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

Kolesnyk, I.

Publication date
2010

Document Version
Final published version

Citation for published version (APA):
Blocking effects of the renin-angiotensin system in long-term peritoneal dialysis patients
Blocking effects of the renin - angiotensin system in long-term peritoneal dialysis patients
PhD thesis, University of Amsterdam, The Netherlands
ISBN/EAN 978-90-9025043-4

Inna Kolesnyk, Amsterdam, The Netherlands
All rights reserved. No part of this thesis may be reproduced, stored or transmitted in any way or by any means without prior permission of the author. A digital version of this thesis can be found at http://dare.uva.nl

Cover and lay-out by W.L. Rijnen, Hopknijking 2000©
Printed by Gildeprint Drukkerijen, Enschede

This thesis was supported by Baxter Healthcare through the research grant from the RENAL DISCOVERIES Extramural Grant Program

The printing of this thesis was financially supported by: Baxter BV, Genzyme Nederland, Amgen BV, Roche Nederland BV, Abbot BV, Fresenius Medical Care Nederland BV, Shire Belgium BVBA.
Blocking effects of the renin - angiotensin system in long-term peritoneal dialysis patients

ACADEMISCH PROEFSCHIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam, op gezag van de Rector Magnificus prof. dr. D.C. van den Boom ten overstaan van een door het college voor promoties ingestelde commissie, in het openbaar te verdedigen in de Agnietenkapel op dinsdag 2 februari 2010 te 14:00 uur

door
Inna Kolesnyk
Geboren te Kiev, Oekraïne
Promotiecommissie

Promotor: Prof. Dr. R.T. Krediet

Co-promotores: Dr. D.G. Struijk, Dr. F.W. Dekker

Overige leden: Prof. Dr. N. Lameire, Prof. Dr. M.M. Levi, Prof. Dr. R.J.M. ten Berge, Prof. Dr. G.J. Navis, Dr. J.C. Korevaar

Faculteit der geneeskunde

The studies presented in this thesis have been prepared and conducted in the Renal Unit, Department of Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
Contents

Chapter 1
General introduction, aims and outline of the thesis 7

Chapter 2
Effects of AngiotensinII inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients
The impact of ACE inhibitors and AII receptor blockers on the peritoneal membrane transport characteristics in long-term PD patients 17
Perit Dial Int, 2007; 27:446-453

A positive effect of AII-inhibitors on peritoneal membrane function in long-term PD patients 35
Nephrol Dial Transplant 2009; 24:272-277

Chapter 3
Treatment with A-II inhibitors and residual renal function in PD patients 51
Perit Dial Int, in press

Chapter 4
Effects of Angiotensin-converting enzyme inhibitors and Angiotensin II receptor blockers in patients with chronic kidney disease 67
Neth J Med, in press
Chapter 5
Use of Angiotensin II inhibitors in patients who developed encapsulating peritoneal sclerosis: case-control study 89
Submitted

Chapter 6
Time dependent reasons for PD technique failure and mortality 99
Perit Dial Int, in press

Chapter 7
General discussion 115

Summary 123
Samenvatting 128
Aknowledgement 132
Chapter 1

General introduction, aims and outline of the thesis
General Introduction

Peritoneal dialysis

Being one of the methods of renal replacement therapy (RRT) peritoneal dialysis (PD) prolongs life of patients with end stage renal disease (ESRD). Since 1976 this method in form of continuous ambulatory peritoneal dialysis (CAPD) is used for treatment of patients with terminal renal failure \cite{1}. There is evidence that in the first couple of years survival of ESRD patients is better when treated with PD rather than with hemodialysis (HD) \cite{2}. But, later on this difference disappears. The latter probably happens due to complete loss of residual renal function (RRF) and failure of the ultrafiltration capacity of the peritoneal membrane – the basic instrument for PD \cite{3}.

The peritoneal membrane

The peritoneal membrane consists of peritoneum and interstitial tissue with blood and lymphatic vessels \cite{4}. The peritoneum is made of a single layer of mesothelial cells and underlying connective tissue; it has parietal and visceral part. Mesothelial cells produce different substances among which are the lubricant solution which prevents frictions of serosal surfaces and cancer antigen CA5. The function of the latter is not known yet. However when measured in the effluent of PD patients it is used as marker of mesothelial cell mass and cell turnover \cite{5}.

During peritoneal dialysis only a part of the peritoneal surface area is actively involved into the transport process – the actual contact area between the membrane and dialysis solution \cite{6}. The interstitium also has been recognized as a significant barrier for the peritoneal transport, it contains hyaluronan which has a negative charge. It restricts membrane permeability of proteins \cite{7}, but a charge selectivity has been shown for peritoneal protein clearance during CAPD \cite{8}. However, the most important part influencing membrane’s permeability is endothelium of the peritoneal vessels.

Peritoneal transport

The effective peritoneal surface area is determined by the number of perfused peritoneal capillaries \cite{9}. Under the normal condition only 25% percent of these vessels are open \cite{10}, but in the process of PD the splanchnic blood flow is increased enlarging the size of the peritoneal surface area \cite{11}. During peritoneal dialysis, solutes and water are transported through a system of pores \cite{12}. The large pores allow the transport of macromolecules, such as serum pro-
teins. The small pores are involved in transport of small solutes and water, while ultrasmall pores are exclusively permeable for water.

The transport of low molecular weight solutes (e.g. creatinine, urea, glucose) occurs mainly by diffusion and to a more limited extent by convection. Diffusion is based upon a difference in solute concentration on two sides of the membrane while convection (or solvent drag) is associated with water transport and is more applicable for solutes with a higher molecular weight \(^{(13)}\). The small solute transport capacity of the membrane is given by the product of the membrane’s permeability to that solute, and its effective surface area, called the mass transfer area coefficient (MTAC).

Transport of water through the peritoneal membrane is one the most important parts of PD treatment. Failure of ultrafiltration directly leads to insufficiency of the PD therapy. Ultrafiltration is dependent on the hydrostatic pressure gradient between the pressure in the capillaries and in the peritoneal cavity and on the colloid osmotic pressure gradient induced by plasma proteins. It is also dependent on the crystalloid osmotic pressure gradient caused by the osmotic agent (glucose), on the hydraulic permeability of the peritoneal membrane and its effective surface area. As mentioned above, the free water transport occurs through the ultrasmall channels, aquaporin-I. Its contribution to the total fluid removal averages to 40% with a large interindividual variability \(^{(14)}\). The function of water channels can be estimated by a number of methods. One is measuring of sodium level changes, sodium “sieving”, during the hypertonic dwell \(^{(15)}\). The other way is to measure a difference in net ultrafiltration, achieved with 1.36% and 3.86% glucose solution \(^{(16)}\). Recently another method to estimate free water transport directly was developed \(^{(14)}\); the method is described in detail in Chapter 2.

**Long-term effects of peritoneal dialysis**

After long-term PD treatment the membrane can show various morphological alterations. These include increased thickness of the peritoneum, loss of the mesothelial layer and fibrosis of the omental tissue \(^{(3;17)}\). Apart from this, the new vessels formation together with extensive vascular abnormalities in venules and arterioles often present \(^{(18)}\). An increased effective peritoneal surface area paradoxically leads to a disturbance of the main function of the membrane – removal of uremic waste products and water, which consequently results in PD technique failure.
Renin-Angiotensin system

The renin-angiotensin system (RAS) is a major regulator of blood pressure and vascular response to injury. Renin is released from the kidneys into the circulation in response to ischemia and decreased renal perfusion. In the lung renin turns angiotensin into inactive angiotensin – I, which is consequently converted into the active octapeptide angiotensin –II by angiotensin-converting enzyme (ACE) (19). From this cascade start the majority of central effects of RAS. In recent years the major interest about effects of the local RAS has risen. It is present in most of body’s tissues and in the local settings Angiotensin – II plays an important role as a growth factor in processes of inflammation and fibrosis (20).

Angiotensin-II receptor antagonists

There are two groups of medications that inhibit effects of Angiotensin – II: angiotensin-converting enzyme inhibitors (ACEi) and angiotensin – II receptor blockers (ARB). Both groups represent the class of antihypertensive medications and are used extensively. There is a big body of evidence that the field of action for these medications is much wider than lowering blood pressure alone. They also can provide end-organ protection, especially in patients with chronic kidney disease (21-23). In patients with ESRD the effects of these drugs were analyzed in a very few studies which had rather controversial outcomes (24-27).
**Aim and outline of the thesis**

Although evidence exist that support of the patient's life could be successfully done with either form of dialysis, in the majority countries in the world peritoneal dialysis has been always considered as a “second choice” therapy. There are lots of possible explanations for underutilization of PD, but relatively short technique survival when compared to hemodialysis (HD) is one of the most relevant. Recent experimental, animal and human studies suggested that in peritoneal dialysis patients inhibition of the Angiotensin-II effects can result in preservation of peritoneal membrane and residual renal function, and, therefore, positively influence the survival of PD technique. However, the results of these studies were often controversial and more investigations were required.

The aim of this thesis was to analyze effects of Angiotensin II inhibitors, ACEi and ARB, in long-term peritoneal dialysis patients and their possible impact on PD technique and patients’ survival.

In *Chapter 1* a short general introduction on the subject of the thesis is given.

*Chapter 2* is dedicated to the impact of ACEi/ARB on peritoneal membrane function in patients undergoing PD treatment from 2 to 4 years. Firstly, a single-centre study was performed which in detail investigated changes of the peritoneal transport of solutes and fluid over time with regard to use of AII inhibitors. Secondly, a database of the national multicenter prospective follow-up study NECOSAD was used to confirm the earlier found results on effects of ACEi/ARB on peritoneal transport as well as to analyze their impact on patients’ and technique survival.

*Chapter 3* deals with questions regarding the possible preservation of residual renal function in PD patients treated with ACEi/ARB. In order to find parallels with previously shown results the analysis was done with two different approaches: on a basis of an intention-to-treat and as treated.

In *Chapter 4* a review of data on effects of ACEi and ARB in patients with chronic kidney disease is given. The review was aimed to give a summary of today’s evidence on the use of these medications in nephrology with a particular focus on ESRD patients, treated with peritoneal dialysis.

In *Chapter 5* possible membranoprotective features of AII inhibitors against the development of encapsulating peritoneal sclerosis (EPS) are investigated.
In Chapter 6 reasons for PD technique failure and patients’ mortality are analyzed in a large number of incident patients with regard to 4 different time periods of PD treatment. Chapter 7 is a General discussion, in which the main findings together with controversial issues of the presented studies are summarized.

Reference List

Chapter 2

Effects of Angiotensin II inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients
The impact of ACE inhibitors and All receptor blockers on the peritoneal membrane transport characteristics in long-term PD patients

Inna Kolesnyk, Friedo W. Dekker, Marlies Noordzij, Saskia le Cessie, Dirk G. Struijk, and Raymond T. Krediet

Perit Dial Int, 2007; 27:446-453
Chapter 2. Effects of Angiotensin II inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients

ABSTRACT

**Background:** Long-term PD may lead to peritoneal fibrosis and ultrafiltration failure (UFF). The latter occurs due to high solute transport rates and diabetiform peritoneal sclerosis. Angiotensin-II is known to be a growth factor in fibrosis development and a number of animal studies have made it likely that inhibition of AII effects by ACE or ARB will attenuate these complications.

**Objective:** To investigate the effects of ACE/AII inhibitors in long-term PD patients.

**Patients and settings:** We analyzed data from 66 patients, treated with PD therapy at our center for at least 2 years, during which at least 2 standard peritoneal permeability analyses (SPA) were performed. 36 patients were treated with ACE/AII inhibitors-ACE/ARB group; the other 30 received none of the above drugs during the entire follow-up - controls. The two groups were compared with regard to the changes of peritoneal transport over follow-up time.

**Results:** A significant difference in time course of peritoneal transport was found between the two groups: in the ACE/ARB group small solute transport had decreased while it had increased in the controls. This finding was confirmed by analysis using mixed model for repeated measures: the value of mass transfer area coefficient (MTAC) of creatinine was influenced by the duration of PD therapy ($p = 0.017$) and this interaction was different with regard to use of ACE/AII inhibitors ($p = 0.037$). The trend was not found in protein clearances and fluid kinetics.

**Conclusion:** Our findings suggest that ACE/AII inhibition is likely to prevent the increase in MTACs that occurs in long-term PD, which is in line with results of animal experimental studies.
The impact of ACE inhibitors and All receptor blockers on the peritoneal membrane transport characteristics in long-term PD patients

Introduction

The initial survival advantage of peritoneal dialysis compared to hemodialysis changes to a disadvantage after long-term PD (1). This is likely to be due to loss of the residual GFR and development of peritoneal membrane alterations (2). These include fibrosis, neoangiogenesis and vasculopathy (2-4). Neoangiogenesis leads to a rapid disappearance of the osmotic gradient between blood and dialysate and thereby to ultrafiltration failure (5). The development of peritoneal alterations is mediated by growth factors of which vascular endothelial growth factor (VEGF) (6-9) and transforming growth factor beta (TGF-ß) are probably the most relevant ones (10-13).

ACE inhibitors and Angiotensin-II receptor blockers (ACE/ARBs) are frequently prescribed in PD patients, primarily for the control of hypertension or due to the heart failure. The last years it has become evident that Angiotension II (All) is an important growth factor in the development of renal fibrosis (14). Its stimulatory effects on synthesis of extracellular matrix proteins are likely to be mediated by TGF-ß (15;16). This may explain why treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin-II (A-II) receptor blockers was found to be renoprotective, especially in patients with diabetic nephropathy (17-19). Until shortly the renoprotective effects of ACE/ARBs were only evident in patients with mostly mild forms of renal insufficiency. Recently their renoprotective effect was also found in CAPD patients (20). Beneficial effects of ACE inhibitors on the development of morphological peritoneal alterations have been reported in experimental models (21;21;22;22). They showed decreased angiogenesis and fibrosis.

We hypothesized that long-term treatment with ACE inhibitors or All receptor blockers attenuates the peritoneal alterations that can develop in long-term PD patients. A randomized controlled trial is the best way to confirm or reject this hypothesis. However, given the other beneficial effect of ACE/ARBs this is hard for ethical reasons in countries where these drugs are available for everybody. A well-conducted cohort study is an alternative in this situation (23). The objective of the present study was therefore to compare the time course of peritoneal transport characteristics in PD patients who received the above drugs for treatment of hypertension, proteinuria or heart failure to those who did not. All patients were treated with PD for at least 2 years and had to have at least 2 standard peritoneal permeability analyses. The transport of low molecular weight solutes was considered to reflect the vascular peritoneal surface area.
Chapter 2. Effects of AngiotensinII inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients

**Patients and methods**

We selected our patients based on the following criteria: 1) PD as initial RRT for at least 2 years with therapy breaks for no more then 1 month, 2) the presence of at least 2 standard peritoneal permeability analyses (SPA), the first of which performed during first year on PD. SPAs are done routinely on a yearly basis. 3) The follow-up was limited to a maximum duration of 4 years (mean follow-up was 36 months). The selection procedure was as follows. From our database which contains data from all PD patients who were treated in the AMC from January 1st 1992 till January 1st 2005, we could select by an electronic query 57 patients who had been treated for at least two years. From those we had to exclude 9 patients because of interruption of PD therapy for more then 3 months, a PD interruption due to a failed transplant, age below 16 and the presence of less then two SPAs. The patients who had to be excluded were not different from the study population with regard to age (59 vs 59 y.o.), baseline blood pressure (138/80 vs 142/80 mmHg) and underlying renal disease. They had somewhat lower residual GFR at the start of PD (3.9 vs 5 ml/min) and an equal gender distribution, but none of these parameters differed significantly.

The remaining patients were in a stable clinical condition and free of peritonitis at and during 4 weeks before and 2 weeks after the test. It appeared that 36 patients had been treated with ACE/AII inhibitors for at least 20% of their follow-up time (ACE/ARB group), while 30 patients had never received them during the entire follow-up. These were considered the control group.

**Data collection**

All demographic and PD-therapy related data in the study were collected from the center’s electronic database DIAMANT. This database contains complete information per patient on comorbidity, residual renal function, medications, dialysis dose and peritonitis. Detailed data of the peritoneal transport assessment were taken from the individual SPA protocols.

**Standard permeability analysis**

Each SPA was performed during a four hour dwell under standardized conditions, as described previously. In brief: the peritoneal cavity was pre-rinsed using 1.36% glucose concentration dialysate. It was immediately drained after inflow was completed. Then a fresh 3.86% glucose dialysis (test) bag was instilled for a 4 hour dwell. To determine peritoneal
fluid kinetics including the residual volume, dextran 70 (Hyskon®, Pharmacia AB, Sweden), 1 g/L was added (24;25). The dialysate samples were taken before and at 10, 20, 30, 60, 120, 180 and 240 minutes after inflow of the test solution. To avoid the dead space effect, 100 to 200 ml were temporary drained before dialysate sampling. Immediately after drainage of the test solution at 240 minutes, the peritoneal cavity was rinsed again, with a 1.36% glucose solution that was drained directly after completion of inflow (rinsing bag). Blood samples were taken before and at the end of the test. After the first blood sample was taken, 20 mL of dextran 1 (Promiten®, Gynotec, Malden, the Netherlands) was administered intravenously to prevent possible anaphylaxis to dextran 70. The SPA provides information on the transport of low molecular weight solutes, proteins, sodium, fluid kinetics and effluent cancer antigen (CA) 125.

**Measurements**

The total dextran concentration in dialysate was measured by high performance liquid chromatography (26). Urea in plasma and effluent was determined with an enzymatic method on another automated analyzer (Hitachi H747, Boehringer Mannheim, Germany). The glucose concentration was determined by the glucose oxidase - peroxidase assay (SMA II, Technicon, Tarrytown, NJ, USA). Albumin, IgG and alpha2-macroglobulin were all measured by nephelometry (BN 100, Behring, Marburg, Germany) with commercial antisera (Dakopatts, Glostrup, Denmark). Beta2-microglobulin was determined with a microparticle enzyme immunoassay with an IMx system (Abbot Diagnostics, North Chicago, IL, USA). The mesothelial cell marker CA 125 was measured in the 4hr effluent of the SPA by means of a microparticle enzyme immunoassay using a monoclonal antibody against CA 125 (Abbot Laboratories IMx, IL, USA).

**Calculations**

Peritoneal transport and fluid transport parameters were calculated as described previously (24;25). Mass transfer area coefficients of low molecular weights solutes (MTAC) were calculated according to the Waniewski model (25;27;28). The percentage of peritoneal glucose absorption was calculated as the difference between the amount of glucoseinstilled and the amount recovered, related to the amount instilled x 100%.

The transcapillary ultrafiltration during the dwell was calculated by subtracting the initial intraperitoneal volume from the theoretical intraperitoneal volume at any time point.
when both, lymphatic absorption and the sampling, are neglected\(^{(26)}\). The changes in intraperitoneal volume arise from transcapillary ultra- and back-filtration, and lymphatic absorption. The changes in intraperitoneal volume during the dwell were calculated by the means of dextran dilution after correction for incomplete recovery\(^{(27)}\). Net ultrafiltration is the difference between the in-situ intraperitoneal volume and the initial i.p. volume.

Small pore fluid transport and free water transport were calculated in every patient using the convective transport of sodium, as described by Smit et al\(^{(29)}\). Correction for sodium diffusion from the circulation to the dialysate using the mass transfer area coefficient of urate was done according to Zweers et al\(^{(30)}\). Small pore and free water transport were calculated for the first 1 hour of the dwell time. Small pore transport was calculated by multiplying the theoretical intraperitoneal volume at the beginning and after 1 hour by the dialysate sodium concentration, corrected for diffusion. The time point 10 minutes after completion of inflow was taken as start value. By subtracting the amount of sodium at 10 minutes from the amount at 1 hour of a dwell, the quantity of sodium transported within first hour was calculated. The fluid transport through the small pores was computed by dividing the amount of transported sodium with the sodium concentration in small pores, which is the average of the plasma and the dialysate sodium concentration. Afterwards the amount of small pore fluid transport after 1 hour was subtracted from the total fluid volume ultrafiltered during mentioned time, resulting in free water transport within the first hour. The free water transport and the small pore transport are expressed as absolute values.

The residual glomerular filtration rate (\(rGFR\)) was calculated as the mean of 24 hour creatinine and urea clearance, and corrected for body surface area. The amount of used solutions with 3.86% glucose concentration was calculated from the delivery records of the local suppliers. Peritonitis incidence was expressed as the absolute number of episodes per patient, divided by the duration of follow-up.

**Statistical analysis**

Results are expressed as means and standard deviations unless stated otherwise. Appropriate statistical tests (t-test, Mann-Whitney, Chi-square) were used for comparisons between the various baseline characteristics.

Different approaches were used to analyze the transport data. First, comparisons of the mean MTAC creatinine values between the first and last available SPA tests were performed using the paired and unpaired t-test. To account for repeated observations in the same pa-
tients, we used a linear mixed models with unstructured covariance matrix to analyze the effect of treatment and time (1, 2, 3, 4 years as factor), as well as an interaction between these two, on the MTAC creatinine.

Statistical analyses were performed by using SPSS statistical software, version 12.0 (SPSS, Inc., Chicago, Illinois). P values less than 0.05 were considered significant.

**Results**

The demographic data of the patients are given in Table 1. The two groups were similar for most parameters with the exception of glomerulonephritis as primary kidney disease (lower in ACE/ARB group) and the number of antihypertensive medications (higher in the ACE/ARB group). The mean time period of using ACE/ARBs in the ACE group was 66% (±28%) of follow-up time. We expressed these data in percentage for reader's convenience, as follow-up time ranged from 2 to 4 years. Peritonitis incidence was 0.08 (±0.07) episodes/patient/follow-up months in both groups. No difference between the groups was found with regard to residual GFR: at the start for both groups its median value was 5 ml/min (Table 1) and at the end of follow-up vast majority of patients from both groups lost their rGFR completely (data not shown). In order to estimate an approximate glucose exposure we calculated the number of exchanges with 3.86% glucose solutions during the entire follow-up: the patients from ACE/ARB group on average had 20% of exchanges with highest glucose concentration per month while controls had 12% (p=0.1).

The changes of transport characteristics for small solutes and fluid between the first and last available SPA are shown in Table 2 and Table 3. The MTACs of urea, creatinine and urate, obtained during the initial SPA, were higher in the ACE/ARB group compared to the controls. No differences between the two groups were found for the last SPA. During follow-up a decrease was found in the ACE/ARB group for all parameters of solute transport, while it was absent in the controls. Consequently, the delta MTAC (last minus first SPA) was significantly lower in the ACE/ARB group than in the controls. Figure 1 shows the differences for MTAC creatinine in the two groups. No difference was found in the protein clearances (data not shown) and fluid kinetics (Table 3), except for a borderline decrease in small pore fluid transport during the follow-up in ACE/ARB group.
Table 1: Baseline patient characteristics.

Numerical data are given as medians and ranges.

<table>
<thead>
<tr>
<th></th>
<th>ACE/ARB</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>Age</td>
<td>58(25-86)</td>
<td>60(23-83)</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>23/13</td>
<td>17/13</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>36(24-49)</td>
<td>36(25-51)</td>
</tr>
<tr>
<td>Primary kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>3</td>
<td>11*</td>
</tr>
<tr>
<td>Renovascular nephropathy</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Blood pressure at the start (mmHg)</td>
<td>142/80</td>
<td>140/81</td>
</tr>
<tr>
<td>PD technique at the start (CAPD/APD)</td>
<td>28/8</td>
<td>22/8</td>
</tr>
<tr>
<td>Residual GFR at the start (ml/min)</td>
<td>4.6(0-10)</td>
<td>4.7(0-11)</td>
</tr>
<tr>
<td>Number of antihypertensive drugs at the start</td>
<td>2.3(0-4)</td>
<td>1.2(0-4) **</td>
</tr>
<tr>
<td>No drugs</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>ACE/ARBs only</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Other antihypertensives only</td>
<td>10 ²</td>
<td>21</td>
</tr>
<tr>
<td>ACE/ARBs and other</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

* - p = 0.05  
** - p < 0.001  
1 - The drugs combinations are given in exact numbers  
2 - ACE/ARBs were not given at baseline but during follow-up
Table 2. A comparison between longitudinal changes in peritoneal transport of small solutes in the period between the first and last standard permeability analyses.

Data presented as means ± standard deviations. Comparisons were made within the groups, (significant differences shown by letter index) and between the groups (p-values presented in the table).

<table>
<thead>
<tr>
<th></th>
<th>ACE/ARB</th>
<th>Controls</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial MTAC Ur, (mL/min)</td>
<td>20.5±4.7</td>
<td>17.8±3.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Last MTAC Ur, (mL/min)</td>
<td>18.5±3.9 b</td>
<td>18.7±4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Δ MTAC Ur, (mL/min)</td>
<td>-1.8±4.9</td>
<td>+0.8±4.9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ACE/ARB</th>
<th>Controls</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial MTAC Cr, (mL/min)</td>
<td>11.3±3.4</td>
<td>9.6±9.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Last MTAC Cr, (mL/min)</td>
<td>9.8±2.7 a</td>
<td>10.6±4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Δ MTAC Cr, (mL/min)</td>
<td>-1.5±3.4</td>
<td>+1.03±4.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ACE/ARB</th>
<th>Controls</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial MTAC Urate, (mL/min)</td>
<td>9.2±3.1</td>
<td>7.4±2.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Last MTAC Urate, (mL/min)</td>
<td>7.9±2.5 c</td>
<td>8.4±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Δ MTAC Urate, (mL/min)</td>
<td>-1.2±3.0</td>
<td>+1±4.0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ACE/ARB</th>
<th>Controls</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Glucose abs, (%)</td>
<td>63±</td>
<td>59±</td>
<td>NS</td>
</tr>
<tr>
<td>Last Glucose abs, (%)</td>
<td>58± a</td>
<td>59±</td>
<td>NS</td>
</tr>
<tr>
<td>Δ Glucose abs, (%)</td>
<td>-5±</td>
<td>0±</td>
<td>NS</td>
</tr>
</tbody>
</table>

a p=0.01, b p=0.03, c p=0.02

Abbreviations: MTAC: mass transfer area coefficient; Δ: delta; Ur: urea; Cr: creatinine; Glucose abs: glucose absorption.
Table 3. *A comparison between longitudinal changes in peritoneal transport of fluids between the first and last standard permeability analyses.* Data presented as medians and ranges. Comparisons made within the groups (significant differences shown by letter index) and between the groups (p-values presented).

<table>
<thead>
<tr>
<th>Group</th>
<th>ACE/ARBs</th>
<th>Controls</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Net UF, (mL/4h)</td>
<td>677 (326 to 1114)</td>
<td>699 (23 to 1709)</td>
<td>NS</td>
</tr>
<tr>
<td>Last Net UF, (mL/4h)</td>
<td>669 (24 to 1393)</td>
<td>669 (171 to 1240)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ Net UF, (mL/4h)</td>
<td>+8 (-532 to 832)</td>
<td>-39 (-600 to 479)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial SPT 0-60, (mL)</td>
<td>445 (126 to 647)</td>
<td>296 (150 to 412)</td>
<td>NS</td>
</tr>
<tr>
<td>Last SPT 0-60, (mL)</td>
<td>260 (32 to 539) a</td>
<td>240 (59 to 579)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ SPT 0-60, (mL)</td>
<td>-150 (-568 to 311)</td>
<td>-17 (-851 to 303)</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Initial FWT 0-60, (mL)</td>
<td>141 (98 to 242)</td>
<td>137 (61 to 238)</td>
<td>NS</td>
</tr>
<tr>
<td>Last FWT 0-60, (mL)</td>
<td>151 (2 to 300)</td>
<td>160 (44 to 277)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ FWT 0-60, (mL)</td>
<td>6.5 (-215 to 192)</td>
<td>23 (-142 to 94)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial FWTC 0-60, (%)</td>
<td>26 (15 to 64)</td>
<td>31 (9 to 61)</td>
<td>NS</td>
</tr>
<tr>
<td>Last FWTC 0-60, (%)</td>
<td>37 (8 to 55)</td>
<td>38 (17 to 82)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ FWTC 0-60, (%)</td>
<td>14 (-40 to 36)</td>
<td>9 (-26 to 46)</td>
<td>NS</td>
</tr>
</tbody>
</table>

a p < 0.0001

Abbreviations: Net UF: net ultrafiltration; SPT: small pore transport; FWT: free water transport; FWTC: free water transport contribution.
The impact of ACE inhibitors and ARB receptor blockers on the peritoneal membrane transport characteristics in long-term PD patients

Results of mixed model analysis for repeated measures which shows the time course of MTAC creatinine including its values from all available annual SPAs are graphically displayed in Figure 1. This analysis showed a significant influence of year of follow-up (number of SPA) on the value of MTAC creatinine ($p=0.017$). There was a significant interaction between year of follow-up and the patient group ($p=0.037$), which implies that the SPA pattern over time differs significantly between the two groups. From the model, the estimated mean MTAC creatinine was $9.57 \text{ mL/min}$ (95% confidence interval (CI) 7.7 to 11.3 mL/min) at 4 years on PD in the ACE/ARB group and $12.17 \text{ mL/min}$ (95% CI, 10.3 to 14.1 mL/min) in the control group. Also no significant difference was found with regard to drop-outs after the 3d year of follow-up (19 vs 15 patients). The drop-out reasons appeared not to be significantly different as well, though ACE/ARB group had more deaths and transplantations, but controls more often had been transferred to hemodialysis. The effluent concentration of CA-125 was similar in both groups and followed same pattern – a significant decrease over follow up time (Figure 2).

![Figure 1. MTAC creatinine changes during follow-up time, estimated by linear mixed model for repeated measurements. The number of patients in the ACE/ARB group was 36 at 1st year, 31 at 2nd year, 34 at 3d year and 17 at 4th year. The respective values for the controls were 30 at the 1st, 2nd and 3d years, and 15 at the 4th year of follow-up.](image-url)
Concern about the alterations in peritoneal membrane morphology and function, which can develop during peritoneal dialysis, motivates to search for prevention. The results of our study have shown that ACE inhibitors and Angiotensin II receptor blockers are likely to have a membranoprotective effect: they prevent the increase in small solute transport that often occurs in long-term PD\(^{(31)}\), and that is probably related to a larger number of perfused peritoneal microvessels\(^{(2;4)}\). These findings are in accordance with the results of some experimental studies, showing a lower number of peritoneal blood vessels and less fibrosis than without administration of these drugs\(^{(22;32)}\). Taking to account that ACE/ARB are mostly prescribed for blood pressure regulation and never for their possible membranoprotective effects, the administration of these drugs can be considered a random process and thereby increasing the evidence value of the results\(^{(23)}\).

We selected our patients based on the duration of PD, which had to be at least 2 years, the availability of one SPA during the first year and at least one SPA thereafter. This was done because the long-term changes in peritoneal function do not occur during the first few years on PD. Furthermore we wanted to study a population without early drop-outs which happened for other reasons.

Previous clinical studies in PD patients investigated short-term effects of ACE inhibitors
The impact of ACE inhibitors and Ang II receptor blockers on the peritoneal membrane transport characteristics in long-term PD patients

on blood pressure and membrane transport after oral and/or intraperitoneal administration (33-37). The results of membrane transport were inconclusive. To the best of our knowledge, the present study is the first analysis of long-term effects of ACE/ARB treatment on prospectively collected peritoneal transport data. These drugs were mainly prescribed for hypertension, proteinuria or heart failure but never for protection of the peritoneal membrane. Consequently, their use can be regarded as a random assignment concerning peritoneal morphology and function. This may explain that the two groups were similar for the most parameters with the exception of glomerulonephritis as primary kidney disease and the number of antihypertensive drugs at the start of PD. Factors that might influence the development of high solute transport rates are recurrent peritonitis (38) and the cumulative peritoneal glucose degradation products exposure (31). Peritonitis incidence was similar in the two groups, but the CAPD patients of the ACE/ARB group tended to use a larger percentage of 3.86% glucose solutions. Therefore, a marked increase in small solute transport could be expected in them. However, the opposite was found. This suggests a protective effect of ACE/ARB treatment on the peritoneal membrane.

The changes over time we found for the MTAC creatinine were also present for MTAC urea and MTAC urate. In the ACE/ARB group the peritoneal glucose absorption also showed a decrease during follow-up. No effect could be detected on the transport of macromolecules. The most likely explanation is that their transport is not only dependent on the vascular peritoneal surface area but also on the intrinsic permeability. Parameters of fluid transport were not different between the two groups with the exception of small pore fluid transport: it decreased more in the ACE/ARB group than in the controls. Small pore fluid transport is to a large extent dependent on the hydrostatic pressure gradient. We do not know whether this decreased more ACE/ARB group than in the controls.

With regard to the rate of decline of residual GFR our findings differ from those shown before by Li et al (20). The most likely explanation is the fact that our study is not a randomized controlled trial and therefore the influence of various confounding factors (e.g. more use of antihypertensives in ACE/ARB group, etc. as well as duration of follow-up in mentioned RCT was limited to one year) might have influenced the outcome. Beside the difference in design, in the study of the Hong Kong group a different analysis was performed for the changes in rGFR.
The MTAC creatinine was analyzed in more detail, using the values of all SPAs in the mixed linear model for repeated measurements. It confirmed that the changes in small solute transport are time dependent and different with regard to the use or non-use of ACE/ARB. It also showed that the time course of MTAC creatinine is not a straight line, but follows a “U”-shape profile. Such a “U”-shape has been reported by us previously (39) and was especially present in the control group.

It can be concluded that the present study has shown evidence that the normal time course of peritoneal small solute transport is influenced by the use of ACE/ARB. It suggests protection for the development of an enlargement of the peritoneal vascular surface area. These findings and results are in accordance with those in long-term animal models. Although not proven, our findings suggest that ACE/AII inhibition in patients with the applied selection criteria can prevent the increase of small solutes MTACs that often occurs in long-term PD.

Reference List

Chapter 2. Effects of Angiotensin II inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients


Chapter 2. Effects of Angiotensin II inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients
A positive effect of All-inhibitors on peritoneal membrane function in long-term PD patients

Inna Kolesnyk, Marlies Noordzij, Friedo W. Dekker, Elisabeth W. Boeschoten and Raymond T. Krediet

Nephrol Dial Transplant 2009; 24:272-277
ABSTRACT

Background: Experimental studies showed that inhibition of AII effects attenuates the development of peritoneal membrane fibrosis and neoangiogenesis. The latter leads to increase of peritoneal solute transport and ultrafiltration failure. The results of a single-center study showed that use of ACEI/ARB can prevent the increase of small solute transport in long-term PD patients. Our aim was to investigate whether these results would also be present in larger population and influence patients and technique survival in long-term PD.

Methods: We analyzed data from 217 long-term CAPD patients, participating in the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). Included patients underwent CAPD therapy for at least 2 years; 120 of them were treated with ACE/AII inhibitors-ACEI/ARB group. The control group consisted of 87 patients who received none of the above drugs and 10 patients who had them for less than 25% of their time on PD.

Results: A significant difference in the time course of peritoneal transport was found between the two groups. The value of 24 hour D/P creatinine was associated with the PD duration (p = 0.01) and its time course was influenced by use of ACEI/ARB (p = 0.05). We found no effect of ACEI/ARB on patient survival, but some benefit was found for the technique survival: in a multivariate model the hazard ratio for the group with the longest use of ACEI/ARB was 0.5 (CI 0.22 to 1.4), p = 0.19.

Conclusion: We conclude that AII inhibition prevents the increase in small solute transport in long-term PD. These drugs may also have some positive influence on PD technique survival.
**Introduction**

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) are used extensively in patients with renal diseases because of their beneficial effects on the cardiovascular system, their ability to reduce proteinuria and influence the time course of the decline in GFR in patients with various forms of glomerulopathies [1,2]. The latter is likely due to the fact that angiotensin II (AII) has properties of a growth factor [3]. That explains an ability of AII inhibitors to attenuate development of renal fibrosis [4], predominantly by suppressing the activity of transforming growth factor-ß (TGF ß) [5].

The fibrotic and diabetiform vascular alterations that can be found in long-term peritoneal dialysis (PD) patients [6,7] are likely to be mediated by TGF ß and vascular endothelial growth factor (VEGF) [8,9]. This has focused interest on the possibility to use ACEI/ARB to influence these membrane changes. In vitro studies using cultured mesothelial cells showed that AII mediates the upregulation of TGF ß, induced by high glucose exposure [10]. Another study found that ACEI/ARB suppressed the production of vascular endothelial growth factor (VEGF) [11]. Earlier experimental studies have shown that ACE inhibitors had a positive impact on the development of peritoneal membrane morphological alterations such as fibrosis and neoangiogenesis [12].

To our knowledge, there are no studies other than the ones done by our group, which focused on long-term effects of ACEI/ARB in humans, treated with PD. We reported previously about effects of AII inhibitors on peritoneal membrane function in long-term PD patients in a single-center study [13]. The major finding was a different time course of small solute transport during the first 3 to 4 years of PD treatment. Patients receiving ACEI/ARB showed a slight decrease of the mass transfer area coefficient (MTAC) of creatinine. This was different from the controls in which an increase with time of treatment was found. It suggested inhibition of peritoneal angiogenesis. Therefore, these findings were in accordance with the results of the animal studies.

Although detailed information on various aspects of peritoneal transport changes over time was obtained, it was impossible to analyze effects of ACEI/ARB on PD technique and patient survival due to the relatively small number of patients. For this purpose, and also for the confirmation of our previous results in a larger patient group, we studied the CAPD population of the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). Being focused mostly on long-term effects of the drugs, we excluded cases with early drop-outs and included only patients who had been treated with CAPD for 2 years.
Patients and methods

Patients

For the current analyses we have selected patients from the database of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). This is a large prospective multicentre cohort study which contains data of incident dialysis patients from 38 dialysis units in the Netherlands. To be included into the study a patient needed to be at least 18 years old and should have started renal replacement therapy with either form of dialysis. Afterwards patients are followed as long as dialysis treatment continues.

Our study’s inclusion criteria were the following: patients had to start renal replacement therapy with continuous ambulatory peritoneal dialysis (CAPD) and remain on it for at least 2 years with breaks in therapy for not more than 3 months. Besides, patients needed to follow the standard CAPD prescription with a minimum of 8 liters and a maximum of 10 liters of dialysis fluid per day with 4 - 5 exchanges. Out of the NECOSAD database we selected all incident patients who had started renal replacement therapy with PD in the period between January 1 1997 and June 2006 and remained on PD for the next 3 months. 617 patients were found, 500 of which stayed alive on PD for at least a year. Out of these 500 patients 321 were treated with CAPD for at least 1 year, the other 179 were excluded because they were treated with either automated or nightly intermittent peritoneal dialysis. The following year 104 CAPD patients had stopped their PD treatment due to transfer to hemodialysis (28), receiving a kidney transplant (40), death (25) and other reasons (12). The other 217 patients remained on CAPD after 2 years of treatment and were included into the study.

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, use of antihypertensive medications, residual renal function and 4 hour D/P creatinine ratios were collected at 3 and 6 months after start of dialysis. Afterwards data were collected on a half yearly basis.

Primary kidney disease was classified according to the codes of the European Dialysis and Transplant Association – European Renal Association Registry. Comorbidity was scored on the basis of Davies’ comorbidity index. 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 cerebral-vascular accident.
Residual renal function was expressed as residual glomerular filtration rate (rGFR) and was calculated as mean of creatinine and urea clearance, corrected for body surface area (ml/min/1.73m²).

Peritoneal transport characteristics could be assessed by the dialysis adequacy and transport test (DATT) [14]. In this test the dialysate/plasma creatinine (D/P creatinine) is calculated from a 24-hour dialysate collection. The DATT provides reliable results in CAPD patients, but not in those on APD [15]. For this reason the current analysis had to be restricted to the CAPD population. If the CAPD treatment with a standard regime was interrupted (e.g. number of exchanges/volume was raised/lowered) or the patient completely switched to APD – such D/P values were treated as missing. There were 38 patients from ACEI/ARB group and 36 from controls who had switched to other PD regimens during the follow-up period. Such therapy changes could have been temporary or permanent. In total we excluded up to 30% of D/P creatinine values, which ranged from 15 to 25% per check-up time point. The number of excluded values was not different between the groups.

The number of patients using icodextrin for the long dwell was documented at every time point and also the mean glucose concentration of the dialysis solutions used was calculated. The use of ACEI/ARB was documented “yes” or “no” at every check-up time point (see above). In case when “yes” was indicated, the patient was considered to have used the medication during the period, preceding the check-up. We expressed the use of ACEI/ARB as percentage of the patient’s follow-up period, because the latter varied from 2 to 4 years.

Statistical analysis
To compare patients’ baseline characteristics we used standard descriptive statistics. Results are expressed as means and standard deviations as well as medians and ranges in case of non-normal distribution. Reasons for PD drop-out were explored with the chi-square test.

To analyze the time course of D/P creatinine in relation to exposure to the drugs, we used a generalized linear mixed model for repeated measures. The generalized linear mixed model method was applied to take into account the correlation between repeated measurements (DATT) within the same patient. The random effects mixed model with unstructured covariate matrix was applied to test the interactions between variables. The multivariate model contained 24h D/P creatinine as dependent variable and treatment group and the number of DATTs as independent variables. The independent variables were first analyzed separately, and then with an interaction.
To investigate whether there is an effect of ACEI/ARB on the rate of decline of residual GFR we performed a linear mixed model which is described above.

Statistical analyses of patients’ and PD technique survival were performed by the Cox proportional hazards model. In the analysis of patient survival the event was death during PD treatment period, while transplantation and other reasons for PD drop-out were censored observations. For the analysis of technique survival the event was transfer to hemodialysis and censored observations were death, transplantations and loss to follow-up.

In both patients’ and technique survival models adjustments were made for a number of possible confounding effects as well as for some differences in baseline characteristics between the groups. These included age, gender, diabetes, cardiovascular comorbidity and mean arterial blood pressure at the start of dialysis.

All statistical analyses were performed using SPSS statistical software, version 12.0 (SPSS Inc., Chicago, Illinois, USA). A p-value of 0.05 or less was considered significant.

Results

Patients and baseline characteristics

217 CAPD patients were included into the study. It appeared that 120 patients were treated with ACE/AII inhibitors (ACEI/ARB) for at least 25% of their follow-up time and 87 patients did not receive these drugs during the entire follow-up. Ten patients received the drugs for less than 25% of the follow-up period and used them mostly at the start of PD. We considered it a minor use of the medications and added these patients to the controls in order to have the more equal groups regarding the number of patients. The control group consisted of the 87 patients without any ACEI/ARB treatment and the 10 patients who used them for less than 25% of time – 97 patients in total.

Data on demography, primary kidney disease, comorbidity and other baseline characteristics are given in Table 1. Patients on the ACEI/ARB were younger and had a higher prevalence of cardiovascular disease. They also had a higher blood pressure and used more antihypertensive medications at the start of PD treatment.

To study the effect of duration of exposure to the drugs, the ACEI/ARB group was also divided into 2 subgroups - patients treated with the drugs for more than 75% of their follow-up time – 1st group (59 patients) and those treated with ACEI/ARB from 25 to 75% of the follow-up – 2nd group (61 patients). Controls remained the same. Demographical and baseline data of the 3 groups are not given separately, but the group with longest exposure to ACEI/ARB had the highest cardiovascular comorbidity.
**Table 1:** Patients’ baseline characteristics. Numerical data are given as means ±SD and as medians with ranges, unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>ACEI/ARB</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>120</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50(20-78)</td>
<td>55(20-78)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>70</td>
<td>58</td>
<td>0.06</td>
</tr>
<tr>
<td>Primary kidney disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>17</td>
<td>11</td>
<td>0.3</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>23</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Renovascular nephropathy</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>47</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiovascular comorbidity</td>
<td></td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Davies comorbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidity</td>
<td>60</td>
<td>65</td>
<td>0.3</td>
</tr>
<tr>
<td>Moderate comorbidity</td>
<td>30</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Severe comorbidity</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Blood pressure at the start (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>148 (±25)</td>
<td>143 (±23)</td>
<td>0.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87 (±13)</td>
<td>83 (±11)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean</td>
<td>108(±15)</td>
<td>103(±13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Residual GFR at the start (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5(±4.3)</td>
<td>3.7(±2.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of antihypertensives at the start ( %)</td>
<td>92</td>
<td>80</td>
<td>0.007</td>
</tr>
</tbody>
</table>

1 percentage of patients treated with antihypertensive medications at the start of CAPD therapy.
The percentage of glucose in the PD solutions used by the patients per every time point was not different among the groups. Also the number of patients who used icodextrin during the follow-up was similar (data not shown).

Figure 1. Time course of 24-hour D/P creatinine, estimated by a linear mixed model for repeated measures. Data shown for 2 groups (a) and 3 groups (b) analyses. The number of patients in the ACEI/ARB group was 120 at 1st year and 2nd year, 64 at 3rd year and 36 at 4th year. The respective values for the controls were 97 at the 1st and 2nd year, 44 at 3rd year and 28 at the 4th year of follow-up.
**Peritoneal transport**

The number of patients values of D/P creatinine per time point of measurement, included for the analyses was not different between the groups. The analysis showed a significant influence of time (year of follow-up) on the D/P creatinine curves ($p = 0.01$) (Figure 1). It also showed a significantly different time course of D/P creatinine for the two study groups (Figure 1a), $p = 0.05$. The subanalysis of the three groups showed that the group with the longest use of ACEI/ARB had the lowest D/P creatinine ratios during the follow-up, $p = 0.1$ (Figure1b).

**Mortality**

The mean follow-up period was 3 years (range 2 to 8 years). Forty-eight patients died, seventy-eight received a kidney transplant and thirty-nine were transferred to hemodialysis. Fifty-two patients were lost to follow-up due to various reasons (refusal to participate, transfer to another center, etc.) or still continuing PD treatment at the time of censoring. Table 2 presents the reasons for PD drop out for the two groups separately. None of the differences was significant. Also no effects were found in three groups’ analysis (data not shown).

**Table 2.** Reasons for drop-out from PD (data given in exact numbers).

<table>
<thead>
<tr>
<th>Reason for drop-out</th>
<th>ACEI/ARB</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer to HD</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Transplantation</td>
<td>48</td>
<td>30</td>
</tr>
<tr>
<td>Death</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Other$^1$</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Continuing PD$^2$</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

$^1$includes loss to follow-up (transfer to another center, refuse to participate by patient /or center, etc); $^2$continuing PD treatment after date of censoring.

None of the differences was significant.
No effect on patient survival was found between the ACEI/ARB and control group. In the univariate Cox proportional hazard model the relative risk of death (Hazard Ratio, HR) for the ACEI/ARB group was 1.03 (95% Confidence Interval (CI) 0.5 to 1.8). After adjustment for age, sex, cardiovascular comorbidity, diabetes and mean arterial blood pressure at baseline, the HR was 1.1 (95% CI 0.6 to 2.2). In the three groups analysis, the relative risk of death for group1 (ACEI/ARB >75%) was 0.9 (95% CI 0.4 to 2.1) and for group2 (ACEI/ARB 25-75%) 1.2 (95% CI 0.6 to 2.7). Age and the presence of cardiovascular comorbidity were found to be significant predictors of death.

PD technique survival

Figure 2. PD technique survival for the 3 groups of patients.

Technique survival
We found some positive effect of ACEI/ARB on PD technique survival, although statistical significance was not reached, p = 0.19 (Figure 2). Patients who received ACEI/ARB for the
longest duration tended to have the best PD technique survival and controls did the worst (Table 3). No difference was found between the two groups in the reasons for transfer to HD.

**Table 3.** Unadjusted and adjusted hazard ratios for PD technique survival (results of 3 subgroups analysis).

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard ratio (95% CI)</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB &gt;75% vs controls</td>
<td>0.65 (0.2 to 1.4)</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB 25-75% vs controls</td>
<td>0.77 (0.3 to 1.6)</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB &gt;75% vs controls</td>
<td>0.5 (0.22 to 1.4)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease.</td>
</tr>
<tr>
<td>ACEI/ARB 25-75% vs controls</td>
<td>0.8 (0.3 to 1.9)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease.</td>
</tr>
<tr>
<td>ACEI/ARB &gt;75% vs controls</td>
<td>0.64 (0.23 to 1.7)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease + baseline rGFR.</td>
</tr>
<tr>
<td>ACEI/ARB 25-75% vs controls</td>
<td>0.75 (0.31 to 1.7)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease + baseline rGFR.</td>
</tr>
</tbody>
</table>

**Decline of residual GFR**

We found no difference between the two groups with regard to the rate of decline of residual GFR (Figure 3).

**Discussion**

The results of the present study have shown that treatment with ACEI/ARB in CAPD patients may prevent or retard the increase in D/P creatinine that often occurs during long-term
peritoneal dialysis\textsuperscript{[16]}. As $D/P$ creatinine is dependent on the vascular peritoneal surface area, the data suggest less peritoneal angiogenesis than in those who did not receive ACEI/ARB. Our results are in line with those of a smaller single center analysis in a different patient population, using mass transfer area coefficients during a standardized peritoneal permeability analysis\textsuperscript{[13]}. The suggestion of less neoangiogenesis during ACEI/ARB supports the findings in animal models\textsuperscript{[12]}. These showed a beneficial effect on the number of peritoneal vessels and on the amount of fibrosis.

Protection of the peritoneal membrane has never been the reason for prescribing ACEI/ARB. The common indications were applied such as hypertension or heart failure. Two studies on a beneficial effect of ACEI/ARB on the time-course of residual renal function in a selected population of incident PD patients have been published in 2003-2004\textsuperscript{[17, 18]}. The inclusion of patients in our study ended in 2003. Therefore, preservation of rGFR is highly unlikely to

Figure 3. Time course of residual GFR, estimated by a linear model for repeated measures.
A positive effect of All-inhibitors on peritoneal membrane function in long-term PD patients

have been a reason to prescribe ACEI/ARBs in our cohort. As such the use of these drugs can be considered as a random process with regard to the peritoneal membrane and residual renal function preservation. However, a formal randomized controlled trial (RCT) with a sufficiently long follow-up period would be the approach to confirm or reject the hypothesis that All-inhibitors have a peritoneal protective effect. Yet, this may also be subject to a bias, at least in countries where these drugs are available for everyone who needs them. In case of exclusion of patients who have generally accepted indications for ACEI/ARB treatment, there is a risk to end up with highly selected group of randomized patients. In such a situation, when an RCT is not possible to perform or may be inadequate, the results of a properly controlled observational cohort study can give valuable conclusive information.

Duration of PD for at least 2 years was required to be included in the present study. This is different from other studies performed in PD patients that were all short term and focused on effects of ACEI/ARB on blood pressure and peritoneal clearances, as discussed in [13]. The results of these investigations on the peritoneal transport were inconclusive. The reason to restrict the study to patients having completed 2 years was our objective to study long-term peritoneal changes and the fact that these do not occur before 3 to 4 years on peritoneal dialysis.

We also excluded patients who were not treated with a standard CAPD regimen. The reason for that is the use of the DATT. This parameter is influenced by the dialysis volume and by the dwell time. For instance, large volumes and short dwell times, as often used in automated peritoneal dialysis (APD), will give low values for 24 hour D/P creatinine. Therefore the volumes and the dwell times had to be standardized to some extend (see methods). We do not think that excluding the various forms of APD has influenced the results of our study, because no data are available suggesting that the time course of peritoneal transport would be different in CAPD and APD.

Our study enabled us to analyze patient and technique survival. For patient survival it is important that some differences were present between the ACEI/ARB group and controls. Patients on ACEI/ARB were younger, had more cardiovascular comorbidity, higher blood pressure and a greater proportion of them used antihypertensives. This reflects the common indications for the prescription of these drugs. Taking these risk factors into account one can presume that patients who received ACEI/ARB would have a higher mortality risk than the controls. However, both in the unadjusted and the adjusted analyses neither a negative nor a positive effect on patient survival was found. It may be that the higher comorbidity...
counteracted a potential positive effect of ACEI/ARB on patient survival.

Analysis of PD technique survival indicated some positive effect of ACEI/ARB, which was mainly present for the group who received the drugs for at least 75% of the follow-up. After correction for age, gender, diabetes, blood pressure and cardiovascular disease, the effect was even stronger. We found no influence of baseline rGFR. We also did not find any effect of the drugs on the rate of decline of rGFR which is different from the results of the earlier studies [17,18]. It should be noted, however, that both studies were RCTs with a highly selected patient population like a low cardiovascular comorbidity and a short follow-up. A favorable effect of ACEI/ARB on residual GFR might be different in a cohort with higher comorbidity and a long-follow-up.

It can be concluded that ACEI/ARB prevents the increase of small solute transport that often takes place in long-term PD. This is in line with some experimental study results and with our previous finding obtained in a single-center study. Besides, the results of the current study also suggest that a membranoprotective effect of AII inhibitors may positively influence PD technique survival in long-term patients.

Reference list

Chapter 2. Effects of AngiotensinII inhibitors on peritoneal membrane function, patients’ and technique survival in long-term peritoneal dialysis patients
Chapter 3

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

Inna Kolesnyk, Marlies Noordzij, Friedo W. Dekker, Elisabeth W. Boeschoten and Raymond T. Krediet

Perit Dial Int, in press
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 glomerular 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 5% 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 \(^1\text{–}^3\). Better preserved RRF is associated with less comorbidity \(^4\text{–}^6\), 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 \(^9\text{–}^11\). 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 glomerular 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 (β-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 &lt;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.

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

¹percentage of patients with the comorbidity conditions existing prior to PD initiation.
²percentage 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, \( p = 0.52 \).

![Graph showing unadjusted and adjusted curves for rGFR decline.](figure1.png)

**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/1.73m²). 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.

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

1percentage of patients with the comorbidity conditions existing prior to PD initiation.
2percentage 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).

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 11 patients 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/1.73m²(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.
Reference List


All inhibitors and residual renal function in long-term PD patients


Chapter 4

Effects of Angiotensin-converting enzyme inhibitors and Angiotensin II receptor blockers in patients with chronic kidney disease

I. Kolesnyk, D.G. Struijk, F.W. Dekker and R.T. Krediet

Neth J Med, in press
ABSTRACT

Since about three decades inhibitors of the Renin - Angiotensin system are available in clinical practice. Although Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARB) were primarily aimed for treatment of hypertension and heart failure, more of their positive effects were discovered later on. Patients with chronic kidney disease were recognised to profit the most from treatment with these agents; however, some blind spots are still present. Patients with advanced renal failure are almost always excluded from the trials, patients with ESRD are the least studied population of all and outcomes of treatment with ACEi/ARB are still uncertain in these cohorts. The aim of this review is to summarise and update the evidence about effects of AII inhibitors in patients with chronic kidney disease with the specific emphasis on patients treated with dialysis. Lately a novel approach for ACEi/ARB administration especially for PD patients has been proposed. It is based on their capacity to inhibit local tissue renin-angiotensin system which results in less peritoneal fibrosis development and longer life of the peritoneal membrane.

The most recent available data are presented in this review.
Controlling hypertension

Hypertension is the major risk factor in developing and progression of non-diabetic and diabetic chronic kidney disease (CKD). Currently the prevalence of hypertension in the general population is about 1 billion people worldwide and a further rise is predicted for a near future. Development of hypertension is highly associated with older age (over 60 years), non-Hispanic black race and body mass index $\geq 30$. In order to prevent end-organ damage and development of major cardiovascular events, blood pressure (BP) should be well-controlled. However the current situation is far from being optimal worldwide, especially in CKD patients. In patients with existing nephropathy the goal of hypertension management involves not only cardiovascular protection by lowering BP to the appropriate level, but also slowing the progression of kidney disease. The latter often includes management of proteinuria, which is itself associated with both the risk of cardiovascular disease and progression to end-stage renal disease. Therefore a choice for an appropriate antihypertensive agent is of a great importance for patients with CKD.

An increase in the renin-angiotensin-aldosterone activity is one of the major factors involved in the hypertension in patients with CKD. Angiotensin II is known to mediate systemic haemodynamic changes as well as ones in intra-renal circulations. Moreover, this hormone has been recognised to play a key-role in sustaining proteinuria and progression of kidney disease. Therefore, inhibiting effects of angiotensin II (AII) and lowering blood pressure with drugs that block the renin-angiotensin system (RAS) is a major component of CKD treatment.

Can ACEi and ARB achieve the optimal blood pressure target? This usually depends on how aggressive BP management should be. According to the different guidelines the majority of CKD patients would benefit from a BP level lower than 130/80 mm/Hg. However one should be aware about serious side effects of aggressively lowering BP in patients with advanced kidney disease and end-organ damage. Besides, there is currently no evidence whether diabetic patients and patients with non-diabetic nephropathy with proteinuria $>1$ g/d would definitely benefit from the low BP target. In patients without diabetes and a level of proteinuria between 0.3 and 1g/dl strong consideration is given to achieve a BP level lower than 130/80 mm/Hg, until a specific trial would show otherwise. However, as stated above, one should be aware of the difficulty to reach such a BP target, especially in diabetic patients. In four randomised controlled trials (RCTs) in diabetic nephropathy the usual number of antihypertensive drugs to achieve a diastolic BP of $<85$mmHg was three, which indicates that such a task requires multiple drug therapy. However, in patients with CKD
AII inhibitors should be considered to be a first line therapy because of their effects beyond BP control alone and additional benefit for high-risk patients.

**AII inhibitors and cardiovascular protection**

Primary ACEi were aimed to treat hypertension and management of heart failure. Knowing AII to be involved in vasoconstriction, hypertrophy of cardiovascular cells as well as in fibrotic process in the heart and vessels, cardiovascular protection can be expected from ACEi/ARB treatment.\(^\text{12,13}\) The classical SAVE and SOLVD trials showed a significant lower mortality risk in patients with heart failure receiving the ACEi captopril and enalapril.\(^\text{14,15}\) Later the HOPE study confirmed these findings by showing a reduction of the risk of myocardial infarction, stroke and risk of death due to a CV event by 20-30% in patients with or without heart failure treated with ramipril.\(^\text{16}\) Afterwards two trials with contradicting results have been published: one showed that perindopril reduced CV mortality, non-fatal MI and cardiac arrest in patients with stable angina pectoris,\(^\text{17}\) the other could not confirm such results by using trandolapril.\(^\text{18}\)

Cardiovascular disease (CVD) is a leading cause of death among CKD patients.\(^\text{19}\) Retrospective analyses of the SAVE and HOPE trials came to the conclusion that treatment with ACEi was associated with an equal or even a greater risk reduction of all-cause mortality in the group of patients with renal insufficiency compared to the ones with a normal GFR.\(^\text{20,21}\) A sub study of HOPE showed that adding ramipril to the antihypertensive regimen in patients at high risk of cardiovascular events, decreased cardiovascular events by 25%.\(^\text{22}\)

Medications that inhibit the RAS are known to reduce CVD complications in patients with diabetic nephropathy.\(^\text{9,11,23}\) In diabetic nephropathy two studies reported CVD outcome as a secondary end-point. One showed that congestive heart failure was less frequent in the losartan-treated group compared to placebo or the group, treated with amlodipine.\(^\text{11}\) However, in this trial no difference was shown with regard to CV morbidity, like the occurrence of MI, stroke, unstable angina, etc. Another trial also reported less admissions for heart failure and a trend towards less non-fatal MI for patients receiving losartan.\(^\text{9}\) However, both of these trials were not aimed to study cardiovascular morbidity and mortality in the first place.\(^\text{24}\) Recently new data have become available: results of a big multinational RCT in which primary outcomes were cardiovascular events in high risk individuals with various vascular disease, treated either with ARB alone or in combination with ACEi.\(^\text{25}\) In the ONTARGET trial both
Effects of Angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers in patients with chronic kidney disease

Ramipril and telmisartan appeared to be equally effective to prevent a major cardiovascular event in the wide range of high-risk patients, including ones with CKD. Overall there is not enough evidence on effects of ACEi/ARB treatment of patients with CKD and CVD to reduce cardiovascular complications. Patients with advanced kidney disease are very often excluded from the big RCTs and therefore a clinical trial powered specifically for such outcomes in high-risk CKD patients is required.

Effects on proteinuria and progression of kidney disease

Proteinuria is very often present in CKD and its magnitude directly influences the rate of renal function deterioration. For more than a decade ACEi/ARB are known to have pronounced antiproteinuric and renoprotective properties, independently from their primary antihypertensive effect. This was first shown in patients with type I diabetic nephropathy in a CAPTOPRIL trial in 1993. The study showed that compared with placebo, in patients receiving captopril there was 30% reduction in proteinuria, 43% reduction in the risk of doubling of serum creatinine and 50% reduction in combined end point of death, need for dialysis or transplantation. These changes were observed independently of the BP levels. In the recent decade a number of studies have been performed investigating the ability of ACEi/ARB to decrease the rate of progression of proteinuria and diabetic nephropathy. The main findings of the biggest trials performed with AII inhibitors in patients with CKD I-IV were primary focused on renal outcomes and are summarized in Table 1.

In patients with nondiabetic kidney disease several big studies confirmed the pronounced antiproteinuric and renoprotective effects of ACEi: ramipril was associated with a major reduction of proteinuria, slower GFR decline and risk of doubling serum creatinine or progression to ESRD. Two studies comparing benazepril with placebo on top of other antihypertensive regimens confirmed the above effects of ACEi. It is worth mentioning that one of them, an AIPRI study, was focused on renoprotective properties of benazepril in patients with CKD of various aetiologies, but patients with glomerular disease were found to have the biggest profit from such treatment compared to the ones with polycystic kidney disease, nephrosclerosis or interstitial nephritis. The data on major trials in patients with non-diabetic CKD are given in Table 2.

The classic CAPTOPRIL study provided evidence that the stage of CKD and the amount of proteinuria are the main factors that determine the benefit from the use of an AII inhibitor.
Patients with serum creatinine of >180 mmol/l had the greatest effect of using ACE when compared to those with minor renal insufficiency (<90 mmol/l). A couple of other studies together with a meta-analysis showed ACEi/ARB to have their best renoprotective effect in patients with the largest amounts of proteinuria\textsuperscript{31,33} and an estimated GFR of <60ml/min.\textsuperscript{34} Therefore, ACEi/ARB have renoprotective qualities, which are the most pronounced in patients with proteinuria and advanced kidney disease.

Table 1. Randomised controlled trials on effects of ACEi/ARB with primary renal endpoints in patients with diabetic nephropathy, mild to moderate renal insufficiency and proteinuria.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Regimen compared</th>
<th>Mean follow-up</th>
<th>Effect on reduction of proteinuria</th>
<th>Effect on renal function preservation</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPTOPRIL, 1993</td>
<td>409</td>
<td>Captopril vs placebo</td>
<td>3 years</td>
<td>+</td>
<td>+</td>
<td>reduction in combined end point of death and need for dialysis reduction in combined end point of death, progression to ESRD reduction in combined end point of death, progression to ESRD</td>
</tr>
<tr>
<td>RENAAL, 2001</td>
<td>1513</td>
<td>Losartan vs placebo</td>
<td>3.4 years</td>
<td>+</td>
<td>+</td>
<td>reduction in combined end point of death, progression to ESRD</td>
</tr>
<tr>
<td>IDTN, 2001</td>
<td>1715</td>
<td>Irbesartan vs amlodipine vs placebo</td>
<td>2.6 years</td>
<td>+</td>
<td>+</td>
<td>reduction in combined end point of death, progression to ESRD</td>
</tr>
<tr>
<td>BENEDICT, 2004</td>
<td>1200</td>
<td>Trandolapril vs verapamil vs both vs placebo</td>
<td>48 months</td>
<td>+</td>
<td>+</td>
<td>ACEi slowed progression to microalbuminuria</td>
</tr>
<tr>
<td>REIN – 2, 2005</td>
<td>338</td>
<td>Ramipril vs Ramipril +Felodipine; usual vs low BP target</td>
<td>19 months</td>
<td>-</td>
<td>-</td>
<td>No differences in renal outcomes</td>
</tr>
</tbody>
</table>
Effects of Angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers in patients with chronic kidney disease

**Table 2. Randomised controlled trials on effects of ACEi/ARB with primary renal endpoints in patients with non-diabetic nephropathy, moderate renal insufficiency and proteinuria.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Regimen compared</th>
<th>Mean follow-up</th>
<th>Effect on reduction of proteinuria</th>
<th>Effect on renal function preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIPRI, 1996</td>
<td>583</td>
<td>Benazepril vs placebo</td>
<td>3 years</td>
<td>+</td>
<td>Reduction of risk of doubling of serum creatinine or progress to ESRD</td>
</tr>
<tr>
<td>REIN, 1997</td>
<td>166</td>
<td>Ramipril vs placebo</td>
<td>16 months</td>
<td>+</td>
<td>Lower risk of GFR decrease, doubling of serum creatinine or progression to ESRD</td>
</tr>
<tr>
<td>AASK, 2001</td>
<td>1094</td>
<td>Ramipril vs metoprolol vs amlodipine; usual vs low BP goal</td>
<td>3-4 years</td>
<td>Patients with proteinuria &gt;1g/d in the group with low BP goal had slower GFR decline</td>
<td>Lower risk of combined endpoint of death, 50% decrease of GFR or reaching ESRD</td>
</tr>
<tr>
<td>Hou et al, 2006</td>
<td>224</td>
<td>Benazepril vs placebo</td>
<td>3-4 years</td>
<td>+</td>
<td>Decreased risk of doubling of serum creatinine, ESRD or death</td>
</tr>
</tbody>
</table>

**ACEi “vs” or “and” ARB?**

Generalizing all information available today, it appears that both ACEi and ARB can provide sufficient renal and cardiovascular protection. However, more evidence is needed to prove these medications to be equivalent in patients with similar clinical conditions. A couple of trials already contributed to this. One compared telmisartan and enalapril with regard to their effects on the change of GFR, proteinuria, serum creatinine, BP level, rates of ESRD and cardiovascular events and all-cause mortality in patients with type 2 diabetes. The study's conclusion was that these two agents are similar in providing long-term cardio- and renoprotection. One of the main objectives of the recent ONTARGET trial was to compare long-term cardiovascular effects of telmisartan and ramipril in high-risk patients with different vascular illnesses. The investigators found ACEi and ARB to be equal from that prospective.
With regard to renal outcomes, although this was not the primary aim of the study, it appeared that telmisartan’s effects on major renal outcomes was similar to ramipril in patients with a high vascular risk. However the same trial confirmed the earlier observation, that ARBs in general are better tolerated then ACEi which have a higher incidence of hyperkalemia, cough and may induce angioedema. On the other hand more evidence is available for the effectiveness of ACEi in the clinical practice. Together with the higher cost of ARB this may influence the choice of the clinician. With regard to the combination of ACEi and ARB there is a still ongoing discussion. In theory such a combination could provide better blockade of the RAS and therefore be more effective in reaching the goal to protect renal function. However, the up-to-date findings are controversial. From one hand such a combination was shown to be effective in terms of treatment of proteinuria regardless of BP changes. On the other hand, the recent ONTARGET trial did not show any advantage over monotherapy with regard to the decline of GFR and the need for chronic dialysis, as well as the rate of cardiovascular events. Additionally, monotherapy has been proven to be well-tolerated while combination therapy showed a higher risk for developing hypotension and hyperkalaemia.

To summarize all of the above it should be noted that for patients with chronic kidney disease both ACEi and ARB can provide appropriate control of blood pressure and proteinuria as well as similar renal and cardiovascular protection. Today there is still more evidence for efficacy of ACEi, but already many good-quality studies have shown ARB to be equivalent. Regarding the combined use of these two RAS blocking agents, more evidence is needed to answer specific questions for the treatment of patients with different type and severity of CKD.

**Use of ACEi/ARB in patients treated with dialysis.**

After reaching the end stage of chronic kidney disease majority of patients will start renal replacement therapy with either form of dialysis. It has been stated that in dialysis patients the risk of cardiovascular mortality is 10 to 20-fold higher than in age- and sex-matched general population without kidney damage. Hypertension is one of the most important risk factors of cardiovascular complications in patients treated with dialysis. About 80% of patients requiring dialysis treatment are hypertensive. Controlling the hypertension in ESRD patients is a well-recognised problem which often requires administration of multiple medications. Antihypertensive agents of different groups are applicable for blood pressure control; however there is a lack of evidence neither about their efficacy nor about BP targets for patients...
Effects of Angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers in patients with chronic kidney disease

on dialysis. A couple of recent systematic reviews and meta-analyses collected evidence from randomised trials and concluded that hypertension should be treated in patients on dialysis; however no superiority of any antihypertensive medications was proven.\textsuperscript{43,44}

Although ß-blockers, calcium-channel blockers and AII inhibitors have been shown to be suitable for BP control in patients on dialysis,\textsuperscript{44,45} the latter may provide an additional benefit in this high-risk patient population. Activation of the RAS is recognised to be essential for hypertension and the increased risk of cardiovascular events in dialysis patients. It has been shown that in such patients a chronic overactivity of RAS is often present, together with increased activity of plasma rennin.\textsuperscript{46} These factors together with expansion of the extracellular volume and inter-dialytic weight gain create a vicious circle in which management of hypertension in HD patients remains to be difficult. However, there is enough grounding to state that HD patients, especially those with increased plasma renin activity (PRA), would benefit from adding drugs that inhibit AII into their antihypertensive regimen. A number of studies was done, which showed significantly reduced mortality risk for ESRD patients with cardiovascular disease treated with ACEi.\textsuperscript{47,48} Two studies showed a survival benefit for HD patients receiving ACEi;\textsuperscript{49,50} however, data suggest that only 30 to 50\% patients on dialysis are prescribed these medications.\textsuperscript{45,46,51-53}

Apart of their direct effect on BP, ACEi/ARB also have shown an ability to reduce an increased sympathetic nerve discharge in patients with chronic kidney disease and high renin levels.\textsuperscript{54} Patients on HD often have overactivity of the sympathetic nervous system which is another reason for development of hypertension.\textsuperscript{55} Such symptoms as xerostomia and thirst were found to be highly associated with higher inter-dialytic weight gain and chronic fluid overload.\textsuperscript{56} The later have direct impact on hypertension in HD patients and makes it more treatment resistant. AII has also been claimed to be a dipsogenic agent and couple of studies have shown previously that ACEi could reduce thirst in patients undergoing HD.\textsuperscript{57-59} In the first double blind, placebo controlled trial with a crossover design in 25 HD patients, the use of enalapril was associated with a reduction of thirst, oral fluid intake and, consequently, in weight gain between dialysis sessions.\textsuperscript{58} However, the other studies could not confirm such effect of ACEi and ARB.\textsuperscript{60,61} One recent study investigated the antidipsogenic effect of dual blockade of RAS with ACEi and ARB, and also failed to confirm the hypothesis.\textsuperscript{62} The possible explanations for such discrepancy could be small size of the referenced studies (mostly less than 30 patients), as well as differences in the studied population; however anti-dipsogenic properties of AII inhibitors need more investigation.
ACEi/ARB use in patients on peritoneal dialysis.

Until recent in patients undergoing peritoneal dialysis (PD) AII inhibitors were mostly used because of their effects on cardiovascular system. In a recent decade a number of studies have been done to investigate also an ability of these medications to suppress local RAS and attenuate peritoneal fibrosis development, and therefore to prolong an effective life of the peritoneal membrane. Experimental and clinical studies which were focused on specific effects of AII inhibitors in long-term peritoneal dialysis patients are presented in the last part of this review.

AII inhibitors as anti-fibrotic agents

PD has a survival advantage over hemodialysis in the first couple of years of renal replacement therapy (RRT). However, after long-term PD (> 2 years) technique and patients’ survival deteriorates. This could partially be explained by the loss of the residual renal function (RRF) and the development of peritoneal membrane alterations. During long-term treatment with peritoneal dialysis the peritoneal membrane is being altered by solutions with high concentrations of glucose and glucose degradation products (GDPs). Besides, uremic toxins as well as inflammatory cytokines induced by acute and chronic inflammation, may also contribute to the damaging process. Peritoneal membrane’s morphological alterations associated with long-term peritoneal dialysis treatment include interstitial fibrosis, loss of the mesothelial cell layer, neoangiogenesis and vasculopathy. These are associated with the main functional disturbances – high solute transport and ultrafiltration failure, which lead to insufficient PD treatment. The development of peritoneal membrane alterations is mediated by several growth factors. The most relevant ones are vascular endothelial growth factor (VEGF) and transforming growth factor ß1 (TGF-ß1). The latter appears to be related to the AII, which is produced by the local RAS, and is present in human peritoneal mesothelial cells (HPMC). Locally produced AII regulates cell growth and synthesis of extracellular matrix and therefore has all properties of a growth factor. In HPMC, AII acts as a pro-fibrotic agent, inducing production of a fibronectin and glucose-induced TGF-ß1. It has been shown that their expression can be significantly reduced by the ACEi and ARB. Production of VEGF, the growth factor essential for the development of ultrafiltration failure, was also shown to be attenuated by ACEi/ARB in recent in vitro study.
Animal studies
A number of studies have been done in experimental animal models, which confirmed the findings of the above cell culture studies. The use of ACE inhibitors enalapril and lisinopril in rats showed decreased fibrosis and angiogenesis. Also lisinopril and valsartan (an ARB) have been found to reduce levels of TGF-β1 and VEGF in rats’ PD effluent. ARBs irbesartan and olmesartan also showed protection from peritoneal fibrosis caused by bacterial peritonitis and PD fluid with acidic pH. ACE inhibition was also beneficial in a murine model of chlorhexidine/ethanol induced encapsulating peritoneal sclerosis (EPS); in this model oral administration of quinapril for up to 56 days markedly reduced peritoneal thickening.

Studies in humans
Relatively little is known about specific effects of ACEi/ARB in PD patients. The most relevant of these include their impact on peritoneal membrane function, residual renal function, PD technique and patients’ survival.

Effects on peritoneal transport
Studies, focused on effects of these medications on peritoneal membrane transport can be divided into short- and long-term. In the first short-term study a decrease in peritoneal protein loss was observed in 12 CAPD patients treated with the ACE inhibitor captopril. After a couple of years the same group found a similar effect of the ARB, irbesartan. In contrast, the study of Favazza et al. comparing effects of clonidine, enalapril and nifedipine, showed higher peritoneal clearances of creatinine and β2-microglobulin on enalapril. Other authors were not able to show any effect of enalapril or losartan on peritoneal transport in CAPD patients in short term. Given the discrepancy of these results, more studies are needed to provide clarity. Knowing that long-term peritoneal membrane changes do not occur before 2-3 years on PD, studies with sufficiently long follow-up could give an answer whether the long-term use of AII inhibitors can influence peritoneal transport. A first single-centre study, focused on effects of ACEi/ARB on peritoneal membrane transport in long-term PD patients was performed by our group. The major of our findings was a different time course of small solute transport during the first 3-4 years of PD treatment. Patients, treated with ACEi/ARB showed a slight decrease of the mass transfer area coefficient (MTAC) of creatinine and urea. This was different from the controls in which an increase with time of treatment was found.
It suggested inhibition of peritoneal angiogenesis which is in agreement with results of experimental studies. In another study we were able to confirm the above results on 217 incident CAPD patients participating in the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD) treated with PD for at least 2 years. Once again, patients treated with ACEi/ARB showed a slight decrease of their 24 hour dialysate/plasma creatinine ratio during the follow-up while an increase was observed in controls.

**Effects on PD technique and patients’ survival**

Given all of the above findings, it was also hypothesized that membranoprotective properties of ACEi/ARB could positively influence the technique survival of PD. Our study showed a tendency for patients, treated with ACEi/ARB for at least 75% of their time on PD, to have better technique survival although such an assumption could not be statistically confirmed. A possible explanation for this could be the fact, that in the NECOSAD database a very small number of patients is documented to be switched to hemodialysis (HD) due to problems with peritoneal transport, and therefore the real magnitude is hard to detect.

With regard to survival of PD patients' the effects of ACEi/ARB were found to be controversial. Recently, Fang et.al showed a significantly lower mortality risk in those receiving ACEi/ARB versus untreated. Use of these medications was associated with reduced all-cause mortality. Factors, associated with mortality were age, low serum albumin and congestive heart failure. In contrast, a study done by our group did not find a survival benefit with regard to ACEi/ARB treatment. A possible explanation for the discrepancy of these results is the difference between the studied cohorts. Besides, in observational studies it is hard to prove a link between treatment and outcome as confounding by indication can never be avoided.

**Effects on residual renal function**

A number of clinical trials provided evidence for a survival benefit for PD patients with preserved residual renal function (RRF). This can be explained by the fact that, unlike dialysis, native kidneys not only remove small solutes, but also protein bound substances by active secretion in the proximal tubules. Better preserved RRF is also associated with less comorbidity, better fluid and nutritional status. Although there is plenty of evidence for the renoprotective effects of AII inhibitors in patients with chronic kidney disease stage I-IV, the presence of such effect in PD patients is a subject of controversy.
Effects of Angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers in patients with chronic kidney disease

A large observational study in more than 1000 PD patients showed that development of anuria was delayed in those receiving ACE inhibitors. However, these results were not confirmed by a smaller single-centre study. Two randomised controlled trials (RCTs) also suggested renoprotective properties of ACEi/ARB in PD: they both showed a different time course of residual glomelurar filtration rate (rGFR) as well as a longer duration of anuria development for treated versus untreated patients. However, the findings of these two RCT’s are somewhat contradicting: one showed a temporary decrease of rGFR following the beginning of treatment with lisinopril, while the other reported a major increase after instillation of losartan.

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 an RCT can provide evidence for a causal relationship because they have the potential to avoid confounding by indication. The patients most often prescribed ACEi/ARB use these drugs because of hypertension, heart failure and diabetes mellitus. However, these conditions themselves are associated with a more rapid decline of residual renal function.

Use of ACEi/ARB in patients after kidney transplantation
After receiving a kidney transplant CKD patients form another special cohort in which possible effects of other but immunosuppressive medications have been barely studied. Not much evidence exists with regard to a potential positive influence of ACEi/ARB on cardio-protection, patients’ and graft survival. Available data from observational and randomised controlled trials provide rather controversial results. The most recent observational studies reported better outcomes in patients treated with ACEi/ARB compared to untreated, which included improved patient and graft survival. On the other hand, recently published systematic review and meta-analysis of randomized controlled trials on the use of antihypertensives in kidney transplant recipients concluded that the use of ACEi/ARB lead to clinically important reductions in GFR, and therefore may have detrimental effects on clinical outcomes. However, it should be mentioned that such a conclusion was made on the basis of few studies with a rather small patient size, which did not report highly relevant end-points, such as graft loss, cardiovascular events and patients’ death. The controversy of existing results together with a general lack of evidence creates big diversity in ACEi/ARB use in kidney transplant recipients. The latter was confirmed by investigators of the ongoing
Long-Term Deterioration of Kidney Allograft Function (DeKAF) study, which also showed that many patients taking these medications at the time of transplantation, have those medications discontinued, due to a fear of suboptimal allograft function postoperatively, and possible contribution to significant anemia after transplantation.\(^{118}\)

**Conclusion**

Drugs that inhibit RAS are proven to be effective in the treatment of hypertension and heart failure. In patients with chronic kidney disease these medications appeared to bring benefit beyond their direct effects on the cardiovascular system, resulting in preservation of renal and peritoneal function and improved patients survival. There is some evidence that patients with ESRD and after receiving kidney transplant may also profit from these main properties of ACEi/ARB, but more research is needed for clarity. It has been shown that ACEi/ARB are usually prescribed in less than a half of patients on dialysis, which means that underutilization of these drugs is present. The novel effects of these drugs discovered makes the target population for their administration much wider, especially in patients on renal replacement therapy.

**References**


36 Mann JF, Schmieder RE, McQueen M et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008; 372: 547-53.


Ref Type: Abstract
Chapter 5

Use of Angiotensin II inhibitors in patients who developed encapsulating peritoneal sclerosis: case-control study

Denise E. Sampimon, Inna Kolesnyk, Mario R. Korte, Marien Fieren, Dirk G. Struijk, Raymond T. Krediet

Submitted
ABSTRACT

**Background:** Animal studies suggest that angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) may prevent the development of peritoneal adhesions and fibrosis. Encapsulating peritoneal sclerosis (EPS) is a severe complication of PD and causes bowel obstruction due to adhesions. The aim of this study was to investigate the exposure to ACEi/ARBs and its duration in PD patients who developed EPS and matched controls.

**Methods:** 24 EPS patients from 2 large PD centers in the Netherlands were selected and matched for PD duration and PD centre to 24 controls. The use of ACEi/ARBs and its duration was calculated in months for the total treatment time on PD and additionally expressed as a percentage. A Wilcoxon test and $\chi^2$ - test were used to compare the groups.

**Results:** The median age of the EPS group was 30 (7-68) years versus 45 (6-81) years in controls ($p=0.03$) at the start of PD. The median time on PD was 77 (30-222) months for the EPS group versus 78 (33-135 months) for the controls ($p=0.16$). EPS patients and controls were not different with regard to their primary kidney disease, the number of peritonitis episodes and the number of transplanted patients. However EPS patients received more transplantations per patient compared to controls ($p=0.02$).

The median duration of ACEi/ARBs during PD was 20 (0-134) months in the EPS group and 26 (0-116) months in the control group ($p=0.45$). The median percentage of ACEi/ARBs use was 14% in the EPS group and 41 % in the control group ($p=0.33$).

**Conclusion:** We could not find a protective effect of ACEi/ARBs on the development of EPS.
Introduction

Encapsulating peritoneal sclerosis (EPS) is a rare but severe complication of PD (1). EPS causes severe peritoneal fibrosis and adhesions which lead to bowel obstructions. Several risk factors for EPS such as long-term PD, a high glucose load and peritonitis, have been proposed (2). Neoangiogenesis and peritoneal fibrosis are important features of the development of EPS (3-5). However, we still do not know how the development of EPS in PD patients can be prevented.

Angiotensin II (Ang II) is an important growth factor in the development of renal fibrosis (6). Ang II inhibitors attenuate the development of fibrosis mostly by suppressing transforming growth factor-beta (TGF-beta) (7,8). TGF-beta is considered to be an important factor in the regulation of extracellular matrix turnover (9-10). Ang II may also be an important growth factor for fibrosis in other tissue cells besides the kidney. In vitro studies showed that in human peritoneal mesothelial cells angiotensin converting enzymes inhibitors (ACEi) and angiotensin receptor blockers (ARBs) inhibit the production of TGF-beta induced by high glucose concentrations (11,12). Animal studies have shown that ACEi/ARBs may be protective against peritoneal alterations such as peritoneal fibrosis (12,13). Furthermore, rats treated with lisinopril showed fewer adhesions after bowel surgery when compared to controls (14). A study of our group showed less fibrosis in rats treated with lisinopril and chronically exposed to dialysis fluids when compared to controls (15). Similar results of the inhibitory effect of ACEi on the development of fibrosis have been found in other animal studies (16,17). In EPS animal models treated with ACEi less fibrosis (18), higher ultrafiltration, less peritoneal vessels and a thinner peritoneal membrane, have been observed when compared to control animals (19).

All of the above suggest beneficial effects of ACEi/ARBs against the development of peritoneal fibrosis and EPS in humans. To our knowledge the exposure to ACEi/ARBs of PD patients who have developed EPS, has not been studied yet. The present study was designed to investigate the association between the development of EPS and prior ACEi/ARB treatment. For this aim we investigated the duration of the exposure to ACEi/ARBs in PD patients who developed EPS and compared them to controls matched for the duration of PD.

Patients and Methods

Patients

Out of two large PD centers in the Netherlands, PD patients who developed EPS in the period
between July 1995 and December 2008 were selected. The diagnosis of EPS was based on predefined criteria (2). These included clinical features such as bowel obstruction, ascites, and blood stained effluent in combination with ultrafiltration failure (UFF), confirmed either by findings at radiology, laparotomy or autopsy, and reviewed by two experienced nephrologists (1).

For each EPS patient a control patient was selected based on the duration of PD and PD centre. Patients were followed until three years after the discontinuation of PD or until the censoring on December 2008. Control patients did not develop EPS during the three years follow-up.

**Data collection**

The duration of ACEi/ARB use was calculated in months during the total treatment time on PD and additionally expressed as a percentage. Also the period of ACEi/ARB treatment with respect to the PD treatment e.g. beginning of PD, end of PD, were studied. PD duration was calculated from the start of PD, intervals of more than three months were noted as temporary discontinuation of PD.

Variables in the patients’ histories such as the number of bowel surgeries, exposure to beta blockers and the number of kidney transplantations were compared. Bowel surgery also included kidney transplantation, catheter implantation and removal.

**Statistical analysis**

Data is presented as medians and ranges unless stated otherwise. Groups were compared with a Wilcoxon test or a $\chi^2$-test.
Results

Baseline characteristics are given in Table 1 and events during PD in Table 2. The median time on PD was 77 (30-222) months for the EPS group versus 78 (33-135) months for the controls (p=0.16). EPS patients were younger, had more abdominal surgeries including more kidney transplantations per patient when compared to controls. No difference in gender, peritonitis incidence and exposure to beta blockers was present. At the end of follow-up 14 EPS patients had died, 6 patients were treated with hemodialysis (HD) and 4 had a functioning graft. In the control group 13 patients had died, 3 patients switched to HD, 5 patients had a functioning graft and 3 patients were censored. Causes of death are given in Table 3.

EPS patients received ACEi/ARB treatment for a median of 0 (0-34) months and controls for 0 (0-116) months (p=0.45, Figure 1). The median duration of ACEi/ARB use expressed as a percentage of total PD time was 14% for EPS patients and 41% for controls, but not different between the groups (p=0.33, Figure 2). No differences in the start or discontinuation of ACEi/ARB treatment at the beginning or end of PD were present. No difference was present between the groups for the continuation of ACEi/ARB treatment during a temporary discontinuation of PD treatment. Three patients in each group received ACEi/ARB treatment during the total duration of PD treatment.
### Table 1 Baseline characteristics at start PD

<table>
<thead>
<tr>
<th></th>
<th>EPS N=24</th>
<th>Control N=24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 (7-68)</td>
<td>45 (6-81)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/9</td>
<td>13/11</td>
<td>0.35</td>
</tr>
<tr>
<td>Primary kidney disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>3</td>
<td>4</td>
<td>0.08</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Events during PD

<table>
<thead>
<tr>
<th></th>
<th>EPS N=24</th>
<th>Control N=24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD duration (months)</td>
<td>77 (30-222)</td>
<td>78 (33-135)</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of patients that used beta blockers (yes/no)</td>
<td>14/10</td>
<td>11/13</td>
<td>0.37</td>
</tr>
<tr>
<td>Abdominal surgeries per patient</td>
<td>6 (2-11)</td>
<td>3 (1-6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peritonitis episodes per patient</td>
<td>3 (0-15)</td>
<td>4 (0-15)</td>
<td>0.64</td>
</tr>
<tr>
<td>Peritonitis incidence</td>
<td>0.44 (0-3.10)</td>
<td>0.51 (0-1.45)</td>
<td>0.53</td>
</tr>
<tr>
<td>Kidney transplantation (yes/no)</td>
<td>20/4</td>
<td>13/11</td>
<td>0.06</td>
</tr>
<tr>
<td>Number of kidney transplantations per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
difference between the groups (p=0.33).

Figure 2: Box-and-Whisker plots of the duration of ACEi/ARB treatment expressed as a percentage of the total time on PD treatment in the EPS group and control group. There was no difference between the groups (p=0.33).

Table 3 Causes of Death

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>EPS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal ischemia/perforation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Septicemia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Voluntary discontinuation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Unknown/other</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
**Discussion**

In the present study no protective effect of ACEi/ARB treatment on the development of EPS could be demonstrated. No differences in time of ACEi/ARB treatment between PD patients who developed EPS and their time matched controls were present.

Two experimental studies investigated the effect of ACEi/ARBs on EPS. One of these studies investigated the treatment effect of ACEi/ARBs after the development of EPS. Although the study reported beneficial effects of ACEi/ARBs on ultrafiltration, it did not investigate the protective effect of these drugs on EPS. In the other EPS model the protective effect of ACEi in a long-term EPS mouse model was analyzed. However in this model the animals were neither uremic nor were they exposed to dialysis fluids. Therefore the results cannot be compared to EPS after long-term PD.

In the present study PD patients developed EPS despite the use of ACEi/ARBs. This may be explained by several factors. The process of EPS is probably multifactorial. Many risk factors have been proposed for the development of EPS such as long-term PD, recurrent peritonitis, use of beta-blockers, abdominal surgery, kidney transplantation, genetic background and exposure to PD fluids specifically high glucose concentrations, low pH and high osmolarity. In the present study there were no differences between the two groups for the use of beta-blockers and peritonitis incidence. However age, the number of abdominal surgeries and kidney transplantations were different. Bowel operations included kidney transplantation and catheter removal. Young age and kidney transplantation are risk factors according to a recent multicenter study performed in the Netherlands (unpublished). These risk factors may be important in the development of EPS despite the use of ACEi/ARBs.

Two previous studies done in the Netherlands showed a possible membrane protective effect of ACEi/ARB treatment in long-term PD patients. ACEi/ARB treatment attenuated the increase of solute clearances found in long-term PD patients. This suggests protection of ACEi/ARBs against the development of an enlargement of the peritoneal surface area. However, it must be emphasized that the included patients were treated with PD for 2-4 years. The membrane protective effect of ACEi/ARB in patients treated with PD for a longer duration may be influenced by other factors for instance involvement of a variety in growth factors.

There are several shortcomings in this investigation. First of all due to the rareness of EPS, only 24 EPS patients were diagnosed in a period of 13 years. Therefore our inability to show an effect of ACEi/ARB treatment does not exclude some protective effect, when the groups would have been larger. Yet, when the effect would have been dramatic, we should have found some indication of a difference. Second, there was no information on the kind of
ACEi/ARBs prescribed and the dose. Also, the kind of ACEi/ARB and the dose often changed during follow-up. Due to the limited number of patients it was impossible to include these data in our analysis. Finally, we are not informed on the compliance of the patients in taking the drugs prescribed to them.

In conclusion, we could not find a protective effect of ACEi/ARBs on the development of EPS. Reasons for this are speculative.

Reference List


(23) Summers AM, Brenchley PE. An international encapsulating peritoneal sclerosis registry and DNA bank: why we need one now. Perit Dial Int 2006; 26:559-63.


Chapter 6

Time dependent reasons for PD technique failure and mortality

Inna Kolesnyk, Friedo W. Dekker, Elisabeth W. Boeschoten and Raymond T. Krediet

Perit Dial Int, in press
ABSTRACT

Background: Peritoneal dialysis (PD) technique failure remains high when compared to hemodialysis (HD). There is lack of data about an impact of the duration of PD treatment on technique survival and whether there is a difference in risk factors with regard to early and late failure. The aim of this study was to clarify these issues by performing a time-dependent analysis of PD technique and patients’ survival in large cohort of incident PD patients.

Methods: We analyzed 709 incident PD patients participating in the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD), who started their treatment between 1997 and 2007. We compared technique and patient survival on PD in 4 periods of follow-up: within the first 3 months, 3-12 months, 12-24 months and 24-36 months of treatment. Cox proportional hazards model was used to analyze survival on PD and technique failure. The risk factors were also identified by comparing patients who were transferred to HD with the ones who remained on PD. Incidence rates for every cause of drop-out for each period of follow-up were calculated to establish their trends with regard to PD treatment duration.

Results: There was a significant increase of transplantation rate after the 1st year of treatment while rate of switches to HD was the highest in the first 3 months and decreased afterwards. One-year technique survival was 87%, two and three-year 76% and 66%, respectively. Age, cardiovascular disease and diabetes appeared to be risk factors for death on PD or switch to HD. One-year increase in age was associated with a relative risk (RR) of PD failure of 1.04 (95% CI, 1.003 to 1.06). Diabetes had increased RR to stop PD after 3 months of treatment from 1.8 (95% CI, 1.1 to 3) in a 1st year up to 2.2 (95% CI 1.3 to 4) after the 2nd year. Cardiovascular disease had a major impact in the earliest period: RR 2.5 (95% CI 1.2 to 5) and had a stable influence further on, RR 2 (95% CI 1.1 to 3.5). Loss of 1ml/min of residual GFR appeared to be a significant predictor for PD failure after 3 months of treatment but within the first 2 years: RR 1.1 (95% CI 1.04 to 1.25).

Conclusion: In the Netherlands transplantation is a main reason to stop with PD treatment. The incidence of PD technique failure is the highest in the earliest months after treatment initiation and decreases later due to fewer catheter and abdominal complications as well as less influence of psychosocial factors. Risk factors for PD discontinuation are the ones responsible for patients’ survival: age, cardiovascular disease, diabetes and rGFR.
Introduction

Concern about the decrease in utilization of peritoneal dialysis (PD) in many countries has risen over the last years \(^{(1,2)}\). Attempts to explain this process led to the conclusion that many factors are involved, which are rather complex and vary much from country to country\(^{(1)}\).

Relatively high technique failure when compared to hemodialysis always was one of the main reasons for PD deprivation: some studies reported a 3-year technique survival slightly higher than 50\% \(^{(3,4)}\). A number of studies analyzed patients’ and technique survival trying to identify the risk factors for PD failure \(^{(3-10)}\). It was shown that renal center characteristics such as the number of PD patients make a big impact on patients and technique outcome \(^{(8,10)}\). Some analyses showed a rise in PD modality success over the last years due to technical progress \(^{(4,7,8,11)}\).

There is lack of data on the exact reasons for PD technique failure and whether they are different with regard to the treatment duration. The study of Guo et al. done in large incident cohorts suggested that the first 6 months of PD therapy are critical for technique failure \(^{(7)}\). The latest published work of Descoeudres et al. confirmed this finding and reported about the importance of early drop-out from PD in a single center study\(^{(12)}\). However more data is needed for better understanding the reasons for technique failure and their correlation with PD duration in order to improve the outcome.

We aimed to perform a detailed analysis of technique and patients survival in the PD cohort of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). Our main goal was to update and extend the earlier published data \(^{(3,9)}\) and make a precise analysis of the reasons and risk factors for PD mortality and technique failure with regard to the duration of treatment.

Methods

Patients and follow-up period

The patients were selected from the database of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). This database contains data on patients with end stage renal disease out of 38 dialysis centers in the Netherlands. At the start of dialysis all patients were older than 18 years and had never received renal replacement therapy in the past. We could include 585 patients who had started renal replacement therapy with peritoneal dialysis in the period between January 1 1997 and July 1 2007. Patients, who started with hemo-
dialysis but were switched to PD within the first 3 months after therapy initiation (n=124) were also included. Altogether 709 patients were eligible for the current analysis. 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 and residual renal function were collected at 3 and 6 months after the start of dialysis. Afterwards data were collected on a half-yearly basis.

Primary kidney disease was classified according to the codes of the European Dialysis and Transplant Association – European Renal Association Registry. Comorbidity was scored on the basis of Davies’ comorbidity index. 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 cerebral-vascular accident.

Residual renal function was expressed as residual glomerular filtration rate (rGFR) and was calculated as the mean of creatinine and urea clearance, corrected for body surface area (ml/min/1.73m²).

**Analytical methods**

The primary end points of the study were failure of PD technique, defined as a permanent switch to hemodialysis and death on PD. To identify the risk factors for earlier and later PD failure, we divided the study follow-up into 4 periods: the first 3 months of PD therapy – period I, after 3 months but within the first year – period II, 2 years of therapy - period III and period IV - 3 years of PD therapy. We compared data on demography, primary kidney disease, comorbidity, baseline residual renal function and mean arterial blood pressure between the patients who had switched to hemodialysis and those who remained treated with PD within each period of follow-up. For this comparison we used standard descriptive statistics: Student’s t – test, chi – square test.

Reasons for PD drop-out within the different periods of PD treatment were compared with the chi-square test. In order to evaluate the difference in reasons to stop with PD therapy in a time dependent way, we calculated the incidence rates for every cause of drop-out per 1000 patient years for
every period of follow-up.

Statistical analysis of PD technique survival alone and combined with patients’ survival on PD, “stay on PD”, was performed by several multivariate Cox proportional hazard models. In the analysis of technique survival the event was permanent switch to hemodialysis; transplantation and death were censored observations. In the “stay on PD” analysis the events were switch to HD or death on PD while transplantation was a censored observation. In order to identify time-depended predictors for the drop-out from PD we performed Cox regression analysis separately for each period of follow-up: 0-3 months, 3-12 months, 12-24 months and 24-36 months, and added variables to the model. We constructed the following multivariate models: crude effects of age and gender on survival; effect of diabetes, adjusted for age and gender; effect of cardiovascular disease, adjusted for age and gender; influence of residual GFR, measured at the start of every follow-up period adjusted for age, gender, diabetes and cardiovascular disease. Data on comorbidity are taken at the start of dialysis treatment.

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 statistically significant.

**Results**

**Patients and baseline characteristics**

All 709 NECOSAD patients who had started PD within the first 3 months after initiating renal replacement therapy (RRT) were included in the study. Figure 1 shows the changes in the cohort during 4 predefined periods of follow-up. A comparison of data on demography and baseline clinical factors between the patients transferred to hemodialysis and those who remained on PD are shown in Table 1. Within the first 3 months of PD therapy the patients who were transferred to HD were older, more often women and had a higher comorbidity score. No differences between the patients were observed in the second period (between 3-12 months) but between the 1st and 2nd year of treatment those who were switched to HD were older, had more often diabetes and cardiovascular disease. After 2 years of PD treatment the comorbidity score alone appeared to be associated with the technique survival.
The mean follow-up period was 8 months (range 0.8 to 99 months). 59 Patients died, received a kidney transplant, 0 dropped out from the study for various non-medical reasons, like a refusal to participate or transfer to another center and 8 were transferred to hemodialysis. Infectious complications like peritonitis, exit site and tunnel infections were the main reason for transfer to HD. This occurred in 77 patients. Underdialysis with ultrafiltration failure was the reason for transfer to HD in 9 patients. Abdominal and

**Events**

The mean follow-up period was 28 months (range 0.28 to 99 months). 159 Patients died, 226 received a kidney transplant, 102 dropped out from the study for various non-medical reasons, like a refusal to participate or transfer to another center and 186 were transferred to hemodialysis. Infectious complications like peritonitis, exit site and tunnel infections were the main reason for transfer to HD. This occurred in 77 patients. Underdialysis with ultrafiltration failure was the reason for transfer to HD in 19 patients. Abdominal and
Table 1. Baseline characteristics. Patients are compared within the group for each period.

<table>
<thead>
<tr>
<th>Group</th>
<th>I (0 - 3 months)</th>
<th>II (3 - 12 months)</th>
<th>III (12 - 24 months)</th>
<th>IV (24 – 36 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Switched to HD</td>
<td>Stayed on PD</td>
<td>Switched to HD</td>
<td>Stayed on PD</td>
</tr>
<tr>
<td>Number of patients</td>
<td>26</td>
<td>649</td>
<td>44</td>
<td>515</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59(^1) (29-77)</td>
<td>53 (18-86)</td>
<td>55 (27-78)</td>
<td>52 (18-86)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>50(^1) 67</td>
<td>67</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Primary kidney disease (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>12</td>
<td>16</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>4</td>
<td>20</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>23</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>61</td>
<td>52</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>23</td>
<td>20</td>
<td>26</td>
<td>19(^1)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>34</td>
<td>25</td>
<td>24</td>
<td>20(^1)</td>
</tr>
<tr>
<td>Davies score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no comorbidity</td>
<td>42(^1) 61</td>
<td>57</td>
<td>61</td>
<td>65(^1) 47</td>
</tr>
<tr>
<td>moderate</td>
<td>58</td>
<td>33</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>severe</td>
<td>0</td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Residual GFR at baseline (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.9 (0-15)</td>
<td>5.5 (0-16)</td>
<td>3.2 (0-11)</td>
<td>4.1 (0-16)</td>
</tr>
<tr>
<td>Mean blood pressure at baseline (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>105 (±15)</td>
<td>107 (±15)</td>
<td>107 (±17)</td>
<td>101 (±15)</td>
</tr>
<tr>
<td>Patients on APD, %</td>
<td>NA(^2)</td>
<td>NA</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics. Patients are compared within the group for each period.

Data are presented as % or medians (ranges). Values for mean arterial blood pressure are given as means (SD). Values for rGFR and mean arterial blood pressure are taken from the beginning of each period.

1 \( p \leq 0.05 \)

2 data on type of PD modality is not available within the first 3 months of treatment initiation
catheter-related complications occurred in 16 and 19 patients, respectively. 55 Patients were transferred to HD for either psychosocial (patient’s preference, etc) or unknown reasons. 36 Patients were still treated with PD after the censoring date.

**Technique failure**
One-year PD technique survival was 87%, two-year technique survival was 76% and three-year technique survival was 66%.

**Survival on PD at different periods of follow-up.**
Figure 2a shows differences in the various reasons for PD drop-out during the 4 periods of follow-up. During each period approximately 25-30% of patients died. Thirteen percent of patients received a kidney transplant in the first 3 months of PD therapy; afterwards 30%, 42% and 43% of patients were transplanted during the 1st, 2nd and 3rd year, respectively. Infectious complications were the reason for transfer to HD in 10 - 18% of patients. Catheter problems occurred in 15% and 7% of patients during the first two periods and decreased after the 1st year down to 1 - 2%. Also abdominal problems were the reason to switch to HD in 5-7% of patients in the 1st year and only for the 2% afterwards. During the first two periods 2% of patients was considered to be underdialyzed or had problems with ultrafiltration; within the 2nd year 4% patients experienced this complication and 6% after 2 years of PD. Psychosocial or unknown reasons for PD drop-out varied from 20% in first 3 months period to 7-9% later on.

When comparing reasons for PD drop-out between the 4 periods of follow-up it turned out that the contribution of transplantations had remarkably increased during the follow-up period. The number of people who received a kidney graft in the first 3 months was significantly lower than in later periods (p-values from 0.014 to <0.0001). Also the number of patients transplanted after 3 months but within the first year of PD was lower than in the next two periods (p-values ≤ 0.04). A similar number of transplantations were performed during the 2nd and 3rd year of PD treatment. Regarding the problems with peritoneal access which led to switch to HD we observed a reversed trend: the number of these complications significantly decreased. There was no difference between the periods before and after 3 months of PD but after 1 year the number of catheter complications had decreased very much, p≤0.002. There was no difference in other reasons for PD drop-out between the periods of follow-up.
Time dependent reasons for PD technique failure and mortality

**Figure 2.**

a) Reasons for drop-out from PD during 4 periods of follow-up.

b) Incidence rates for each reason for PD drop-out during 4 periods of follow-up.
Figure 2b graphically displays the incidence rates for reasons for PD drop-out during 4 periods of treatment. Thus, incidence rates of mortality, kidney transplantation and underdialysis/ultrafiltration failure increased over periods of follow-up while other causes for PD failure followed a decreasing pattern. The incidence rates for every cause for PD drop-out per each period of follow-up are given in Table 2.

Table 2. Incidence rates of each cause of drop-out from PD during 4 periods of follow-up. Rates with 95% confidence intervals are given per 1000 patient years.

<table>
<thead>
<tr>
<th>Time period (months)</th>
<th>No of patients</th>
<th>Rate of death</th>
<th>Rate of transplantation</th>
<th>Rate of infections</th>
<th>Rate of catheter failures</th>
<th>Rate of psychosocial/unknown problems</th>
<th>Rate of underdialysis/UFF</th>
<th>Rate of abdominal problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3</td>
<td>709</td>
<td>81 (45-136)</td>
<td>35 (13-76)</td>
<td>35 (13-76)</td>
<td>40 (16-83)</td>
<td>52 (24-99)</td>
<td>5 (0-32)</td>
<td>17 (6-51)</td>
</tr>
<tr>
<td>3 to 12</td>
<td>649</td>
<td>77 (53-108)</td>
<td>77 (53-108)</td>
<td>45 (28-70)</td>
<td>18 (7-36)</td>
<td>18 (7-36)</td>
<td>5 (0-16)</td>
<td>14 (5-30)</td>
</tr>
<tr>
<td>12 to 24</td>
<td>515</td>
<td>97 (70-132)</td>
<td>161 (125-204)</td>
<td>57 (36-85)</td>
<td>7 (1-20)</td>
<td>35 (20-59)</td>
<td>14 (5-31)</td>
<td>7 (1-20)</td>
</tr>
<tr>
<td>24 to 36</td>
<td>327</td>
<td>113 (77-161)</td>
<td>164 (120-221)</td>
<td>36 (18-67)</td>
<td>3 (0-20)</td>
<td>29 (13-58)</td>
<td>25 (10-53)</td>
<td>7 (0-26)</td>
</tr>
</tbody>
</table>

The results of a multivariate Cox analysis of PD technique survival showed that age had a borderline effect on switching to HD in the first 3 months of treatment: HR 1.03 (95%CI 1.01 to 1.06) and residual renal function had an impact on technique survival during 2nd year of treatment: HR 1.17 (95%CI 1.03 to 1.3). Furthermore, none of the chosen factors appeared to be a significant predictor for switching from PD therapy to HD regardless of treatment duration (data not shown). Table 3 shows the results of Cox analysis for probability to stay on PD treatment, when events are a switch to HD and death on PD. Thus, age appeared to have an effect on staying on PD therapy regardless the duration of treatment. Diabetes seemed to have a somewhat increasing influence with time and cardiovascular disease had a major effect in the first 3 months and remained a significant predictor for PD failure afterwards. Residual GFR at the baseline of II and III treatment periods was a significant risk factor for discontinuation of PD.

Transplantation was the main reason for drop-out for patients who stayed on PD for more than 3 years—49% of remained patients received a kidney graft. Also none of these
patients had catheter problems as a cause of switching to HD. Otherwise for this group of patients reasons to stop with PD were not different from the previous ones (data not shown).

We did not find a difference in the probability to stay on PD between CAPD and APD patients (data not shown). Also no difference was found with adjustment for a center effect (data not shown).

**Mortality**

Probability for PD patients’ survival curve together with patients’ survival and “stay on PD” curves is shown in Figure 3. One-year patient survival was 91%, two-year patient survival was 81% and 3 year patient survival was 74%. Causes of death were classified as cardiac (n = 44), vascular, including stroke and hemorrhages (n = 14), infectious complications.

| Table 3. Multivariate Cox proportional hazards model for survival on PD at the various baselines. |
| a – values for residual GFRs are taken at the beginning of each period of follow-up. |

<table>
<thead>
<tr>
<th>Factor</th>
<th>I (0 - 3 months)</th>
<th>II (3 - 12 months)</th>
<th>III (12 - 24 months)</th>
<th>IV (24 – 36 months )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>95% CI</td>
<td>Relative risk</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age 1 year</td>
<td>1.04</td>
<td>1.0 - 1.06</td>
<td>1.04</td>
<td>1.02 - 1.05</td>
</tr>
<tr>
<td>Gender (male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.82</td>
<td>0.3 - 1.9</td>
<td>1.8</td>
<td>1.1 - 3.0</td>
</tr>
<tr>
<td>Age 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.82</td>
<td>0.3 - 1.9</td>
<td>1.8</td>
<td>1.1 - 3.0</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.5</td>
<td>1.2 – 5.2</td>
<td>2.0</td>
<td>1.1 - 3.0</td>
</tr>
<tr>
<td>Age 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rGFR* (1ml/min)</td>
<td>0.93</td>
<td>0.9 - 1.2</td>
<td>1.1</td>
<td>1.04 – 1.25</td>
</tr>
</tbody>
</table>
not-related to the treatment (n=12), abdominal complications not-related to treatment (n=5), pd-related complications (including peritonitis and peritoneal sclerosis (n=6), other reasons, including malignancy and treatment refusal (n=37) and unidentified causes (n = 41). There was no difference in reasons for death between the periods of follow-up (data not shown).

**Discussion**

In the present study we analyzed technique and patient survival of incident peritoneal dialysis patients according to the duration of follow-up. Most other studies published so far
Time dependent reasons for PD technique failure and mortality

performed their Cox proportional hazard analyses for the total follow-up period, thereby assuming that the hazards do not change with time. To our knowledge, this study is the first to use a time depended approach to analyze PD technique survival and mortality. With this new approach we were able to show that there are differences in reasons to stop PD treatment at various points of follow-up and risk factors of PD failure are also time-depended.

The main reasons for discontinuation of PD were kidney transplantation or death. The latter contributed for on average 25-30% in all periods of follow-up. Drop-out due to transplantation increased from 10% during the first year of PD treatment up to 50% after 3 years. This increase over time corresponds with a median time on the transplant waiting list in Europe. Transfer to hemodialysis decreased during follow-up from 40% during the first 3 months to 25% after 2 years, mainly because of fewer abdominal and catheter complications. A high prevalence of catheter related problems in the earliest period of PD treatment has been also reported in other studies. After the first 3 months of PD treatment reasons to switch to HD are mostly represented by infectious complications and psychosocial reasons, which was also found by others. Unlike the rate of infections which follows a reversed “U”-shape trend, psychosocial factors appeared to be more dominating in the earliest stage of PD treatment. Partially this might be explained by pitfalls in appropriate patients’ selection. A relatively low incidence of stopping PD due to underdialysis or ultrafiltration failure might be explained by assumption that some of these could be partially carried by any cause to transfer to HD. For instance, should a patient with an insufficient ultrafiltration or signs of underdialysis develop an infectious or catheter complication, his transfer to HD will be documented as due to the latter reason.

Some recent studies found a significant contribution of early failure to the general PD outcome: a group from Switzerland found that up to one third of all PD failures in one center happened within the first couple of months. The study of Guo reported a decline of PD technique failure between the 1st and 2nd years of therapy. Our findings suggest that the incidence rate for PD failure is the highest in the first 3 months, and then remains rather stable for the next 3 years.

We could not find a single risk factor for switch from PD to HD therefore it is most likely that the reason for transfer is usually more complex then the one pointed as final. However, the risk factors for staying on PD treatment are the ones mostly responsible for patients’ survival: older age, diabetes and cardiovascular disease. These were also found by others to be significant predictors of death on PD. Residual renal function though seemed to
make a significant impact on staying on PD therapy after the first 3 months and within the first 2 years of treatment.

When comparing patients who switched to HD with those who remained treated with PD, it appeared that older patients with a higher comorbidity tend to switch to HD in the first 3 months. Besides, there were more women among them. Female gender associated with early drop-out from PD was also found by Descoeudres et al.\(^{(12)}\). The NECOSAD group has reported earlier that when given a free choice, older women tend to choose HD over PD\(^{(18)}\). Probably, this preference may also contribute to the early switch from PD to HD. Some studies also reported about women to have worse survival on PD\(^{(19,20)}\). However we could not confirm such a finding.

Generally PD technique survival in the Netherlands when compared to the reports from previous decade\(^{(3,9)}\) continues to improve. It was also shown by the study on Dutch National Registry, although we could not find a marked center effect as previously been reported by Huisman et al.\(^{(8)}\). Patients’ survival on PD in the Netherlands has somewhat improved for the last 10 years\(^{(3)}\). The rate we found corresponds with the one found in another national study\(^{(21)}\) and is higher than rates reported from some American studies\(^{(4,7)}\) and somewhat lower than in Asian ones\(^{(22,23)}\).

To our knowledge, this is the only study that provides such detailed data on survival on PD technique. The fact that this analysis was performed on the database of the national multi-centre study with a relatively big number of patients makes the obtained information quite representative. We conclude that in the Netherlands the chance to switch from PD to HD is highest in the first couple of months of treatment. There is a high rate of transplantation during PD treatment and therefore an “integrated care” approach is being used widely. However, the technique success can still be improved when attention is paid to the major reasons for early drop-out, like problems with peritoneal access and psychosocial factors, such as appropriate patients’ selection.
Reference List

Chapter 7

General discussion
**General discussion**

Relatively short PD technique survival when compared to hemodialysis, is possibly one of the main reasons that may contribute to underutilization of this method of RRT. There is an opinion that limited effective life of the peritoneal membrane and loss of renal function are the main reasons to discontinue PD treatment. Medications, which inhibit activity of central and local RAS, have recently been proposed to have protective effects on the peritoneal membrane, residual renal function and survival of patients on PD.

The present thesis includes studies on possible effects of AII inhibitors (ACEi/ARB) in patients undergoing long-term PD treatment, as well as a detailed analysis of actual reasons to discontinue PD. Some of the issues, raised by the performed studies, are discussed below. They include the effect of ACEi/ARB on the peritoneal membrane, possible effects of these drugs on patients’ and technique survival and suggestions for future studies.

**Effects of ACEi/ARB on the peritoneal membrane**

Efficacy of PD treatment is first of all based on the transport properties of the peritoneal membrane to remove excess of fluid and uremic waste products from the circulation. Fibrosis of the peritoneum and neoangiogenesis are the main long-term morphological alterations that lead to PD technique insufficiency \(^{(1)}\). The latter results in an increased effective peritoneal surface area, rapid disappearance of the osmotic pressure gradient and, as a consequence, fast solute and water transport, which are the features of ultrafiltration failure (UFF) \(^{(2)}\). Previous experimental studies showed that the use of ACEi and ARB was associated with less fibrosis and less formation of new vessels in the peritoneal membrane \(^{(3-5)}\). However, most of earlier research in humans failed to confirm such findings in peritoneal transport studies, most likely due to their short follow-up \(^{(6,7)}\). It is known, that long-term changes in peritoneal membrane occur after 2-3 years of continuous PD therapy. Therefore, to study effects of ACEi/ARB on long-term membrane changes, a study follow-up of at least 2-3 years was needed. The mean follow-up of our single-centre study was 3 years with a maximum of 4. The main difference in long-term changes of small solute transport was observed exactly between the 3 and 4 years of treatment: MTACs of creatinine, urea and urate stayed stable in the ACEi/ARB group, while they increased dramatically in controls \(^{(8)}\). Interestingly, we could not find similar effects on transport of fluid and proteins. However, a significant decrease in small pore water transport was observed in the ACEi/ARB group, while in the control group this value did not change, and at the end of study small water transport was similar for both
groups. Thus, in ACEi/ARB patients clearances of small solutes and small pore fluid transport followed the same time-course, as was previously reported by others \(^{(9)}\). Small pore transport as well as transport of small solutes is dependent on the effective vascular surface area. In the 1st year of our study, given their values for MTACs of low molecules, patients treated with ACEi/ARB could have been characterized as fast transporters. This could be explained by twofold higher number of diabetics when compared to controls. A marked decrease in low molecules transport parameters after the 1st year on PD in fast transporters was previously shown by others \(^{(9,10)}\), and was explained by a reduced production of cytokines and vascular endothelial growth factor (VEGF) by mesothelial cells \(^{(11,12)}\). The later increase of peritoneal transport, which most likely happened due to neoangiogenesis and enlargement of vascular surface area, was observed in the control group and absent in ACEi/ARB patients and therefore suggests a protective effect of these medications.

Improved ultrafiltration capacity in respond to treatment with ACEi or ARB was reported from animal studies \(^{(13,14)}\). In those studies a positive result was seen in cases of severe fibrosis and even sclerosis of the peritoneum. The possible explanation why we could not find a difference in fluid kinetics between the two groups is probably the relatively short follow-up: the mechanisms of water transport were still intact in the control group. It is known, that only one third of patients develops ultrafiltration failure after 4 years of PD treatment \(^{(15)}\). In late (>5 years) ultrafiltration failure the passage of water through the water channels – free water transport – is usually reduced. The latter happens due to an impaired osmotic conductance of the peritoneal membrane \(^{(16)}\). In our study in both groups neither small pore nor free water transport were found to be impaired at the end of follow-up.

With regard to an effect on transport of proteins, we could not confirm earlier results of Coronel et al. that oral administration of ACEi or ARB leads to a reduced leakage of proteins from the circulations into the dialysate \(^{(17,18)}\). In a recent study with a cross-over design in 15 prevalent PD patients these authors reported decreased protein clearances after 30 days of irbesartan treatment \(^{(18)}\). The transport of macromolecules is more dependent on the intrinsic permeability of the membrane, rather than on the vascular surface area and the number of large pores. The intrinsic permeability of the membrane would be impaired in case of marked fibrosis or even sclerosis of the peritoneum \(^{(19)}\). Most likely, in our studied population such membrane alterations did not take place and the number of large pores was similar in both groups.

We could not find any associations between use of the AII inhibitors and the develop-
ment of encapsulating peritoneal sclerosis (EPS). Compared to the controls matched for PD duration, the use of ACEi/ARB seemed to be similar in both groups. A potential shortcoming of such a retrospective analysis is that initially there was no study set up to investigate effects of ACEi/ARB. Patients, who developed EPS, more often had kidney transplants during their PD treatment. Absence of follow-up in periods without PD treatment (functioning graft, HD therapy) together with no information about patients compliance makes it difficult to draw a conclusion. On the other hand, during such a long time-course of PD peritoneal membrane is exposed to so many altering factors, that potential membranoprotective effects of ACEi/ARB could have been attenuated.

**Influence of ACEi/ARB treatment on PD technique and patients survival**

The main shortcoming of observational studies on potential effects of medications is bias by indication. In case of treatment with ACEi/ARB only studies on their impact on peritoneal membrane function could be considered free from such a confounding factor, as these medications had never been prescribed with the purpose to protect the membrane. A big body of evidence exists on the positive influence of ACEi/ARB on residual renal function preservation and survival in patients with chronic kidney disease (CKD). Although not proven in the ESRD population, for some physicians such effects could have been a reason for administration of ACEi/ARB in PD patients. Given an amount of evidence on beneficial effects of AII inhibitors, one could expect the majority of PD patients to be prescribed ACEi/ARB. However, observational studies in literature report only 25-50% of patients on PD receiving these medications. Reasons, why exactly these drugs were prescribed to some patients and were not to others, remain uncertain. When comparing PD patients with and without ACEi/ARB treatment in the Netherlands, we found treated patients to be slightly younger, more often to have diabetes, higher blood pressure at the baseline, and more cardiovascular comorbidity. This supports the fact that the common indications for ACEi/ARB prescription are hypertension and heart failure, especially in patients with diabetes. In contrast, the only study with such a comparison recently reported a much bigger age difference together with similar comorbidity between treated and untreated patients. On the other hand this study population generally contained a higher percentage of diabetics than in the Netherlands. Such differences in studied populations could explain the discrepancy of the obtained results: the study of Fang et al. reported a significant positive effect of ACEi/ARB on PD patients’ survival while we could not show any. In our study a potential positive effect of ACEi/ARB treat-
ment on survival could have been opposed with higher comorbidity in treated patients and presence of older age in untreated patients. In the study of Fang et al. the much younger age of patients on ACEi/ARB and a comorbidity, similar to controls, could explain the obtained effect on survival. Correction for age cannot exclude residual confounding.

Absence of data on reasons for ACEi/ARB prescription in patients undergoing PD makes it also difficult to analyze their effect on residual renal function in an observational study. Although the patients from both groups did not differ very much, more subjects among the treated patients had strong indications for these medications, like diabetics, higher BP, etc. The same type of patients is characterized by a more rapid decline in RRF (23;24). Thus, the bad effect may have balanced the good and that is why at the end there was no difference between treated and controls. On the other hand, the only study design, which could confirm an unbiased effect of the drug, is a randomised controlled trial (RCT). Two RCTs, recently investigated this subject, studied a very selective group of PD patients which are not representative for the general PD population and yet showed some discrepancy in their results (25;26). Therefore, up-to-day any explanation for an absence or presence of a positive effect of ACEi/ARB on rGFR in PD patients remains speculative.

The hypothesis that membranoprotective properties of AII inhibitors could positively influence PD technique survival was partially supported by our study: patients with the longest exposure to ACEi/ARB stayed longer on PD while untreated patients had the shortest PD duration. However, after the in-depth study of actual reasons for PD treatment discontinuation, we concluded that in the Netherlands the highest risk to switch from PD to HD is during the first 3 months after the start, and it is mainly caused by catheter complications and psychosocial reasons. Reasons for technique failure due to worsening of membrane’s function, like ultrafiltration failure, are much more relevant after 3-4 years of PD treatment and yet still accounted for less than 10% of all drop-outs. But, as we previously mentioned, the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD) was not initially aimed to study survival of PD technique and therefore the documented reasons to switch to HD might be questionable. For example, should a patient, already manifesting signs of ultrafiltration failure, develop peritonitis, his transfer to HD will probably be documented as due to infection. Therefore, most likely the number of PD drop-outs due to a failing membrane function could have been underestimated. On the other hand, patients with diabetes and cardiovascular disease had a higher risk to drop out from PD and, as it is known that such patients more often use ACEi/ARB, the potential positive effect of these medications on survival on
PD is counteracted by comorbidity. Nevertheless, patients with the longest ACEi/ARB treatment tended to stay on PD longer, so a possible positive impact of these medications cannot be ruled out.

**Future investigations**

Confirmation or rejection of the described above findings is possible by conducting a randomized controlled trial, specifically powered to study effects on peritoneal membrane function, residual renal function, patients’ and technique survival. However, there are some limitations that may be difficult to overcome. First of all, many PD patients would probably benefit from the ACEi/ARB treatment and randomization might be considered unethical in countries were these drugs are available for everybody. If only including the ones without strict indications for these drugs the studied cohort would contain much selected patients who do not represent the general PD population. On the other hand, taking to account that literature reports maximum of only 50% of PD patients using these medications and the actual evidence that this cohort would benefit from using these drugs is absent, it may be feasible to conduct such a study. Another difficulty could be a need for a follow-up of at least 4-5 years in order to be able to investigate the long-term effects of ACEi/ARB treatment. Taking to account the median PD technique survival rate, a sufficient number of patients should still be included in the study at the end of the follow-up to show conclusive results. The latter makes such a trial to be an expensive and therefore hard to realize project. However, the evidence it can provide is worth the effort.

Reference List


(5) Westhenen R van, Dragt CAM, Kunne C, Zweers MM, Krediet RT. Lisinopril protects against the development of fibrosis during chronic peritoneal exposure to dialysis fluid. Perit Dial Int 2004; 24 (suppl 2), S10.


Summary

Peritoneal dialysis (PD an effective method of renal replacement therapy (RRT). Especially in young patients with low comorbidity this method offers much flexibility and independence when compared to hemodialysis (HD), it has been shown that transplantation following PD treatment is associated with better outcome than after HD. However, long-term PD technique survival is a challenge in majority of patients and data from literature usually report 50-60% in 3 years. The latter motivates to search for possibilities to prevent such an early drop-out by preserving the peritoneal membrane and maintaining RRF. Long-term protection of the peritoneal membrane has been suggested by experimental trials in vitro and in vivo, which found drugs inhibiting the effects of Angiotensin II (ACEi/ARB) to attenuate development of peritoneal alterations. Effect of preservation of renal function by these medications in stage I –IV chronic kidney disease (CKD) patients is known for more than two decades. Translating such an effect on patients undergoing dialysis would be reasonable. Yet, the population of patients with end-stage renal disease (ESRD) is the least studied, and effects of ACEi/ARB treatment on RRF in PD patients were reported only by a few trials. Possible membrande protective properties of ACEi/ARB in long-term PD patients have not been described yet, and the aim of this thesis was to evaluate such an impact as well as other possible effects on important clinical outcomes.

Chapter 1 provides a short general introduction to the subject of the thesis, particularly to the method of peritoneal dialysis and its functional disturbances that may occur in a long-term treatment.

Chapter 2 presents two studies which investigated effects of ACEi/ARB on peritoneal membrane function in patients undergoing PD for 2-4 years. The first one is given in chapter 2.1 and is a single centre study with 66PD patients included. 36 patients were treated with ACEi/ARB during the follow-up; the other 30 patients did not receive these medications within this period. The two groups were compared with regard to changes in peritoneal transport of small solutes, proteins and fluid. A different time course of the small solute clearances was found between the groups: the untreated group showed the expected “U”-shape trend, with a significant increase of MTACs after 3 years of PD, while the treated group showed a descending trend after the 1st year and stable values further on. This was not present for the transport of macromolecules and water.

The study, described in chapter 2.2 was aimed to confirm results found in 2.1 in population of 217 incident PD patients participating in the Netherlands Cooperative Study on Ad-
equacy of Dialysis (NECOSAD). The included patients were also treated with PD for at least 2 years and were followed from the start of PD therapy for a maximum of 4 years. 120 received ACEi/ARB treatment and 97 did not. In the NECOSAD database, a 24-hour D/P creatinine ratio is the only peritoneal transport parameter available for analysis. When time courses of 24-hour D/P creatinine of both groups were compared, the results confirmed our previous findings: in untreated patients creatinine transport significantly increased during the follow-up while it remained stable in ACEi/ARB patients. Additionally we analyzed patients’ and PD technique survival with regard to treatment with ACEi/ARB. While no effect of these drugs on patients’ survival was found, we showed a tendency for better technique survival in patients who received ACEi/ARB for at least 75% of their follow-up time.

We concluded that in PD patients the use of ACEi/ARB is associated with no increase in small solute transport after 3 years of PD treatment. This suggests less neoangiogenesis in the membrane and could be considered as a membranoprotective effect of the medications. Additionally, the found association between a longer use of ACEi/ARB and a better PD technique survival, when compared to no treatment, suggests a possible link between the above effect of the medications and survival of the technique.

In Chapter 3 the study on possible effect of AII inhibitors on preservation of residual renal function in PD patients is given. The study includes two types of analysis: an intention-to-treat analysis in all non-anuric incident PD patients participating in the NECOSAD and an as-treated analysis of a selected group of patients. Intention-to-treat analysis with 251 patients treated with ACEi/ARB and 201 untreated showed no difference in the rate of decline in residual glomerular filtration rate (rGFR). For the second analysis we selected patients without strict indications for ACEi/ARB who theoretically could be randomized, divided them into 2 groups on an as-treated basis and followed their rGFR during the 1st year of PD treatment. Again, no difference in time-course of rGFR was found between the groups.

We concluded that the found results are in controversy to the literature reports, and this is due to the fact that an observational study is not able to show a conclusive outcome being biased by indication. However, the only study which is free of such a bias is a randomised controlled trial (RCT) which so far also failed to show reliable results. In order to study a possible effect of ACE/ARB on rGFR in PD patients, a well-conducted RCT with sufficient power is needed.

Chapter 4 presents an overview on today’s available evidence on effects of ACEi/ARB treatment in patients with CKD with a separate emphasis on dialysis patients and novel PD find-
ings in particular. The main conclusion from the literature review is that in patients with CKD stage I-IV ACEi and ARB may provide beneficial effects beyond their main indications, that is treatment of hypertension and heart failure. However, very little data exist in patients treated with dialysis or after the kidney transplantation. Observational data suggest a big diversity in the use of ACEi/ARB in these cohorts of patients because of lack of evidence on their effects.

In Chapter 5 we investigated whether the use of ACEi/ARB could also attenuate the development of encapsulating peritoneal sclerosis (EPS). For this purpose we compared 24 EPS patients with long-term controls matched for PD duration and PD centre. Patients who developed EPS were younger and more often underwent multiple kidney transplantations and abdominal surgeries. The exposure to ACEi/ARB during the PD treatment period(s) was not different between the two groups; therefore our assumption that the use of AII inhibitors may also be protective against EPS development was not confirmed. The conclusion was that such a retrospective analysis of the patient data cannot confirm or reject an effect of the medications, because of no initial intention to study this subject. Therefore the number of studied patients, absence of the follow-up in PD-free periods (switch to hemodialysis, transplantation and functioning renal graft) and lack of the data on patients’ compliance makes the obtained results inconclusive. On the other hand, such a long course of PD treatment that usually precedes the development of EPS is associated with influence of many other negative factors that may potentiate an occurrence of this complication. Therefore, a possible protective effect of ACEi/ARB treatment could have been obscured.

Chapter 6 is dedicated to a detailed analysis of PD technique survival in cohort of 709 incident PD patients participating in the NECOSAD. We studied reasons for PD discontinuation time-dependently, comparing 4 time periods: the first 3 months of PD treatment, 3-12 months, 12-24 months and 24-36 months. Interestingly enough, we found that in the Netherlands patients most often discontinue PD treatment due to receiving a kidney transplant. The risk of actual PD technique failure (switch to hemodialysis due to treatment insufficiency) was found to be highest in the earliest couple of months after PD initiation. The leading causes for early switches to HD were mainly related to catheter function and psychosocial issues. The contribution of these reasons is diminishing with time on PD, giving the space for higher rates of peritoneal membrane failure and kidney transplantation. We could not detect specific risk factors for the switch from PD to HD. Risk factors for discontinuation of PD in total are the ones responsible for patients’ survival: age, cardiovascular disease, diabetes and rGFR.
We concluded that in order to improve PD technique survival much attention should be paid to the earliest months after treatment initiation. This would mainly require close monitoring of catheter function and more accurate patients selection. To diminish the number of late PD technique failures, more attention should be paid to protection of the peritoneal membrane and maintenance of its transport capacities. In order to prolong PD treatment, nephrologists should be more focused on preservation of residual renal function and on monitoring peritoneal membrane function on a regular basis.
Samenvatting

Summary in Dutch

Peritoneale dialyse (PD) is een effectieve vorm van nierfunctievervanginge therapie. Vooral jonge patiënten met weinig comorbiditeit hebben baat bij deze vorm van dialyse in vergelijking tot hemodialyse (HD), vanwege de grote flexibiliteit en onafhankelijkheid die de therapie biedt. Daarnaast is aangetoond dat de uitkomst na een niertransplantatie beter is na behandeling met PD dan met HD. Toch is het behoud van de PD techniek in de meerderheid van de patiënten een uitdaging, en uit de literatuur blijkt het 50 tot 60 % te zijn na 3 jaar. Daarom is het belangrijk om naar mogelijkheden te zoeken om een dergelijke vroege uitval te voorkomen, door behoud van het peritoneale membraan en de restnierfunctie. Uit experimentele in vitro en in vivo studies blijkt bescherming van het peritoneale membraan op de lange termijn waardevol, en medicijnen die Angiotensine II remmen (ACEi/ARB) lijken de ontwikkeling van peritoneale veranderingen te verminderen. Dat deze medicijnen ook zorgen voor het behoud van restnierfunctie bij chronisch nierfalen stadium I-IV is al meer dan 20 jaar bekend. Het lijkt aannemelijk dat hetzelfde effect op zou treden bij dialyse patiënten. Toch worden de patiënten met eindstadium nierfalen het minst bestudeerd, en effecten van behandeling met ACEi/ARB op restnierfunctie in PD patiënten zijn slechts in enkele studies onderzocht. Mogelijke beschermende effecten van ACE/ARBi op het peritoneale membraan van chronische PD patiënten zijn nog niet beschreven. Het doel van dit proefschrift was om een dergelijk beschermend effect, naast mogelijk andere effecten op belangrijke klinische uitkomstmaten, te bestuderen.

Hoofdstuk 1 is een korte algemene introductie over het onderwerp van dit proefschrift, voornamelijk de methode van peritoneale dialyse en de functionele problemen die kunnen optreden op de lange termijn.

Hoofdstuk 2 bevat twee studies die de effecten bestuderen van ACEi/ARB op de functie van het peritoneale membraan van PD patiënten die 2 tot 4 jaar dialyseren. De eerste studie wordt beschreven in hoofdstuk 2.1 en betreft een studie die is uitgevoerd in één medisch centrum waarbij 66 PD patiënten werden geïncludeerd. Van deze patiënten werden er 36 behandeld met ACEi/ARB gedurende de studieperiode en 30 niet. Veranderingen in peritoneaal transport van kleine deeltjes, eiwitten en water, werden vergeleken tussen deze twee groepen. Er werd een verschil tussen de groepen gevonden in het beloop van het kleine deeltjes transport: de onbehandelde groep toonde het verwachte U-vormige beloop met een significante toename in MTACs na 3 jaar PD, terwijl de behandelde groep een neerwaartse
trend na het eerste jaar toonde met daarna stabiele waarden. Dit was niet het geval voor het transport van macromoleculen en water.

De studie die in hoofdstuk 2.2 wordt beschreven had als doel de resultaten van eerste studie uit 2.1 te bevestigen in 217 incidente PD patiënten die deelnamen aan de “Netherlands Cooperative Study on Adequacy of Dialysis” (NECOSAD). De geïncludeerde patiënten werden eveneens ten minste 2 jaar met PD behandeld, en werden vanaf de start met PD tot aan een maximum van 4 jaar vervolgd. Van deze groep patiënten werden er 120 behandeld met ACEi/ARB en 97 niet. In de database van de NECOSAD is de enige beschikbare parameter om peritoneaal transport te analyseren een 24-uurs dialysaat/plasma ratio (D/P) van kreatinine. Bij de vergelijking van het beloop van 24-uurs D/P kreatinine werden de resultaten van de eerst genoemde studie bevestigd: er was een significante toename in het transport van kreatinine in onbehandelde patiënten gedurende de studie periode, terwijl dit stabiel bleef in de ACEi/ARB groep. Daarnaast hebben we het behoud van de PD techniek en de overleving van patiënten vergeleken tussen de groepen. Behandeling met ACEi/ARB leek geen effect te hebben op de overleving van patiënten, maar er was wel een neiging tot beter behoud van de PD techniek in patiënten die ten minste 75% van de studie periode werden behandeld. We kunnen hieruit concluderen dat het gebruik van ACEi/ARB in PD patiënten is geassocieerd met het uitblijven van een toename in het kleine deeltjes transport na 3 jaar PD. Dit suggereert dat er minder peritoneale vaatnieuwvorming plaats vindt en dus dat ACEi/ARB een beschermend effect zouden hebben op het membraan. De gevonden associatie tussen langer gebruik van ACEi/ARB en een beter behoud van de PD techniek, suggereert eveneens een mogelijk verband tussen het beschermende effect van deze middelen en het behoud van de PD techniek.

**Hoofdstuk 3** beschrijft een studie naar het mogelijke effect van AII-remmers op het behoud van restnierfunctie. In deze studie zijn twee soorten analyses gedaan: een zogenaamde “intention-to-treat” analyse in alle niet-anure incidente PD patiënten die deelnamen aan de NECOSAD, en een zogeheten “as-treated” analyse voor een geselcteerde groep patiënten. De “intention-to-treat” analyse, met 251 patiënten die behandeld werden met ACEi/ARB en 201 patiënten die deze medicijnen niet kregen, toonde geen verschil in de mate van afname van de restnierfunctie. Voor de tweede analyse hebben we patiënten geselecteerd zonder een strikte indicatie voor het krijgen van ACEi/ARB die theoretisch gerandomiseerd zouden kunnen worden. De hiervoor in aanmerking komende patiënten werden in twee groepen verdeeld op basis van hun behandeling met of zonder ACEi/ARB en hun restnierfunctie werd
gedurende het eerste jaar van de PD therapie vervolgd. Wederom werd er geen verschil in het beloop van de restnierfunctie gevonden tussen de groepen.

Hieruit blijkt dat onze resultaten de in de literatuur beschreven studies tegenspreken. Dit komt waarschijnlijk doordat een observationele studie waarin therapiën met elkaar worden vergeleken zogeheten “confounding by indication” niet kan uitsluiten. Echter, de enige studie waarin dit wel kan, is een gerandomiseerde gecontroleerde studie, die tot nog toe ook geen uitkomst heeft kunnen bieden. Om mogelijke effecten te kunnen bestuderen van ACEi/ARB op de restnierfunctie van PD patiënten is een goed opgezette gerandomiseerde gecontroleerde studie nodig.

**Hoofdstuk 4** is een samenvatting van het huidige beschikbare bewijs van de effecten van ACEi/ARB behandeling in patiënten met chronisch nierfalen. De samenvatting legt specifieke nadruk op dialyse patiënten en nieuwe bevindingen op het gebied van PD. De belangrijkste conclusie van deze literatuur samenvatting is dat de behandeling met ACEi/ARBs een gunstig effect lijkt te hebben bij patiënten met stadium I-IV nierfalen. Dit gunstige effect gaat verder dan het effect van de behandeling van hypertensie en hartfalen, de belangrijkste indicatie voor deze medicijnen. Er is echter maar zeer weinig bekend over de effecten van ACE/ARB therapie bij dialyse patiënten of na een niertransplantatie. De observationele studies geven verschillende aanbevelingen voor het gebruik van ACEi/ARBs in deze specifieke groep patiënten omdat er een gebrek is aan bewijs.

In **hoofdstuk 5** hebben we onderzocht of het gebruik van ACEi/ARBs de ontwikkeling van encapsulerende peritoneale sclerose (EPS) kan afremmen. We hebben 24 chronische PD patiënten die EPS hebben ontwikkeld, vergeleken met controle patiënten. De controle patiënten werden gepaard aan EPS patiënten op basis van een gelijke PD duur en behandeling in hetzelfde centrum. Patiënten die EPS ontwikkelden waren vaak jonger en hadden vaker meerdere niertransplantaties en abdominale operaties ondergaan. De blootstelling aan ACEi/ARB therapie tijdens de PD therapie was niet verschillend tussen de twee groepen. De aannemen dat het gebruik van angiotensine II inhibitoren zou beschermen tegen de ontwikkeling van EPS, werd hiermee niet bevestigd. Er werd geconcludeerd dat een dergelijke retrospectieve analyse van de patiëntgegevens het effect van de medicatie niet kan bevestigen noch kan verwerpen, omdat dit onderwerp niet het oorspronkelijke doel was van het onderzoek. Mede door het aantal bestudeerde patiënten, de afwezigheid van follow-up in de PD-vrije perioden (de overgang naar hemodialyse, transplantatie en een functionerende transplantatienier) en missende data betreft therapietrouw, konden de verkregen resultaten niet
tot een definitieve conclusie leiden. Wel is een dergelijk lange PD duur die voorafgaat aan de ontwikkeling van EPS geassocieerd met vele andere negatieve factoren die de ontwikkeling van deze complicatie zouden kunnen versterken. Hierdoor zou een mogelijk beschermende werking van ACEi/ARB therapie kunnen zijn verduisterd.

**Hoofdstuk 6** bevat een gedetailleerde analyse van het behoud van de PD techniek in een cohort van 709 incidente PD patiënten die deelnamen aan NECOSAD. We hebben de oorzaken van het beëindigen van PD therapie tijdsafhankelijk onderzocht door 4 tijdsperiodes te bestuderen: de eerste 3 maanden van PD therapie, 3-12 maanden, 12-24 maanden en 24-36 maanden. Een interessante bevinding was dat in Nederland de PD therapie voornamelijk beëindigd wordt doordat patiënten een transplantatie naar krijgen. Het risico op het falen van de PD techniek (overgang naar hemodialyse door insufficiënte behandeling) was het grootst tijdens de eerste maanden na het starten van PD. De meest voorkomende oorzaak voor een vroege overstap naar HD werd voornamelijk gerelateerd aan het functioneren van de catheter en psychosociale zaken. De bijdrage van deze oorzaken naarmate de PD duur vordert, waardoor er meer ruimte komt voor oorzaken als peritoneaal membraan falen en niertransplantatie. Wij konden geen specifieke risicofactoren voor de overgang van PD naar HD ontdekken. Risicofactoren voor het beëindigen van PD zijn dezelfde risicofactoren die verantwoordelijk zijn voor de overleving van de patiënt: leeftijd, cardiovasculaire ziekte, diabetes en restnierfunctie.

Om het behoud van de PD techniek te kunnen verbeteren, moet er meer aandacht worden besteed aan de eerste maanden na de start van de therapie. Het monitoren van de catheter functie en een nauwkeurigere selectie van de patiënten zouden dan vereist zijn. Om falen van de PD techniek in een later stadium te voorkomen, zou er meer aandacht moeten worden besteed aan bescherming van het peritoneale membraan en aan onderhoud van zijn transport capaciteit. Voor verlenging van de PD duur, zouden nefrologen meer gericht moeten zijn op het behoud van de restnierfunctie en op het regelmatig monitoren van de functie van het peritoneale membraan.
Aknowledgement

In conclusion, I would like to thank everybody who gave me a hand during my work on this thesis.

First of all, I would like to thank my promoter, Professor Raymond Krediet. Dearest Ray, thank you for actually giving me this opportunity to work here with you. Looking back I do realise how much I have learned during this time. Thank you for the guidance and support through all these years. I can hardly imagine having a better supervisor, which makes me sad to realise that, most likely, this can not happened twice.

Words could hardly express my gratitude to Sarah Prichard. Dear Sarah, people say that everything happens for a reason. Where I am now is definitely a consequence of me getting to know you almost 10 years ago. You have made an enormous impact on my life - I was given an opportunity to listen and to learn from you I will always be thankful for.

I would like to thank my co-promotor, Friedo Dekker. Dear Friedo, I am grateful for all your help and all the time you've managed to find for me in your busy life.

Big “thank you” is dedicated to the co-promotor Dirk Struijk. Dearest Dirk, your kindness and help supported me many times in different situations. I will always remember that.

With a big gratitude I would like to aknowledge members of the promotion commission: Prof. Lameire, Prof. Navis, Prof. ten Berge, Prof. Levi and Joke Korevaar. Thank you for reviewing this thesis; it has been an honour for me.

I am very thankful to Els Boeschoten, director of Hans Mak Institute and a co-author in a number of my publications. Dear Els, thank you for all your support through these years, I will always remember your kindness.

My special thanks to the Baxter Nederland BV and stichting Nephron for their financial support that made it possible to attend international conferences.
To my dear paranymphs, Marlies Noordzij and Anniek Vlijm: Marlies, your genuine “epidemiological” help through all this time was priceless and always kept me on surface, preventing from drowning. Also not to forget our travelling together times! Anniek, a better paranymph I could ever imagine, thank you! There are not enough pages left to acknowledge all your friendly help.

My special words for Vianda Stel: thank you for giving me a hand when I needed it. It would have been very difficult without you.

My dear colleagues from the flexroom: Denise, Wieneke, Marijke, Deiresa, Carmen, Annemieke and Olga. It has been unforgettable times together inside the flex and outside travelling!

Dear NECOSAD colleagues: Renee, Diana, Marion, Melissa, Marike, Ylva and Martijn, thank you for the input and fun together.

Mama and papa, words cannot express all the love and support I felt even from this long distance. It would be much harder without it!

Lau, darling, you were my rock to steady and support me through all this time. Without your loving help it would have been hard to keep going and I thank you for that.