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Comparative Effectiveness of Angiotensin Receptor Blockers *vs.* Angiotensin-Converting Enzyme Inhibitors on Cardiovascular Outcomes in Patients Initiating Peritoneal Dialysis

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Abstract

Background—There is evidence that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) may reduce cardiovascular (CV) risk in patients undergoing peritoneal dialysis (PD), but no studies have compared the effectiveness between these drug classes. In this observational cohort study, we compared the association of ARB *vs.* ACEI use on CV outcomes in patients initiating PD.

Methods—We identified from the US Renal Data System all adult patients who initiated PD from 2007–2011 and participated in Medicare Part D, a federal prescription drug benefits program, for the first 90 days of dialysis. Patients who filled a prescription for an ACEI or ARB in those 90 days were considered users. We excluded patients who used both ACEI and ARB. We applied Cox proportional hazards regression to an inverse probability of treatment-weighted cohort to estimate the hazard ratios (HR) for the combined outcome of all-cause death, ischemic stroke, or myocardial infarction; all-cause mortality; and CV death.

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Research involving Human Participants

Institutional Review Boards of Stanford University and Baylor College of Medicine approved the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

For this type of study formal consent is not required.

Potential Conflicts of Interest

Financial Disclosure: ABS is on the speaker's bureau for Baxter International. None of the other authors have financial conflicts of interest to disclose.

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Results—Among 1,892 patients using either drug class, 39% were ARB users. We observed 624 events over 2,898 person-years of follow-up, for a composite event rate of 22 events per 100 person-years. We observed no differences between ARB *vs.* ACEI users: composite outcome HR: 0.94, 95% confidence interval (CI): 0.79–1.11; all-cause mortality HR: 0.92, 95%CI: 0.76–1.10; CV death HR: 1.06, 95%CI: 0.80–1.41.

Conclusion—We identified no significant difference in the risks of CV events or death between users of ARBs *vs.* ACEIs in patients initiating PD, thus supporting their mostly interchangeable use in this population.

Keywords

peritoneal dialysis; renin angiotensin system blockers; angiotensin converting enzyme inhibitors; angiotensin receptor blockers; cardiovascular

Introduction

Cardiovascular (CV) disease is the leading cause of death among patients with end-stage kidney disease (ESKD) on maintenance dialysis.[1] While angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) are recommended for the reduction of CV events for certain populations without ESKD, there is evidence that these agents may reduce the risk of CV events in patients on maintenance dialysis as well.[2–9] In fact, guidelines recommend the use of either ACEI or ARB as a first-line anti-hypertensive for those with diabetic nephropathy with proteinuria and for patients on dialysis with residual kidney function, and suggest use of either ACEI or ARB for normotensive patients on peritoneal dialysis (PD) with residual kidney function.[10,11]

Notably, the guidelines recommend these two classes of medications equally (ARBs are certainly preferred for patients with ACEI-induced side effects, such as cough). However, ACEI and ARB block the renin-angiotensin system through different mechanisms and thus may not have the same effects. Yet, there is only one study on the comparative effectiveness of ARB *vs.* ACEI in patients on hemodialysis, and none in patients on PD.[12]

In this observational cohort study, we sought to address this evidence gap by comparing the associations of ARB *vs.* ACEI use on CV outcomes in patients initiating PD.

Methods

Study Population

We identified from the US Renal Data System all adult patients who initiated dialysis between January 1, 2007 and October 2, 2011 and were stable on PD (*i.e.*, on the modality for at least 60 days) by day 90 of dialysis, the index date (Figure 1). Thus, index dates ranged from April 1, 2007 to December 31, 2011. Inclusion criteria also included continuous Medicare (a federal health insurance program for people who are 65 or older, certain younger people with disabilities, and people with end-stage kidney disease) Parts A, B, and D coverage from day 1–90 of dialysis, and having filled at least one prescription for either

an ACEI or ARB during those 90 days. We excluded patients who had filled prescriptions for both ACEI and ARB during that baseline window.

ACEI/ARB Use

Use of ARB (*vs.* ACEI use) was the exposure of interest and defined using Medicare Part D claims. Prescription claims contain not only the generic substance and dose, but also the number of days of drug supply dispensed. Patients were categorized as ARB or ACEI users if they filled a prescription for either an ARB or ACEI, respectively, within 90 days of initiating dialysis. We excluded patients who had filled prescriptions for both ACEI and ARB. For analyses using an approach that corresponds to an "intention-to-treat" analysis in trials, baseline exposure was carried forward indefinitely. "As-treated" analyses considered patients exposed for 60 days after the recorded supply from their previously filled prescription was exhausted ("refill grace period"). If patients failed to fill a subsequent prescription during this 60-day grace period, the follow-up time was censored. Follow-up for ARB users was also censored when an ACEI prescription was filled, and vice versa.

Outcomes

For the survival analyses, the primary outcome was a composite of death from any cause, ischemic stroke, and myocardial infarction. We also analyzed all-cause mortality and CV death as separate events of interest. Non-fatal outcomes were ascertained from validated claims-based algorithms. [13,14] Death and cause-specific mortality were ascertained from the USRDS death file as shown in the table (Online Resource 1).

Patient Characteristics

We ascertained demographics [age, sex, race (white, black, other), Hispanic ethnicity, Medicaid (a federal health insurance program for low-income patients) at time of dialysis initiation], comorbidities, body mass index (BMI) and laboratory measurements (hemoglobin, albumin, estimated glomerular filtration rate [eGFR]), baseline medication use, dialysis characteristics (year initiated dialysis, pre-dialysis referral to nephrologist, PD modality), and facility characteristics (size of the PD program, rural/urban location, U.S. census division) from the Medical Evidence Report (form CMS-2728), the ESRD Facility Survey (form CMS-2744) conducted in the year a patient initiated dialysis, and all available Medicare claims data from the first 90 days of dialysis. Facilities were considered urban if they were classified as a metropolitan area in the Rural–Urban Commuting Area (RUCA) Codes version 2.0; all other areas were considered to be rural.[15] Facilities were categorized into one of nine U.S. Census Bureau Divisions based on their state.[16] Details about the comorbidity algorithms have been previously described and can be found in Online Resource 2. [17,18]

Statistical Analysis

We tabulated the characteristics of ARB and ACEI users using percentages and means (+/− standard deviations) or medians (interquartile range). We compared the two groups using standardized differences, with differences >10 indicating unacceptable imbalance between the two groups.[19]

We conducted an inverse probability of treatment weighted (IPTW) survival analysis, a novel method to control for selection bias by observed characteristics between ARB users and ACEI users.[20] We fit a logistic regression model of ARB vs. ACEI use using all available baseline characteristics (Table 1) and calculated each patient's expected probability of receiving an ARB by combining his or her covariate vector with the corresponding coefficients of the model. Patients were then weighted by the inverse of their expected probability of using an ARB for those actually receiving an ARB, and the inverse of the expected probability of using an ACEI for those actually receiving an ACEI, to create a pseudo-population with similar percentage of patients exposed to one drug class *versus* the other in each level of the covariates as the overall percentage in the study population. This way, balance ideally achieved in a randomized study is being simulated, albeit solely for observed characteristics. Since vital signs and laboratory measurements were not available for all patients, we did not use these variables in estimating treatment probabilities. However, note that we still achieved balance in the IPTW cohort for these vital signs and laboratory measurements. Please see Online Resource 3 for detailed information on this method.

To exclude the differential use of direct renin inhibitors (i.e. aliskiren) as a potential confounder, we conducted a sensitivity analysis excluding patients who were prescribed this class of medications. To test whether short follow-times may have biased the results, we also ran sensitivity analyses restricting the cohort to patients we had remained on PD event-free for at least a year.

All survival analyses were conducted using Cox proportional hazard regression with robust standard errors. As patients may have had multiple events, we only analyzed the first event they experienced. Patients were censored on end of database (January 1, 2012). For as-treated analyses, patients were additionally censored for discontinuation of Part D, on the 61st day after their most recent recorded prescription expired and had not been refilled, for ARB users when an ACEI prescription was filled, and for ACEI users when an ARB prescription was filled. Violation of the proportional hazards assumption was checked using interaction terms with time. All hazard ratios (HR) were accompanied by their corresponding 95% confidence interval (CI).

All analyses were performed using SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC). Institutional Review Boards of Baylor College of Medicine, Los Angeles Biomedical Institute at Harbor-UCLA Medical Center, and Stanford University approved the study.

Results

Of the 4,949 patients who initiated peritoneal dialysis from 2007–2011 and who satisfied all eligibility criteria, 2,063 (42%) used either an ACEI or ARB; 171 filled prescriptions for both drug classes and were removed from consideration. Of the remaining 1,892 patients, 741 (39%) were ARB users and 1,151 (61%) were ACEI users. Several baseline characteristics differed between the two treatment groups: ARB users were older and more likely to be female than ACEI users (Table 1). They were also more likely to have seen a nephrologist prior to dialysis initiation and used diuretics, though the dose of diuretics

prescribed was no different than that prescribed to ACEI users. ARB users were less likely to have heart failure or to have been hospitalized in the first 90 days of dialysis. After weighting the cohort by their inverse probability of treatment with ARB, all observed characteristics were balanced between ARB users and ACEI users (Table 1).

In the intention-to-treat analyses, we observed 624 composite events (death, stroke, or myocardial infarction) over 2,898 person-years of follow-up, for a composite event rate of 21.5 events per 100 person-years. There were 17.7 deaths, and 6.8 CV deaths per 100 person-years. The observed rates of all outcomes were no different between ARB and ACEI users, and the confidence intervals accompanying all HR of interest crossed the null value, indicating no associations between drug class and outcomes (Table 2). The “as treated” analyses yielded similar results.

To exclude the use of direct renin inhibitors as a potential confounder, we repeated the analyses excluding 22 patients who were prescribed direct renin inhibitors. The hazard ratios and 95% confidence intervals were unchanged from the primary analysis.

To test whether short follow-up times may have biased the results of the primary analysis, we also repeated the analyses restricting the cohort to patients who had remained on PD event-free for at least a year. The results were materially the same as those from the primary analysis (Table 2).

Discussion

In this large, population-based cohort of patients initiating PD, we did not find any significant differences in the risks of CV events, CV death, or all-cause mortality when comparing those using an ARB *vs.* ACEI. Previous studies have shown an association between ACEI or ARB (*vs.* no use) and a reduction in CV events in patients on PD,[5,21] but, to our knowledge, ours is the first to compare the two classes of medications in PD patients.

There are plausible reasons why ACEI could potentially be more beneficial than ARB. ACEI increase the level of bradykinin and improve endothelial function, which is often impaired in patients on dialysis.[22–25] Meta-analyses have not consistently found one class to be superior to the other in reducing CV outcomes in patients not on dialysis.[26–31] Owing to the paucity of randomized clinical trial data of ACEI and ARB in patients on maintenance dialysis, no comparable meta-analysis has been conducted in the dialysis population, and only one observational cohort study of 22,628 patients on maintenance hemodialysis has addressed the issue. That study also found no difference in CV outcomes between users of ARB *vs.* ACEI (adjusted HR 0.96, 95% CI: 0.89–1.04).[12]

Still, patients on PD differ from those on hemodialysis in that they are regularly exposed to dextrose-containing PD solution. ACEI may lead to a kinin-mediated increase in insulin sensitivity not seen with ARB.[32] This could potentially lower the CV risk in patients on PD who are subjected to high glucose loads that may lead to insulin resistance and its associated CV risk.[33] However, our study suggests that, similar to that observed in patients on hemodialysis, this theoretical advantage does not translate into a clinical benefit of using

ACEI instead of ARB for improving CV outcomes of patients on PD. This lends further credence to the clinical guidelines that currently recommend the two classes of medication equally.

Our study has limitations, including the inability to control for unmeasured confounders such as blood pressure, residual kidney function, serum potassium levels, markers of mineral metabolism, the specific indication for the drug (confounding by indication), and prior duration of its use. It is possible that ARB users had better controlled blood pressure, more residual kidney function, fewer instances of hyperkalemia, or better controlled mineral metabolism and that this outweighed any potential benefit of ACEI use. It is also possible that some ARB users were previously on ACEI pre-dialysis, and that this prior ACEI use rather than the proximate ARB use was driving the results. We also did not have data on scheduled visits after initiation of drug treatment. Thus, it is possible that the ARB group had closer follow-up with a physician which led to lower rates of hypotension and hyperkalemia which in turn improved survival. This scenario is unlikely, though, since visit frequency correlates with facility characteristics, and the facilities were similar in the two groups.[34] Because our cohort was restricted to those receiving Medicare Part D when they initiated PD, the results may not be generalizable to those who do not qualify for this drug benefit, a group that tends to be younger. While the sample size was relatively large for such a study, the confidence limits were too wide to exclude clinically meaningful differences of moderate size. These limitations need to be considered in light of the strengths of the study, which include a large incident cohort of patients on PD with a high burden of comorbidities, a group that is usually excluded from clinical trials.

In conclusion, we did not find any differences in the rates of CV events or death from any cause with the use of an ARB *vs.* ACEI in patients initiating PD, suggesting that both may be equally effective in reducing CV outcomes in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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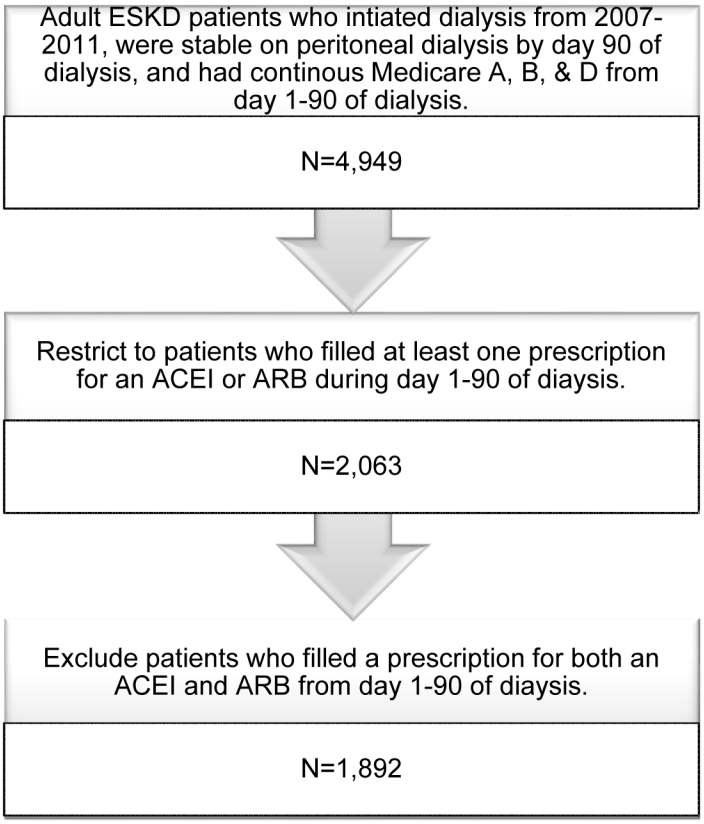

Fig. 1.

Study population selection from the United States Renal Data System. We selected a cohort of adult patients initiating peritoneal dialysis between 2007 and 2011 who survived to day 90 of dialysis and who had continuous Medicare Parts A, B, and D coverage from day 1–90. Patients had to have filled a prescription for either an ACEI or an ARB, but not both, during the first 90 days of dialysis. *ACEI* – angiotensin-converting enzyme inhibitors; *ARB* – angiotensin-II receptor blockers; *ESKD* – end-stage kidney disease.

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Table 1

Characteristics of patients initiating peritoneal dialysis from 2007–2011 who participated in Medicare Part D for the first 90 days of dialysis and had filled a prescription for either an ACEI or ARB.

	Full cohort			IPTW Cohort		
Variable	**ACEI users N=1151**	**ARB users N=741**	**Std. diff.**	**ACEI users**	**ARB users**	**Std. diff.**
Demographics						
Age (yr, mean ± SD)	64 ± 14	67 ± 13	21.9	65 ± 14	65 ± 14	0.4
Male sex	53	42	21.7	49	49	0.8
Race						
Black	19	19	1.1	19	20	1.1
White	77	74	6.6	75	75	1.1
Other	4	8	14.3	5	5	0.1
Hispanic ethnicity	13	11	4.1	12	12	0.5
Medicaid at time of dialysis initiation	32	33	1.8	32	32	0.3
Reported comorbidities						
Cancer	8	8	0.8	8	8	0.6
Cardiac disease, other [a]	24	22	5.2	23	23	0.6
Cerebrovascular disease	13	11	4.3	12	12	0.4
Coronary artery disease	26	25	1.1	26	25	0.4
Diabetes mellitus	65	65	0.7	65	65	0.4
Heart failure	33	26	15.7	30	30	0.0
Hyperkalemia	6	4	7.4	5	5	0.7
Hyperlipidemia	21	19	4.0	20	20	0.0
Hypertension	96	95	5.9	96	96	0.4
Liver disease	4	3	2.2	4	3	1.0
Peripheral vascular disease	18	17	3.3	18	19	1.5
Pulmonary disease	14	15	1.4	14	14	0.2
Tobacco use	8	8	0.1	8	8	0.8
Days hospitalized in in the first 90 days of dialysis (median, IQR)	0 (0–4)	0 (0–2)	13.3	0 (0–3)	0 (0–3)	0.5
Baseline medication use						
Beta blocker	66	64	4.0	65	65	0.9

	Full cohort			IPTW Cohort		
Variable	**ACEI users N=1151**	**ARB users N=741**	**Std. diff.**	**ACEI users**	**ARB users**	**Std. diff.**
Calcium channel blocker	60	64	9.0	61	61	0.1
Diuretic	62	67	12.3	63	62	2.2
Other antihypertensive [b]	46	44	3.7	45	46	1.0
Statin	55	53	2.9	54	54	0.3
Clopidogrel	14	14	2.0	14	14	0.1
Warfarin	8	7	5.3	8	8	1.3
Other cardiovascular med[c]	24	26	4.0	25	26	1.3
Dialysis characteristics						
Saw nephrologist prior to dialysis initiation	86	90	12.9	87	86	2.0
Year initiated dialysis						
2007	18	20	4.7	19	20	1.6
2008	20	18	4.1	19	19	0.8
2009	20	19	1.8	19	19	0.1
2010	23	23	1.8	23	23	0.7
2011	20	19	0.7	20	19	1.6
CAPD (vs. CCPD)	45	45	0.9	45	45	0.0
Vital signs and laboratory measurements						
BMI (mean ± SD) [d]	29 ± 7.1	29.3 ± 6.8	3.6	28.9 ± 7.1	29.3 ± 6.7	5.1
Hemoglobin (g/dL, mean ± SD) [e]	10.5 ± 1.5	10.6 ± 1.5	7.8	10.5 ± 1.5	10.6 ± 1.5	5.3
Albumin (g/dL, mean ± SD) [f]	3.6 ± 0.6	3.6 ± 0.6	10.0	3.6 ± 0.6	3.6 ± 0.6	1.3
eGFR (ml/min/1.73 m^2, mean ± SD) [g]	11.6 ± 4.2	11.8 ± 4.3	4.6	11.6 ± 4.1	11.9 ± 4.3	5.6
Facility characteristics						
Number of PD patients (median, IQR) [h]	25 (14–44)	23 (13–41)	7.2	24 (13–43)	24 (13–43)	0.8
≥20	63	58	9.9	61	61	0.4
Rural	15	13	6.95	14	14	0.9
Geographic location (U.S. census division)						
East North Central	19	14	12.9	17	17	0.3
East South Central	10	9	3.5	10	9	0.6
Middle Atlantic	7	7	1.5	7	7	0.1

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	Full cohort			IPTW Cohort		
Variable	**ACEI users N=1151**	**ARB users N=741**	**Std. diff.**	**ACEI users**	**ARB users**	**Std. diff.**
Mountain	5	5	0.7	5	5	0.7
New England	4	4	0.9	4	4	0.4
Pacific	12	16	12.3	14	14	0.2
South Atlantic	20	24	10.0	22	22	0.5
West North Central	7	7	1.2	7	8	1.2
West South Central	16	13	8.5	14	15	0.5

All numbers are percentages unless indicated otherwise. *ACEI* - angiotensin-converting enzyme inhibitor; *ARB* - angiotensin-II receptor blocker; *BMI* - body mass index; *CAPD* - continuous ambulatory peritoneal dialysis; *CCPD* - continuous cycling peritoneal dialysis; *eGFR* - estimated glomerular filtration rate; *IQR* - interquartile range; *IPTW* - inverse probability of treatment weighted; *PD* - peritoneal dialysis; *SD* - standard deviation; *Std. Diff.* - standardized difference.

[a]Includes atrial fibrillation, arrhythmias, implanted cardiac defibrillators, pacemakers, and valvular disease.

[b]Includes alfuzosin, aliskiren, clonidine, doxazosin, guanfacine, hydralazine, isosorbide, methyldopa, minoxidil, prazosin, ranolazine, and terazosin.

[c]Includes ezetimibe, simvastatin, niacin, amiodarone, aspirin/dipyridamole, colesevelam, colestipol, digoxin, dipyridamole, dronedarone, fenofibrate, flecainide, gemfibrozil, mexiletine, nitroglycerin, omega-3 acid ethyl esters, procainamide, propafenone, and quinidine.

[d]Missing for 1%.

[e]Missing for 13%.

[f]Missing for 26%.

[g]Missing for 1%.

[h]Based on the year the patient initiated dialysis.

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Table 2

Number of events, follow-up time, incidence rates, and hazard ratios for all study outcomes based on an inverse probability of treatment weighted population of ACEI users and ARB users.

Outcome	Analysis	Exposure group	N	Number of events	Follow-up time (years)		Incidence rate (per 100 person-years)	Hazard ratio (95% CI)
					Mean ± SD	Median		
Death, ischemic stroke, or myocardial infarction	ITT	ARB user	741	237	1.55±1.20	1.25	20.6	0.94 (0.79–1.11)
		ACEI user	1151	387	1.52±1.17	1.22	22.1	
	AT	ARB user	741	83	0.73±0.81	0.44	15.2	0.88 (0.66–1.16)
		ACEI user	1151	148	0.73±0.81	0.45	17.6	
	ITT, ≥1 yr on PD[a]	ARB user	432	127	1.32±1.00[b]	1.08 [b]	22.3	0.90 (0.71–1.14)
		ACEI user	662	212	1.27±1.00 [b]	1.07 [b]	25.2	
All-cause mortality	ITT	ARB user	741	209	1.67±1.23	1.43	16.9	0.92 (0.76–1.10)
		ACEI user	1151	346	1.64±1.22	1.33	18.4	
	AT	ARB user	741	65	0.76±0.84	0.46	11.5	0.81 (0.69–1.11)
		ACEI user	1151	123	0.75±0.82	0.46	14.2	
	ITT, ≥1 yr on PD[a]	ARB user	464	128	1.38±1.00 [b]	1.16 [b]	20.0	0.94 (0.75–1.19)
		ACEI user	701	204	1.36±1.00 [b]	1.20 [b]	21.4	
Cardiovascular death	ITT	ARB user	741	88	1.67±1.23	1.43	7.1	1.06 (0.80–1.41)
		ACEI user	1151	126	1.64±1.22	1.33	6.7	
	AT	ARB user	741	31	0.76±0.84	0.46	5.5	0.97 (0.61–1.55)
		ACEI user	1151	48	0.75±0.82	0.46	5.5	
	ITT, ≥1 yr on PD[a]	ARB user	464	51	1.38±1.01 [b]	1.11[b]	8.0	1.13 (0.78–1.66)
		ACEI user	701	68	1.36±1.01 [b]	1.19[b]	7.1	

ACEI – angiotensin-converting enzyme inhibitor; *ARB* – angiotensin-II receptor blocker; *AT* – as treated; *CI* – confidence interval; *ITT* – intention to treat; *SD* – standard deviation

[a]Cohort for this analysis was restricted to those who had been on peritoneal dialysis for at least 1 year event-free.

[b] Note that follow-up for the ≥1 year on PD cohort began on day 455 of dialysis whereas in the other analyses follow-up began on day 90 of dialysis. Thus, patients in the ≥1 year on PD cohort were followed on average until day 930 of dialysis whereas patients in the ITT analysis of the full cohort were followed on average until day 652 of dialysis.