means ±SD and as medians with ranges, unless otherwise stated.

Group	ACEI/ARB	Controls	*P*-value
Number of patients	201	251	
Age (*years*)	52(18-78)	54(20-78)	0.2
Gender (% male)	67	65	0.6
Primary kidney disease (%)			
Diabetes	22	12	*0.002*
Glomerulonephritis	22	15	
Renovascular nephropathy	8.5	13	
Other	47.5	60	
Comorbidity (%)[1]			
Diabetes mellitus	26	15	*0.008*
Cardiovascular comorbidity	25	21.5	0.6
Congestive heart failure	5.5	7.5	0.3
Myocardial infarction	9.5	7.1	0.5
Cerebrovascular accident	6.5	5.6	0.8
Davies comorbidity score			
No comorbidity	55	63	0.2
Moderate comorbidity	37	31	
Severe comorbidity	8	6	
Mean arterial blood pressure (*mmHg*)	102 (±13)	102 (±12)	0.2
Residual GFR (*ml/min*)	5 (±2.4)	4.8 (±2.4)	0.4
Proteinuria (*g/24h*)	1.8 (±2.6)	1.6 (±1.9)	0.4
Body mass index (BMI)	24	24	0.9
Use of antihypertensives [2] (%)	96	83	*0.002*
Diuretics	40	27	*0.001*
Calcium channels blockers	52	33	*0.001*
Beta-blockers	42	36	0.2

[1]percentage of patients with the comorbidity conditions existing prior to PD initiation.
[2]percentage of patients treated with antihypertensive medications at the start of PD therapy.

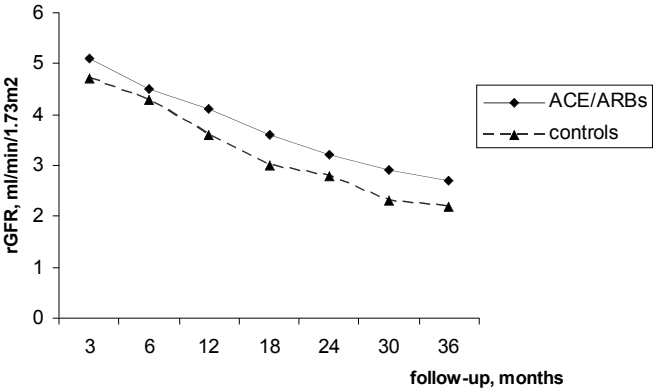
We found no difference in rate of decline of rGFR between the two groups, p = 0. 49. Figure 1b presents the results of the adjusted analysis which also showed no difference, p = 0.52.

a



At risk:								
	ACEi/ARB	201	185	162	123	98	69	50
	controls	251	224	194	160	125	95	69

b



At risk:								
	ACEi/ARB	201	185	162	123	98	69	50
	controls	251	224	194	160	125	95	69

Figure 1. a) Unadjusted curves for the rGFR decline based on a generalized linear mixed model for repeated measures for all incident PD patients with a follow-up of a maximum 3 years.

b) Adjusted curves for the rGFR decline. Adjustments are made for mean arterial blood pressure, proteinuria, use of antihypertensive medications, age, gender, diabetes and cardiovascular disease.

Because the time course of rGFR could be influenced by baseline GFR, we repeated the mixed model analyses in subgroups of patients with low and high level of GFR measured at 3 months after start of dialysis. Subgroups were divided based on the median rGFR value (4. 6 ml/min/1.73m^2). The additional analyses showed a similar time course of RRF in the different subgroups (data not shown). In addition, because the time course of rGFR could be influenced by different duration of ACEi/ARB treatment, we repeated the analysis including into the treated group only the 90 patients who started to use the medications after the start of dialysis. This change in design did not influence the outcome; no difference between the two groups was found (data not shown).

Due to drop-out from the study because of transplantation, death or switch to hemodialysis, we were able to record the development of anuria in only 20% of the patients. These were 49 patients from the ACEi/ARB group and 49 controls, who became anuric within the three years of follow-up. In addition we performed the Cox proportional hazards model to verify the relative risk to develop anuria with regard to the use of ACEi/ARB. A crude analysis showed a similar relative risk of becoming anuric for the treated group vs controls: HR 0.95; [95% confidence interval (CI): 0.6 to 1.44]. In the analyses adjusted for age, gender, diabetes, cardiovascular disease as well as mean arterial blood pressure, proteinuria and rGFR, measured at the 3 months after the start of PD, the relative risk of anuria for the ACEi/ARB group vs controls showed no significant difference: HR 1.05; [95% CI 0.61 to 1.48].

As-treated analysis

Patients

For the analysis based on the as-treated principle, we selected those PD patients who were not anuric at the start of dialysis and remained treated with PD for at least one year. To be included patient either had to be treated with ACEi/ARB for the whole year or not taking these medications at all during this period. We found 151 patients who fulfilled the above criteria. Additionally, to keep only the patients who theoretically could be randomized, we excluded those having severe cardiovascular comorbidity, that is patients with congestive heart failure [7] as well as the ones with myocardial infarction [13] or cerebrovascular accident [8] prior to the start of PD. Out of the remaining 130 patients 37 were treated with ACEi/ARB during the first year on PD, the other 93 did not take these medications within the studied period. Comparison of the baseline characteristics is shown in the Table 2. Patients from the treated and untreated group had similar baseline conditions.

Table 2: Baseline characteristics of patients in "as treated" analysis. Data are taken at three months after the start of PD. Numerical data are given as means ±SD and as medians with ranges, unless otherwise stated.

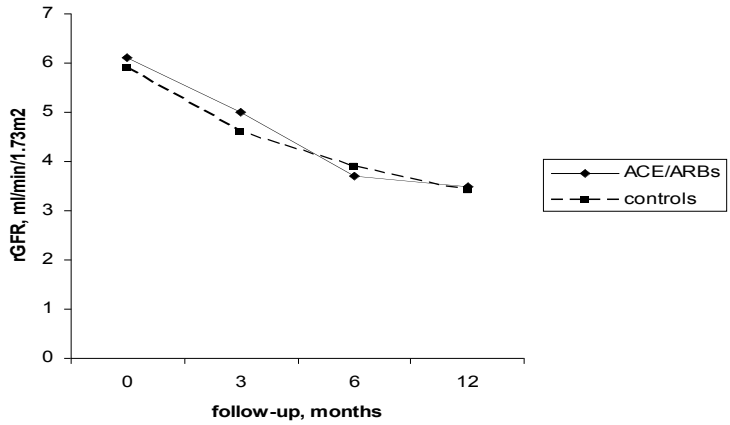
Group	ACEI/ARB	Controls	*P*-value
Number of patients	37	93	
Age (*years*)	49(18-78)	54(20-78)	0.07
Gender (% male)	70	65	0.5
Primary kidney disease (%)			
Diabetes	11	10	0.3
Glomerulonephritis	24	12	
Renovascular nephropathy	3	8	
Other	62	70	
Comorbidity (%)[1]			
Diabetes mellitus	13	11	0.7
Cardiovascular comorbidity	6	11	0.3
Davies comorbidity score			
No comorbidity	75	75	0.8
Moderate comorbidity	24	24	
Severe comorbidity	1	1	
Mean arterial blood pressure (*mmHg*)	103 (±13)	103 (±11)	0.8
Residual GFR (*ml/min*)	4.9 (±2.2)	4.4 (±2.2)	0.2
Proteinuria (*g/24h*)	2 (±2.7)	1.6 (±1.6)	0.2
Body mass index (BMI)	25	25	0.9
Use of antihypertensives[2] (%)			
Diuretics	46	35	0.2
Calcium channels blockers	35	40	0.1
Beta-blockers	40	48	0.2

[1]percentage of patients with the comorbidity conditions existing prior to PD initiation.
[2]percentage of patients treated with antihypertensive medications at the start of PD therapy.

Decline of rGFR

To compare the time course of rGFR between the two groups during the first year of PD treatment we applied the general linear mixed model for repeated measures as described previously. The results of an unadjusted analysis are shown in Figure 2a. No difference in rate of decline of rGFR between the two groups was found, p = 0.2. Adjustment for possible confounders did not bring a difference in the results, p = 0.23 (Figure 2b).

a



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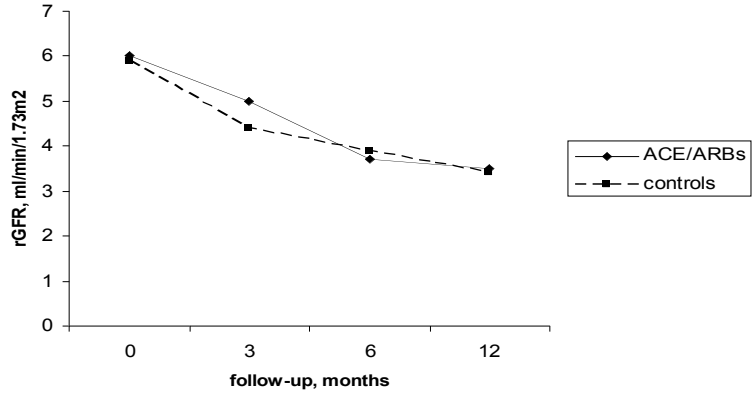

Figure 2.a) Unadjusted curves for the rGFR decline based on a generalized linear mixed model for repeated measures in as treated analysis with 1 year follow-up.

b) Adjusted curves for the rGFR decline. Adjustments are made for mean arterial blood pressure, proteinuria, use of antihypertensive medications, age, diabetes and cardiovascular disease.

One patient from the ACEi/ARB group vs 11patients from the controls developed complete anuria in the first year of treatment, p = 0.1 Because less than 9% of patients developed anuria within the 1st year of PD treatment, the results of the Cox proportional hazards model were not informative (data not shown).

Discussion

The renoprotective effect of ACEi/ARB in PD patients that has been found in two RCT's, could not be confirmed in the present prospective observational cohort study. This may partly be due to the selection of patients in the RCTs, and partly due to "confounding by indication".

The first RCT on a potential renoprotective effect of the ACE inhibitor ramipril was done in 60 prevalent PD patients with a GFR≥ 2ml/min/ 1.73m^2(14). 145 patients could not be enrolled because of the following exclusion criteria: congestive heart failure, myocardial infarction within the preceding 6 months, clinically significant valvular disease, malignant hypertension or hypertensive retinopathy, history of hypertensive encephalopathy or cerebrovascular accident within the preceding 6 months, history of bilateral renal artery stenosis. The hazard ratio for the development of anuria was higher in the ramipril group than in the controls at 3, 6 and 9 months. Only at 12 months the ramipril group had a significantly lower hazard ratio. Accordingly, the rGFR was higher in the ramipril group only at 9 and 12 months.

The RCT with the angiotensin II receptor blocker valsartan was performed in 32 incident patients [15]. The exclusion criteria were similar to those in the ramipril trial. Remarkably, the renal creatinine clearance showed a marked increase after 6 months followed by slow decline to a value at 24 months that still exceeded the baseline one. The controls showed an initial decline, followed by more or less stable values. The discrepancy between the two RCTs is remarkable: the first showed a temporary decrease following the instillation of ACE inhibitor; the second reported an increase after angiotensin II receptor blockade. It can be hypothesized that the relatively small number of patients in the two RCTs could be the cause of the discrepancy.

The largest observational follow-up study in 1032 incident PD patients from the US Renal Data System showed that the development of anuria was positively associated with the presence of diabetes mellitus and congestive heart failure [12]. The use of ACE inhibitors and calcium channels blockers were both independently associated with a longer duration of the development of anuria. These renoprotective effects of ACE inhibitors and calcium channels

blockers could not be confirmed in an observational study in 146 incident PD patients from Australia [13].

In the present study no effect of ACEi/ARB on the decline of rGFR or on the development of anuria was found. This was the case when the whole cohort was analyzed, and also when the exclusion criteria used in the two RCTs were applied. Only a tendency to a longer duration before the development of anuria was found in the latter analysis.

The difference with the RCTs could be partially explained by confounding by indication, also known as selection by prognosis. The distinct difference between RCTs and observational studies, such as cohort studies, is that RCT can provide evidence for a causal relationship because they have the potential to avoid confounding by indication [18].

The patients most often prescribed ACEi/ARB use these drugs because of hypertension, heart failure and diabetes mellitus. These conditions themselves are associated with a more rapid decline of residual renal function [12;19;20]. However, diabetes was not confirmed to be a predictor of anuria development in an earlier NECOSAD analysis [21]. This might be due to a lower percentage of diabetics and other possible differences in the studied population. Also it cannot be excluded that some patients were treated with ACEi/ARB to slow down the decline in rGFR, although the first RCT on this issue in PD patients was only published in 2003. Prescription of ACEi/ARB to prolong survival may have occurred based on results from the studies in predialysis patients [22;23]. A positive effect on survival in HD patients was published in 2002 [24] while in PD patients such an effect is controversial [25;26].

Our study has some additional limitations. First of all, information about treatment with ACEi/ARB before the start of dialysis is not available. It may be that some patients were taking the medications but stopped prior to dialysis initiation. This could have influenced our outcome. Secondly, it is unknown why exactly the patients were prescribed ACEi/ARBs.

We conclude that a number of factors make it difficult to assess the effects of ACEi/ARB on residual renal function in the general PD population. Bias, caused by confounding by indication, can never be excluded despite all the adjustments that can be made. Potential renoprotective properties of AII-inhibitors in PD patients could be overruled by other factors that influence rate of rGFR decline. The results of the two published RCTs suggest a favorable effect, but both have been done in a limited number of selected patients and some of the results are contradictory. Yet, none of the studies suggested a harmful effect of these medications. Given the many established indications for ACEi/ARB treatment in PD patients the threshold for prescribing them should be low.

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