Are ACEI/ARBs associated with the decreased peritoneal protein clearance in long-term PD patients?

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Abstract

Objective. Peritoneal protein clearance (PrC) is recognized as a new marker of systemic endothelial dysfunction and predictor of mortality in patients on peritoneal dialysis (PD). Given that angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARBs) could improve endothelial dysfunction in the general population, we aim to explore whether this benefit is present in the PD population.

Methods. We analysed data from a PD cohort with data prospectively collected. The PrC, defined daily doses (DDDs) of ACEI/ARBs, as well as other clinical variables were recorded at baseline and then repeatedly measured at 3- to 6-month intervals till to death or censoring. A total of 156 patients were treated with ACEI/ARBs with 0.60 of median time-averaged DDDs, the untreated group consisted of 149 patients who received none of the above drugs during the follow-up.

Results. The baseline and time-averaged PrC were 69.9 ± 34.7 mL/day and 75.2 ± 28.3 mL/day, respectively. Time-averaged PrC was an independent predictor of mortality adjusted for recognized confounders in a multivariate Cox regression model (P = 0.037). There were no significant differences in the time course of PrC (P = 0.82) and peritoneal protein loss (P = 0.83) between the ACEI/ARBs group and the untreated group after adjustment for age, gender, diabetes, baseline C-reactive protein, mean blood pressure and baseline PrC or baseline peritoneal protein loss in the generalized linear mixed model.

Conclusions. We conclude that ACEI/ARBs did not correlate with a decreased PrC in this observational study. The effect of higher doses of ACEI/ARBs needs to be determined in future interventional studies.

Keywords: ACEI; ARBs; mortality; peritoneal dialysis; peritoneal protein clearance

Introduction

Cardiovascular disease (CVD) accounts for ~50% of the annual mortality in end-stage renal disease, including peritoneal dialysis (PD) and hemodialysis (HD) [1–3]. Endothelial dysfunction, a pathological state of impairment in endothelium-dependent vasodilation, is now considered to play a principal role in the initiation and progression of atherosclerosis in healthy individuals, patients with hypertension, diabetes as well as chronic kidney disease [4]. Since the endothelium is responsible for regulating systemic vascular permeability, protein leakage through urine is probably preceded by an impaired endothelium [4–7]. Accordingly, a couple studies have shown that microalbuminuria, as a surrogate marker of endothelial dysfunction, is a strong and independent predictor of poor outcome in the chronic kidney disease and dialysis population [8–10].

For PD patients, leakage of protein through the peritoneal membrane resembles the protein loss through urine. A dysfunctional endothelium is supposed to be associated with great protein permeability and protein leakage through the peritoneal membrane [11]. Therefore, peritoneal protein loss or protein clearance (PrC) is also considered as a surrogate marker of endothelial dysfunction. In recent studies, PrC has been shown to be associated with the prevalence of peripheral arterial disease (PAD), cardiovascular events and higher mortality in this population [11–13].

To our knowledge, evidence exists that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) ameliorate microalbuminuria and endothelial dysfunction in the general population [14, 15]. This benefit not only accounts for the antihypertensive effect but also for reducing vascular inflammation, smooth muscle cell remodeling and oxidative stress, which in turn decrease the cardiovascular risk, CVD events and mortality [16–21].

We hypothesized that the inhibition of angiotensin II (AII) effects induced by ACEI/ARBs could also decrease PrC in PD patients. However, the related evidence on this hypothesis is lacking. As shown in two previous pilot studies, treatment with irbesartan for 30 days reduced peritoneal protein loss and thus improved nutrition status in 15 PD patients [22]. Candesartan could also attenuate peritoneal albumin clearance and albumin loss in seven hypertensive continuous ambulatory peritoneal dialysis (CAPD) patients during a
12-week study period [23]. After these two reports, no further study was performed to verify their encouraging findings. In this study, we aimed to determine the association between usage of ACEI/ARBs and time course of peritoneal protein loss and PrC in a large PD population through a longitudinal cohort study.

Patients and methods

Subjects and follow-up

Our study enrolled a total of 305 incident patients who had started PD and had lived > 6 months in our unit between July 2002 to February 2007. All patients could visit a physician at least once every 3 months. Demographic and clinic data were collected within the week preceding PD catheter implantation, including age, gender, body mass index (BMI), presence of diabetes, CVD and PAD. CVD was recorded if one of the following conditions was present: angina, Class III–IV congestive heart failure classified by the New York Heart Association (NYHA) classification, transient ischemic attack, history of myocardial infarction or cerebrovascular accident [24]. PAD was defined as intermittent claudication, or arterial failure classified by the New York Heart Association classification, transient ischemic attack, history of myocardial infarction or cerebrovascular accident [24]. PAD was defined as intermittent claudication, or arterial failure classified by the New York Heart Association classification, transient ischemic attack, history of myocardial infarction or cerebrovascular accident [24]. All patients started PD immediately after catheter implantation.

Biochemistry, fluid, small-molecule solute (peritoneal transport rate) and protein loss were evaluated during the first 3 or 6 months as the baseline values and were repeated at regular intervals. All the measurements throughout the study were calculated as averaged values. All patients were provided with lactate-buffered glucose dialysate, twin-bag connection system (Baxter Healthchare, Guangzhou, China) and treated with CAPD after the first 3 months. All patients were followed until 28 February 2008. All-cause deaths were recorded. The study was approved by the Medical Ethical Committee of Peking University. Written informed consent was obtained from each patient.

Measurement of blood pressure and ACEI/ARBs usage

Systolic and diastolic blood pressure (SBP and DBP) was measured according to the standard method. Mean arterial pressure (MAP) was defined as the diastolic pressure (in millimeter of mercury) plus one-third of the pulse pressure. The SBP, DBP and MAP during the first 3 months were averaged as the baseline values.

ACEI/ARBs was quantified by the defined daily dose (DDD) developed by the World Health Organization [26]. The ACEI and ARBs DDDs were recorded, respectively, at each clinic visit. Then, the mean DDDs for every 3 months were calculated as time-point values for each patient. The averaged ACEI and ARBs DDDs were calculated based on these follow-up data.

Biochemical and inflammation marker

Biochemical indices including hemoglobin (Hb) and serum albumin (Alb) were examined using an automatic Hitachi chemistry analyzer. Biochemical indices during the first 3 months were represented as baseline values. Serum high-sensitive C-reactive protein (CRP) measured by immune rate nephelometric analysis during the first year was represented as baseline value.

Peritoneal transport rate, fluid, small-molecule solute removal and protein loss through dialysate and urine

The 24-h dialysate and urine were collected 1 day before the clinic visit. Peritoneal transport rate was represented as the ratio of 24-h dialysate-to-plasma creatinine (D/Per), which was verified as a reliable method in CAPD patients [27]. The urea and creatinine levels in 24-h dialysate, 24-h urine and serum were simultaneously examined by using the automatic Hitachi chemistry analyzer. Weekly total Kt/V, urea, residual renal clearance (Ccr) and residual renal function (RRF) were calculated using standard methods. Peritoneal and urine protein losses were measured from the 24-h dialysate effluent and 24-h urine, respectively. PrC was calculated by the following equation [28]; 24-h dialysate protein loss/ (serum albumin/0.4783) in the unit of milliliter of plasma per day. All the measurements were evaluated during the first 6 months and represented as baseline values. PrC, 24-h dialysate protein loss and 24-h urine protein loss were collected at a 6-month interval and calculated as time-averaged values.

Statistical analyses

Statistical analyses were performed using the SPSS software package (version 13.0. SPSS, Chicago, IL). All the reported P-values were two tailed, and statistical significance was set at 0.05. Parametric data are presented as mean ± SD. Nonparametric data are presented as median values with their interval from the 25th to 75th percentile. Categorical variables were expressed as percentage or ratio. Patient data were compared by using the chi-square test for categorical variables and by using the Mann–Whitney U-test for continuous variables. Multivariate Cox regression models were performed to test the association of PrC (baseline PrC and time-averaged PrC) and mortality, which were adjusted for age, gender, preexistent CVD, diabetes, baseline or averaged CRP, RRF, dialysate output and D/Per. To determine the effect of ACEI/ARBs, we include the usage of ACEI/ARBs into these models, respectively. The hazard ratios (HR) and their 95% confidence interval (CI) for death were shown in the final results. To analyse the time course of PrC with respect to the use of ACEI/ARBs and drug doses, we use 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 within the same patient. The multivariate model contained PrC as a dependent variable and treatment as an independent variable, adjusted for age, gender, diabetes, baseline CRP, mean blood pressure and baseline PrC.

Results

Subject demographics and follow-up

We followed 305 incident PD patients (129 male and 176 female), with a mean age of 59.4 ± 14.2 years and BMI of 23.4 ± 3.8 kg/m² for 31.4 ± 13.7 months (range: 8–64 months). Diabetes was present in 40.3% (123/305), CVD in 69.1% (206/298) and PAD in 5.7% (17/297) of these subjects. At the end of study, 187 (61.3%) patients were still maintained on PD, 74 (24.3%) had died, 16 (5.2%) had transferred to HD, 24 (7.9%) had undergone renal transplantation and 4 (1.3%) had transferred to other hospitals. Thirty-two (10.5%) patients died of cardiovascular events.

The usage of ACEI/ARBs during the follow-up

A total of 156 (51.1%) patients were treated with ACEI/ARBs during the entire follow-up, 149 (48.9%) patients did not receive these drugs. The median of time-averaged DDDs for the ACEI/ARBs group was 0.60 (0.18–1.24) (Figure 1). The median of ACEI and ARB DDDs are 0.54 (0.15–1.11) and 0.42 (0.13–0.80), respectively. The baseline demographics and clinical data of patients treated with and without ACEI/ARBs were compared as shown in Table 1. The subjects in the ACEI/ARBs group were prone to be male (P <0.001) and young (P = 0.005). They also had higher mean blood pressure (P <0.001) and prevalence of diabetes (P = 0.002) when they started the PD program. In regard to inflammation, subjects in the untreated group had higher baseline CRP levels compared to the ACEI/ARBs group (4.1 versus 2.4 mg/L, P = 0.004). There were no significant differences in the prevalence of CVD and PAD, hemoglobin and serum albumin between the two groups.

Peritoneal transport, renal function and protein clearance

Data on peritoneal transport rate, renal function, protein clearance through urine and dialysate are given in Table 2. The baseline peritoneal transport rate and renal function
were not significantly different between the two groups. Patients in the ACEI/ARBs group had higher urine protein loss (0.97 versus 0.65 g/day, \( P < 0.001 \)) and dialysate output (5965 versus 5485 mL/day, \( P = 0.044 \)), but they had no significant difference in peritoneal protein loss (\( P = 0.25 \)) and PrC (\( P = 0.45 \)).

**PrC is an independent predictor for all-cause mortality**

The baseline and time-averaged PrC were 69.9 \( \pm \) 34.7 mL/day and 75.2 \( \pm \) 28.3 mL/day, respectively, in this cohort. The predictability of PrC was evaluated by multivariate Cox regression models. After adjustment for age, gender, preexistent CVD, diabetes, usage of ACEI/ARBs, baseline CRP, RRF, dialysate output and D/Pcr, baseline PrC was not an independent significant predictor of all-cause death (\( P = 0.096 \)). After adjustment for age, gender, preexistent CVD, diabetes, averaged CRP, RRF, dialysate output and D/Pcr, time-averaged PrC was an independent significant predictor of all-cause death (\( P = 0.037 \)). In this model, for every 10 mL/day increase in time-averaged PrC, the adjustment HR was 1.11 (1.01–1.21, \( P = 0.037 \)) (Table 3).

**Figure 1.** ACEI/ARBs DDDs in the ACEI/ARBs group.

**Table 1.** The baseline demographics and clinical data of patients treated or not treated with ACEI/ARBs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Untreated</th>
<th>ACEI/ARBs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, %</td>
<td>305</td>
<td>149 (48.9)</td>
<td>156 (51.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.4 ( \pm ) 14.2</td>
<td>61.8 ( \pm ) 13.9</td>
<td>57.2 ( \pm ) 14.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Gender, male%</td>
<td>129 (42.3)</td>
<td>47 (31.5)</td>
<td>82 (52.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23.8 ( \pm ) 4.0</td>
<td>23.1 ( \pm ) 3.6</td>
<td>24.2 ( \pm ) 3.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Female</td>
<td>23.8 ( \pm ) 3.5</td>
<td>22.8 ( \pm ) 3.9</td>
<td>23.5 ( \pm ) 4.0</td>
<td>0.26</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>206 (69.1)</td>
<td>97 (67.4)</td>
<td>109 (70.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>17 (5.7)</td>
<td>8 (5.6)</td>
<td>9 (5.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>123 (40.3)</td>
<td>47 (31.5)</td>
<td>76 (48.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>108.3 ( \pm ) 14.2</td>
<td>108.3 ( \pm ) 15.0</td>
<td>108.2 ( \pm ) 13.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35.9 ( \pm ) 3.8</td>
<td>36.2 ( \pm ) 4.0</td>
<td>35.6 ( \pm ) 3.7</td>
<td>0.21</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.2 (1.6–7.1)</td>
<td>4.1 (1.9–8.0)</td>
<td>2.4 (1.2–6.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>31.3 ( \pm ) 13.7</td>
<td>30.5 ( \pm ) 13.7</td>
<td>32.2 ( \pm ) 13.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136.2 ( \pm ) 15.3</td>
<td>131.2 ( \pm ) 15.3</td>
<td>141.1 ( \pm ) 13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.0 ( \pm ) 10.3</td>
<td>77.0 ( \pm ) 10.0</td>
<td>80.9 ( \pm ) 10.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>98.1 ( \pm ) 10.3</td>
<td>95.1 ( \pm ) 10.6</td>
<td>100.9 ( \pm ) 9.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Values are mean \( \pm \) SE, median (25th–75th percentile) or absolute numbers with percentages.

**Time course of PrC and peritoneal protein loss**

In terms of the effect of ACEI/ARBs on PrC during the long-term follow-up, we did not observe a significant difference in the time course of PrC and peritoneal protein loss between patients treated with ACEI/ARBs and untreated groups after adjustment for age, gender, diabetes, baseline CRP, mean blood pressure and baseline PrC or baseline peritoneal protein loss in the generalized linear mixed model (\( P = 0.82 \) and \( P = 0.83 \), respectively, Figure 2 and Figure 3). According to the tertile of time-averaged DDDs in ACEI/ARBs group, we further divided the ACEI/ARBs group into low, medium and high group, the DDDs was 0.11 (0.05–0.19), 0.60 (0.45–0.80) and 1.52 (1.24–1.85), respectively. No significant difference was found in the time course of PrC (\( P = 0.60 \)) and peritoneal protein loss (\( P = 0.51 \)) between patients treated with low, medium and high DDDs of ACEI/ARBs (Figure 4 and Figure 5). A total of 62 (39.7%) patients received ACEI/ARBs for <25% of the follow-up period, 60 (38.5%) patients received the drugs for 25–50% of the follow-up period and 34 (21.8%) patients for more than half. According to the time of usage, we divided the ACEI/ARBs group into minor, medium and major group. Although the statistical significance was marginal in the time course of PrC (\( P = 0.05 \)) and peritoneal protein loss (\( P = 0.059 \)) among patients who were on ACEI/ARBs treatment for a different duration, this might be due to the differences of a 36-month point for a few subjects (Figure 6 and Figure 7).

**Discussion**

It is well known that ACEI/ARBs can improve microalbuminuria and endothelial dysfunction in the general population [14, 15, 29]. In patients on maintenance PD, two previous pilot studies showed that inhibition of AII attenuate peritoneal loss of protein with small samples...
### Table 2. The baseline peritoneal transport rate and protein clearance through urine and dialysate

<table>
<thead>
<tr>
<th>Variables</th>
<th>Untreated</th>
<th>ACEI/ARBs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal protein loss, g/day</td>
<td>5.13 (3.55–6.65)</td>
<td>4.65 (3.53–6.31)</td>
<td>0.25</td>
</tr>
<tr>
<td>Urine protein loss, g/day</td>
<td>0.65 (0.39–1.19)</td>
<td>0.97 (0.54–1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peritoneal protein clearance, mL/day</td>
<td>71.5 ± 36.7</td>
<td>68.4 ± 32.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Dialysate input, mL/day</td>
<td>5840 (4000–6818)</td>
<td>5425 (4000–6600)</td>
<td>0.87</td>
</tr>
<tr>
<td>Dialysate output, mL/day</td>
<td>5485 (4005–6809)</td>
<td>5965 (4350–7650)</td>
<td>0.044</td>
</tr>
<tr>
<td>Urine, mL/day</td>
<td>863 (478–1122)</td>
<td>885 (610–1200)</td>
<td>0.14</td>
</tr>
<tr>
<td>Ultrafiltration, mL/day</td>
<td>250 (125–550)</td>
<td>350 (100–550)</td>
<td>0.32</td>
</tr>
<tr>
<td>RRF, mL/min</td>
<td>1.8 (0.8–3.8)</td>
<td>2.4 (1.3–3.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total Ccr, mL/week/1.73 m²</td>
<td>60.2 (510–72.8)</td>
<td>61.9 (53.1–74.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total Kt/V, unit/week</td>
<td>1.9 ± 0.5</td>
<td>1.8 ± 0.4</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Values are mean ± SE, median (25th–75th percentile) or absolute numbers with percentages. D/Pcr, the ratio of dialysate to plasma creatinine; Ccr, creatinine clearance.

### Table 3. Multivariate Cox regression models on patients survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted HR in Model 1</th>
<th>P-value</th>
<th>Adjusted HR in Model 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per decade</td>
<td>1.25 (0.98–1.60)</td>
<td>0.069</td>
<td>1.40 (1.10–1.76)</td>
<td>0.005</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.53 (0.84–2.81)</td>
<td>0.168</td>
<td>1.67 (0.98–2.84)</td>
<td>0.059</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.52 (0.29–0.95)</td>
<td>0.033</td>
<td>0.58 (0.35–0.96)</td>
<td>0.033</td>
</tr>
<tr>
<td>CVD</td>
<td>0.38 (0.18–0.84)</td>
<td>0.016</td>
<td>0.43 (0.22–0.86)</td>
<td>0.018</td>
</tr>
<tr>
<td>Usage of ACEI/ARBs</td>
<td>0.80 (0.46–1.41)</td>
<td>0.446</td>
<td>0.95 (0.58–1.55)</td>
<td>0.838</td>
</tr>
<tr>
<td>D/Pcr per 0.1</td>
<td>1.04 (0.87–1.25)</td>
<td>0.645</td>
<td>1.21 (0.98–1.49)</td>
<td>0.084</td>
</tr>
<tr>
<td>CRP per 10 mg/L</td>
<td>1.29 (1.14–1.46)</td>
<td>&lt;0.001</td>
<td>1.32 (1.17–1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysate output per 1 L/day</td>
<td>1.01 (0.88–1.16)</td>
<td>0.889</td>
<td>0.97 (0.85–1.10)</td>
<td>0.622</td>
</tr>
<tr>
<td>RRF per 1 mL/min</td>
<td>0.96 (0.88–1.04)</td>
<td>0.306</td>
<td>1.01 (0.94–1.09)</td>
<td>0.738</td>
</tr>
<tr>
<td>PrC per 10 mL/day</td>
<td>1.07 (0.99–1.17)</td>
<td>0.096</td>
<td>1.11 (1.01–1.21)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*D/Pcr, the ratio of dialysate to plasma creatinine. Model 1: multivariates included age, gender, diabetes, CVD, usage of ACEI/ARBs, baseline D/Pcr, CRP, dialysate output, RRF and baseline PrC. Model 2: multivariates included age, gender, diabetes, CVD, usage of ACEI/ARBs, averaged D/Pcr, CRP, dialysate output, RRF and time-averaged PrC.

and short study period [22, 23]. However, we did not observe the same benefit in the present study. At least, ACEI/ARBs at the present doses could not decrease PrC and peritoneal protein loss in long-term PD patients. To date, this is the first study to explore the association between the usage of ACEI/ARBs and endothelial dysfunction expressed as PrC in dialysis population.

There are some potential reasons for this finding. First, the medium of DDDs in ACEI/ARBs group is 0.60 in our study, which is equivalent to a half tablet of valsartan per medium of DDDs in ACEI/ARBs group is 0.60 in our study. Therefore, this is the first study to explore the association between the usage of ACEI/ARBs and endothelial dysfunction expressed as PrC in dialysis population. Although these factors were adjusted in a general linear model to compare the change of PrC or protein loss over time between groups, we could not exclude the possibility that a different extent of endothelial dysfunction existed between groups [14, 36–38]. Furthermore, long-term PD caused morphological changes in the peritoneal membrane including interstitial fibrosis, loss of the mesothelial cell layer and vasculopathy [39, 40]. Peritoneal fibrosis would tend to restrict the passage of protein. This is in line with Denise’s study, which showed that the time course of the large solutes tended to decrease with time on PD [41]. A number of studies in experimental animal models have been done, which showed that the use of ACEI/ARBs ameliorate peritoneal fibrosis [42, 43]. So if ACEI/ARBs have potential effects on prevention of peritoneal fibrosis, it would tend to restrict the protein loss. Therefore, although the findings are not statistically significant, this result is not robust enough to reject our hypothesis based on all above reasons. In the future, a randomized controlled trial with a sufficiently long follow-up period would be the best approach to explore the effect of higher doses of ACEI/ARBs on PrC. Current insights into the mechanisms of progression of PrC will also provide rationales for new therapeutic strategies.
Analysis of PD patient survival indicated that time-averaged PrC was an independent predictor of all-cause death. Our results are partially in line with previous studies [12, 13, 44]. Based on these studies, we believe that PrC is a simple and convenient survival predictor in PD patients. In addition, our data indicated that the usage of ACEI/ARBs was not an independent predictor of mortality after adjustment for other confounders. This finding further supports the results of Kolesnyk et al. and Akbari et al. while going against the results of Fang et al. [34, 45, 46]. Although ACEI/ARBs are now widely prescribed medications to control blood pressure, decrease mortality and morbidity in patients with CVD [19, 20, 22], the evidence of ACEI/ARBs for decreasing mortality and cardiovascular events in the PD population is lacking [46]. Till now, only three randomized controlled trials were conducted but have failed to show any positive results yet [47–49].

The strengths of the study include the relatively large number of patients, long duration of follow-up and adjustment for multiple confounding covariates. To date, other observational studies have used prescribed time of ACEI/ARBs to explore the benefits of ACEI/ARBs in the PD population [34, 35, 45]. Instead, doses of ACEI/ARBs presented as DDDs reflect the intensity of drugs during the study period in this study. Indeed, the regular follow-up and intensive monitoring of antihypertensive medications guarantee this unique analysis showing the
association between doses of ACEI/ARBs and peritoneal protein loss for the first time.

We are also aware of limitations with our study. The single center and observational nature of the study prevent a robust conclusion on this topic. The observational rather than interventional design cannot deal with the potential bias of endothelial dysfunction between ACEI/ARBs group and untreated group at the baseline. We do not have detailed information about the reasons why the untreated group was not prescribed ACEI/ARBs nor do we preclude that the percentage of patients who had not been treated with ACEI/ARBs before initiation of PD was different between groups, although the majority of patients were presumed not to be prescribed medications.

In conclusion, we reported that ACEI/ARBs at the present doses was not associated with a significantly decreased peritoneal protein clearance and peritoneal protein loss in this longitudinal cohort study. The effect of higher doses of ACEI/ARBs needs to be determined in the future randomized controlled trials for this population.

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Conflict of interest statement. None declared.

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