Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use and cardiovascular outcomes in patients initiating peritoneal dialysis

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ABSTRACT

Background: Data on the effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in reducing cardiovascular (CV) risk in patients undergoing peritoneal dialysis (PD) are limited. We investigated the association between ACEI/ARB use and CV outcomes in patients initiating PD.

Methods: In this observational cohort study, we identified from the United States Renal Data System all adult patients who initiated PD from 2007 to 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 applied Cox regression to an inverse probability of treatment weighted cohort to estimate the hazard ratios (HRs) for the combined outcome of death, ischemic stroke or myocardial infarction (MI) and each outcome individually.

Results: Among 4879 patients, 2063 (42%) used an ACEI/ARB. Patients were followed up for a median of 1.2 years. We recorded 1771 events, for a composite rate of 25 events per 100 person-years. ACEI/ARB use (versus nonuse) was associated with a reduced risk of the composite outcome {HR 0.84 [95% confidence interval (CI) 0.76–0.93]}, all-cause mortality [HR 0.83 (95% CI 0.75–0.92)] and CV death [HR 0.74 (95% CI 0.63–0.87)], but not MI [HR 0.88 (95% CI 0.69–1.12)] or ischemic stroke [HR 1.06 (95% CI 0.79–1.43)]. Results were similar in as-treated analyses. In a subgroup analysis, we did not find any effect modification by residual renal function.

Conclusions: ACEI/ARB use is common in patients initiating PD and is associated with a lower risk of fatal CV outcomes.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, cardiovascular, peritoneal dialysis, renin angiotensin system blockers

INTRODUCTION

Patients with end-stage renal disease (ESRD) experience a high burden of cardiovascular (CV) disease. Mortality exceeds 20% in the first year after initiation of dialysis, and 42% of these deaths are attributed to CV causes [1]. In patients with chronic kidney disease (CKD) not on dialysis, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) slow the progression of diabetic nephropathy and reduce CV risk [2–8]. However, data on their effectiveness in patients with ESRD have been mixed. Notably, three randomized clinical trials involving patients with ESRD on hemodialysis and one in kidney transplant recipients found no reduction in CV outcomes with the use of an ACEI or ARB [9–12].

Yet, ACEIs and ARBs may be of some benefit to patients with ESRD on peritoneal dialysis (PD), in contrast to patients on hemodialysis. These medications may preserve residual renal function in patients on PD by decreasing inflammation and glomerulosclerosis [13–16], and residual renal function is consistently associated with better CV outcomes and overall survival rates in PD patients [17–22]. However, previous studies testing the effectiveness of ACEIs/ARBs on CV outcomes in patients on PD are sparse and limited by small patient populations [13, 23, 24].

In this study, we investigated the associations of the use of ACEIs or ARBs with both fatal and nonfatal CV outcomes in a large cohort of patients across the USA initiating PD between 2007 and 2011.

MATERIALS AND METHODS

Study population

From the United States Renal Data System (USRDS), we identified all adult (≥18 years old) patients with ESRD who

initiated dialysis between 1 January 2007 and 2 October 2011 (Figure 1). We restricted the cohort to patients who survived and were stable on PD (i.e. on the modality for at least 60 days) by Day 90 of dialysis, the index date. Thus, index dates ranged from 1 April 2007 to 31 December 2011. Inclusion criteria also included continuous Medicare Parts A, B, and D coverage (a federal health insurance program for people who are ≥65 years of age, certain younger people with disabilities and people with ESRD) from Day 1–90 of dialysis and having had at least one prescription filled during that time as an indication of active participation in Part D, the prescription drug benefit program.

ACEI/ARB use

Use of an ACEI/ARB (versus no 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 ACEI/ARB users if they filled a prescription for either an ACEI or ARB within 90 days of initiating dialysis; everyone else was considered a nonuser. For analyses using an approach that corresponds to an 'intention-to-treat' (ITT) analysis in trials, baseline exposure was carried forward indefinitely. 'As-treated' (AT) analyses considered patients exposed for 60
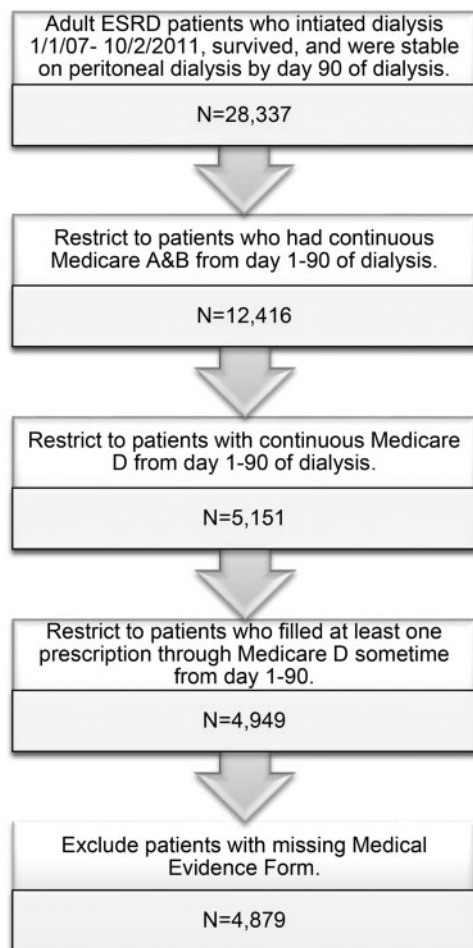
FIGURE 1: Study population selection from the USRDS. We selected a cohort of adult patients initiating PD between 2007 and 2011 who survived to Day 90 of dialysis and who had continuous Medicare Parts A, B and D coverage from Day 1 to 90.

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. Conversely, follow-up for nonusers was censored if an ACEI/ARB prescription was filled.

Outcomes

For the survival analyses, our primary outcome was a composite of death from any cause, ischemic stroke and myocardial infarction (MI). We also analyzed each outcome individually in addition to death from CV causes. Nonfatal outcomes were ascertained from validated claims-based algorithms [25, 26]. Death and cause-specific mortality were ascertained from the USRDS death file (Supplementary data, Table S1).

Patient characteristics

We ascertained demographics [age, sex, race (white, black and other), Hispanic ethnicity, Medicaid 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, predialysis referral to nephrologist) and facility characteristics (size of the PD program, rural/urban location, US 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. Details about these algorithms have been previously described and can be found in Supplementary data, Table S2 [27].

For a subset of patients who initiated dialysis with DaVita, a large national dialysis provider, we had additional laboratory measurements. Patients were classified as having residual renal function if none of the 24-h urine volumes in the first 90 days of dialysis were <200 mL. We also ascertained the first hemoglobin and albumin measurements made within 90 days of dialysis initiation since these data were more complete than those derived from the CMS-2728.

Statistical analysis

We tabulated the characteristics of ACEI/ARB users and nonusers using percentages and means (± SD) or medians (interquartile range). We compared the two groups using standardized differences, with differences >10 indicating significant imbalance between the two groups [28].

We conducted an inverse probability of treatment-weighted (IPTW) survival analysis, a novel method to control for selection bias by observed characteristics between ACEI/ARB users and nonusers [29]. Patients are weighted by their probability of being exposed for those exposed, and the probability of being unexposed for those unexposed, to create a pseudo-population with a similar percentage of patients exposed in each level of the covariates as the overall percentage in the study population, simulating the balance ideally achieved in a randomized study. The weights are based on propensity scores for ACEI/ARB that were estimated using a multivariable logistic regression that included the variables listed in Table 1 with the exception of vital signs and laboratory measurements as these data were not

available for all patients. Note that we achieved balance in the IPTW cohort for the vital signs and laboratory measurements even though they were excluded from the propensity score modeling. See Supplementary data for detailed information on this method.

Given the potential for confounding in this observational study, we examined the robustness of our primary results in three sensitivity analyses:

(i) We restricted the cohort to patients with a low-income subsidy (LIS) for Medicare Part D. This subsidy reduces or eliminates premiums and copayments for prescription medications based on patients' household income level, reducing the likelihood that they will obtain their medications outside of the program, making ascertainment of drug use via claims data more accurate [32].

(ii) We used a new user cohort. Studying prevalent users can lead to bias since these patients have tolerated and adhered to the medication and thus tend to be healthier than those who may have discontinued the drug shortly after initiation [33]. We created a new user cohort by first restricting the population to those ≥66 years of age so that we would have at least 6 months of Medicare Part D claims data prior to the initiation of dialysis. We then excluded anyone who filled a prescription for an ACEI/ARB during that 6-month period. Consequently, patients who filled a prescription for an ACEI/ARB during the first 90 days of dialysis were considered new users.

(iii) We restricted the cohort to users who dialyzed with DaVita, the only group for whom we had information on residual renal function. Residual renal function is a potential confounder since (a) ACEIs/ARBs preserve residual renal function, and could be used more often in patients with residual renal function [13, 14], and (b) residual renal function is associated with better CV outcomes and survival rates in PD patients [17–22]. For these analyses, we included residual renal function in the propensity score model.

All survival analyses were conducted using Cox proportional hazards regression with robust standard errors. As patients may have had multiple events, we only analyzed the first event they experienced. For the outcome of death, patients were censored on end of study (1 January 2012). For all other outcomes, patients were censored for end of study, loss of Medicare Parts A and B coverage and kidney transplantation. For AT analyses, patients were additionally censored for discontinuation of Part D, specifically for ACEI/ARB users when their most recent recorded prescription expired plus the 60-day grace period, and for nonusers if an ACEI/ARB prescription was filled. Violation of the proportional hazards assumption was checked using interaction terms with time. All hazard ratios (HRs) were accompanied by their corresponding 95% confidence interval (CI). We assessed effect modification by age (<66 or ≥66 years, the mean age), sex, race, history of diabetes mellitus, history of coronary artery disease, history of heart failure and residual renal function.

All analyses were performed using SAS Enterprise Guide 6.1 (SAS Institute, Cary, NC). The institutional review boards of Stanford University and Baylor College of Medicine approved the study.

RESULTS

Patient characteristics

Of the 4879 patients we identified as having initiated PD from 2007 to 2011, and who fulfilled the other stated criteria, 42% (2063) were ACEI/ARB users. ACEI/ARB users were younger and more likely to be Hispanic and receiving Medicaid (Table 1). Although there was no difference in the baseline prevalence of coronary artery disease between the two groups, diabetes mellitus and hypertension were more common among users, while heart failure was more prevalent among nonusers. Users had a higher rate of antihypertensive and statin use. However, their use of other medications was comparable with those of non-ACEI/ARB users. On average, ACEI/ARB users had higher BMIs than nonusers, but comparable eGFRs at initiation. The two groups also had similar dialysis and facility characteristics. After weighting the cohort by their inverse probability of treatment with an ACEI/ARB [34], all observed characteristics were balanced between users and nonusers (Table 1).

Association of ACEI/ARB use with outcomes

In the ITT analysis, we recorded 1771 events (death, stroke or MI) over 7131 person-years of follow-up, for a composite event rate of 25 events per 100 person-years. For each individual outcome, we recorded 20.9 deaths, 9.0 CV deaths, 3.9 MIs and 2.5 ischemic strokes per 100 person-years. The rates of the composite outcome, all-cause mortality and CV death were all significantly lower for ACEI/ARB users than nonusers [HR (95% CI): 0.84 (0.76–0.93), 0.83 (0.75–0.92) and 0.74 (0.63–0.87), respectively]. The rates of nonfatal events were no different between the two groups (Table 2, Figure 2). Age (≥66 versus <66 years), sex, race, history of diabetes mellitus, history of coronary artery disease, history of heart failure and diuretic use did not modify any of the associations (data not shown). The AT analyses yielded generally similar results with lower point estimates for the HRs and wider confidence limits (Table 2, Figure 2).

The sensitivity analyses yielded results that were mostly similar except that HRs were nonsignificant for the outcome of CV death, and for the cohort that adjusted for residual renal function, none of the outcomes reached statistical significance even though the point estimates for the HRs were similar to the main analyses (Figure 2, Supplementary data, Tables S3–S8).

DISCUSSION

In a large cohort of patients with incident ESRD undergoing PD, we found that use of an ACEI/ARB was associated, with lower risks of CV outcomes, predominantly driven by a reduction in fatal outcomes. These results were robust across several

Table 1. Characteristics of patients initiating PD from 2007 to 2011 who participated in Medicare Part D for the first 90 days of dialysis

Variable	Full cohort			IPTW cohort		
	Nonusers, (N = 2816)	ACEI/ARB users, (N = 2063)	Std. diff. (%)	Nonusers	ACEI/ARB users	EEStd. diff. (%)
Demographics						
Age (years), mean ± SD	67 ± 13	65 ± 13	14.8	67 ± 14	66 ± 13	0.3
Male sex	53	49	6.6	51	51	0.3
Race						
Black	16	19	8.2	17	18	0.3
White	79	75	8.6	77	77	0.2
Other	5	5	2.3	5	5	0.0
Hispanic ethnicity	8	12	11.9	10	10	0.4
Medicaid at time of dialysis initiation	26	33	13.4	29	29	0.1
Reported comorbidities						
Cancer	11	8	10.6	9	9	1.0
Cardiac disease, other[a]	29	24	12.1	27	26	0.5
Cerebrovascular disease	12	12	0.7	12	12	0.1
Coronary artery disease	27	26	2.0	27	26	0.1
Diabetes mellitus	57	65	16.9	61	61	0.3
Heart failure	35	31	8.0	33	33	0.1
Hyperkalemia	5	5	1.3	5	5	0.1
Hyperlipidemia	19	20	4.2	19	19	0.3
Hypertension	92	96	14.5	94	94	1.7
Liver disease	4	3	1.7	4	4	0.2
Peripheral vascular disease	17	18	0.7	17	17	0.3
Pulmonary disease	17	15	7.0	16	16	0.3
Tobacco use	7	8	2.8	8	8	0.2
Days hospitalized in the first 90 days of dialysis, median (IQR)	0 (0–3)	0 (0–3)	1.1	0 (0–3)	0 (0–3)	0.4
Baseline medication use						
ACEI or ARB	0	100	NA	0	100	NA
ACEI	0	64	NA	0	64	NA
ARB	0	44	NA	0	44	NA
Both	0	8	NA	0	8	NA
β-blocker	60	66	11.1	63	64	1.1
Calcium channel blocker	51	62	23.4	56	57	1.4
Diuretic	54	65	21.8	59	59	0.4
Other antihypertensive[b]	40	46	10.9	43	44	1.2
Statin	47	55	15.6	51	51	0.4
Clopidogrel	14	14	2.4	14	14	0.3
Warfarin	9	8	5.3	9	9	0.5
Other CV med[c]	22	25	7.2	23	23	0.1
Levothyroxine	19	18	2.1	19	18	3.1
Dialysis characteristics						
Saw nephrologist prior to dialysis initiation	86	87	2.1	87	87	0.6
Year initiated dialysis						
2007	17	19	5.4	18	18	0.4
2008	18	20	4.2	19	19	0.5
2009	21	19	3.2	20	20	0.0
2010	24	22	2.8	23	23	0.3
2011	20	19	3.2	20	20	0.2
CAPD (versus CCPD)	42	44	4.8	43	43	0.4
Vital signs and laboratory measurements, mean ± SD						
BMI[d]	28.4 ± 6.7	29.2 ± 7.0	10.5	28.7 ± 6.8	28.9 ± 6.9	4.0
Hemoglobin (g/dL)[e]	10.6 ± 1.6	10.6 ± 1.5	1.6	10.6 ± 1.5	10.6 ± 1.5	0.6
Albumin (g/dL)[f]	3.6 ± 0.6	3.6 ± 0.6	1.1	3.6 ± 0.6	3.6 ± 0.6	0.2
eGFR (mL/min)[g]	12 ± 4	12 ± 4	0.5	12 ± 4	12 ± 4	1.9
Facility characteristics						
Number of PD patients, median (IQR)[h]	24 (14–40)	24 (13–42)	3.7	24 (14–40)	24 (13–42)	2.5
≥20	61	61	0.4	61	61	0.4
Rural[i]	15	14	1.9	15	15	0.4
Geographic location (US census division)[j]						
East North Central	16	17	1.6	17	17	0.1
East South Central	10	10	1.1	10	10	0.3
Mid-Atlantic	10	7	9.4	9	9	0.6
Mountain	4	5	1.8	4	4	0.0

Continued

Table1. Continued

Variable	Full cohort			IPTW cohort		
	Nonusers, (N = 2816)	ACEI/ARB users, (N = 2063)	Std. diff. (%)	Nonusers	ACEI/ARB users	EEStd. diff. (%)
New England	4	4	1.4	4	4	0.3
Pacific	11	14	10.7	12	12	0.4
South Atlantic	23	22	3.0	22	22	0.4
West North Central	8	7	3.4	8	8	0.4
West South Central	13	14	2.8	14	14	0.1

All values 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; NA, not applicable; PD, peritoneal dialysis; SD, standard deviation; Std. diff., standardized difference.

[a]Atrial fibrillation, arrhythmias, implanted cardiac defibrillators, pacemakers and valvular disease.
[b]Alfuzosin, aliskiren, clonidine, doxazosin, guanfacine, hydralazine, isosorbide, methyldopa, minoxidil, prazosin, ranolazine and terazosin.
[c]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% of nonusers and 1% of users.
[e]Missing for 10% of nonusers and 10% of users.
[f]Missing for 23% of nonusers and 20% of users.
[g]Missing for 1% of nonusers and 1% of users.
[h]Based on the year the patient initiated dialysis.
[i]Facilities were considered urban if they were classified as a metropolitan area in the Rural–Urban Commuting Area (RUCA) Codes version 2.0, which are based on 2000 census commuting data and 2004 zip codes; all other areas were considered to be rural [30].
[j]Facilities were categorized into one of nine U.S. Census Bureau Divisions based on their state [31].

Table 2. Number of events, follow-up time, incidence rates and HRs for all study outcomes based on an IPTW population of 2063 (42%) ACEI/ARB users and 2816 (58%) nonusers

Outcome	Analysis	Exposure group	Number of events	Follow-up time (years)		Incidence rate (per 100 person-years)	HR (95% CI)
				Mean ± SD	Median		
Death, ischemic stroke or MI	ITT	ACEI/ARB	695	1.50 ± 1.17	1.21	22.5	0.84 (0.76–0.93)
		Nonuser	1076	1.44 ± 1.14	1.16	26.6	
	AT	ACEI/ARB	256	0.72 ± 0.80	0.44	17.1	0.66 (0.57–0.76)
		Nonuser	770	1.03 ± 1.00	0.71	26.5	
All-cause mortality	ITT	ACEI/ARB	622	1.61 ± 1.20	1.33	18.8	0.83 (0.75–0.92)
		Nonuser	976	1.54 ± 1.18	1.27	22.6	
	AT	ACEI/ARB	206	0.74 ± 0.82	0.46	13.4	0.61 (0.52–0.72)
		Nonuser	682	1.07 ± 1.02	0.75	22.6	
CV death	ITT	ACEI/ARB	249	1.61 ± 1.20	1.33	7.5	0.74 (0.63–0.87)
		Nonuser	440	1.54 ± 1.18	1.27	10.2	
	AT	ACEI/ARB	85	0.74 ± 0.82	0.46	5.5	0.69 (0.54–0.89)
		Nonuser	244	1.07 ± 1.02	0.75	8.1	
Ischemic stroke	ITT	ACEI/ARB	82	1.54 ± 1.19	1.26	2.6	1.06 (0.79–1.43)
		Nonuser	102	1.48 ± 1.17	1.21	2.4	
	AT	ACEI/ARB	40	0.74 ± 0.81	0.45	2.6	1.06 (0.71–1.59)
		Nonuser	69	1.06 ± 1.01	0.73	2.3	
MI	ITT	ACEI/ARB	115	1.54 ± 1.18	1.25	3.6	0.88 (0.69–1.12)
		Nonuser	170	1.47 ± 1.15	1.21	4.1	
	AT	ACEI/ARB	47	0.73 ± 0.80	0.45	3.1	0.80 (0.57–1.13)
		Nonuser	116	1.05 ± 1.00	0.72	3.9	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; AT, as treated; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighted; ITT, intention to treat; MI, myocardial infarction; SD, standard deviation.

sensitivity analyses that probed the potential impact of prevalent versus incident use of these drugs and in a subset of patients in whom we had information on residual renal function. Note that in the latter cohort, the HRs were similar but did not achieve statistical significance due to a smaller sample size. Thus, our findings support the use of ACEI/ARB medications in patients undergoing PD in whom previous evidence had been rather limited.

To our knowledge, only a single randomized trial on this topic in the PD population exists, a randomized control trial of the effect of ramipril versus placebo in 60 prevalent PD patients on the preservation of residual renal function [13]. This study showed no differences in the secondary outcomes of all-cause mortality [HR 1.56 (95% CI 0.24–10.05)] and CV events [HR 1.00 (95% CI 0.19–5.40)]. However, it was underpowered to detect a meaningful difference in these outcomes. In contrast, in the only observational study addressing the issue in PD patients only, ACEI/ARB use was associated with a 62% (95% CI 47–77) reduction in mortality in 306 patients who initiated PD [24]. The magnitude of the association seen in that study versus our own was much larger (HR 0.38 versus 0.83). This difference may have stemmed from their classification of users as anyone

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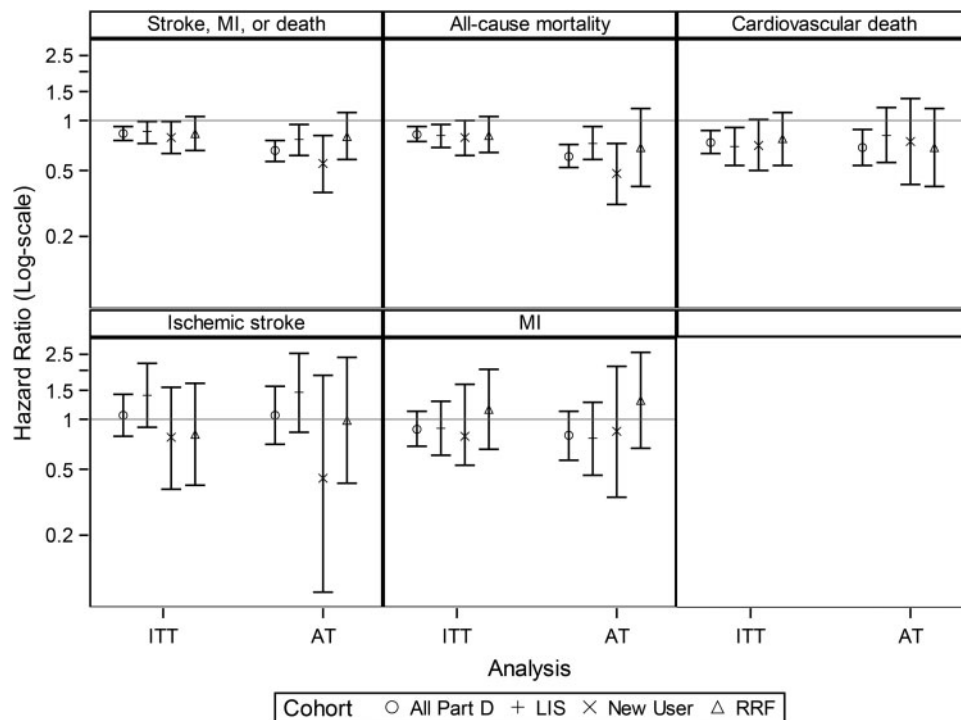
FIGURE 2: HRs for all study outcomes for both the primary analyses [based on the full (all Part D) IPTW cohort] and the sensitivity analyses [based on the LIS cohort, new user cohort and cohort in which we adjusted for residual renal function]. AT, as-treated analysis where patients were censored 60 days after their drug supply ran out; HR, hazard ratio; IPTW, inverse probability of treatment weighted; ITT, intention to treat; LIS, low-income subsidy; MI, myocardial infarction; RRF, residual renal function.

with 6 months of ACEI/ARB use during the follow-up period, which could have led to survivor treatment selection bias and an overestimate of the benefits of ACEIs/ARBs [35].

Observational studies on ACEI/ARB use that have included mixed populations of patients on hemodialysis and PD have not consistently shown a beneficial association of ACEI/ARB use [36–42]. Randomized trials involving only patients on hemodialysis have similarly failed to show a consistent benefit of ACEI/ARB treatment. The Fosinopril in Dialysis (FOSIDIAL) study randomized 397 patients on hemodialysis to fosinopril or placebo and found no significant reduction in CV events [HR 0.79 (95% CI 0.59–1.10)] [9]. In contrast, an open-label trial that randomized 360 patients on hemodialysis to either an ARB (valsaratan, candesartan or losartan) or no ARB treatment found that treatment was associated with a reduction in CV events [HR 0.51 (95% CI 0.33–0.79)], even though the authors note that the large effect may have been a chance finding owing to the small sample size [43]. A smaller trial of 80 patients on hemodialysis randomized to candesartan versus no treatment also found a lower rate of CV events in the treated group (45.9 versus 17.3%) [44]. However, a meta-analysis that pooled the result of these three trials found no significant association of ACEI/ARB use and the risk of CV events [HR 0.66 (95% CI 0.35–1.25)]. Later studies confirmed the negative finding. One such trial randomized 469 patients on hemodialysis to either olmesartan or a non-ACEI/ARB antihypertensive regimen and found no difference in a composite outcome of death, ischemic stroke, MI or coronary revascularization [HR 1.00 (95% CI 0.71–1.40)] [10]. Finally, a trial of 200 patients undergoing hemodialysis who were randomized to either lisinopril or

atenolol was terminated early due to an 'increased' risk of CV events in the ACEI group [incident rate ratio 1.36 (95% CI 1.36–4.23)] [11].

It is plausible that ACEI/ARB use might confer benefit in patients with ESRD on PD but not in those on hemodialysis. A possible mechanism of action might be in the putative ability of ACEIs/ARBs to preserve residual renal function in patients on PD, since residual renal function has been consistently linked to better outcomes [13, 14, 17–22]. While there are limited data showing that ACEIs/ARBs might similarly preserve residual renal function in patients on hemodialysis, the effect on CV outcomes might be limited in the hemodialysis population since they lose their residual renal function sooner than those on PD [46–48]. An alternative explanation is that ACEIs/ARBs may help preserve the peritoneal membrane, providing better ultra-filtration and improved CV function [49]. Finally, ACEIs/ARBs aid in the remodeling of myocardial and endothelial tissue, as evidenced by their ability to reduce left ventricular hypertrophy in patients on chronic dialysis [50, 51]. Perhaps the protective effects of such remodeling are mitigated in patients on hemodialysis, who are subject to large fluctuations in blood pressure and frequent cardiac stunning to which patients on PD are not habitually exposed [52].

Our study has potential implications for clinical practice. While we found that ACEI/ARB use is common among incident patients on PD (42%), it is not as high as it could be, judging by the prevalence of hypertension and the use of other antihypertensives in nonusers. Our data suggest that ACEIs/ARBs are not being used as first-line antihypertensives despite several national guidelines that recommend use for those with

diabetic nephropathy with proteinuria and those on PD with residual renal function [53, 54]. One possible explanation is that ACEIs/ARBs may have been discontinued in the late stages of non-dialysis-dependent CKD due to hyperkalemia and concerns about decreased eGFR, and never restarted once the patient transitioned to PD. Indeed, there is an ongoing multi-center randomized controlled trial of ACEI/ARB withdrawal in patients with Stage 4 or 5 CKD that stemmed from such concerns [55]. Clinicians should not shy away from restarting ACEIs/ARBs in incident PD patients since they are much more likely to exhibit hypokalemia than hyperkalemia due to the continuous nature of the dialysis. If ACEIs/ARBs decrease mortality, consideration should be given to encouraging their use as a first-line antihypertensive for most patients on PD.

Our study has limitations. We could not control for unmeasured confounders, most significantly blood pressure and the specific indication for the drug. It is certainly possible that the ACEI/ARB group had a lower rate of events because they had better control of their blood pressure. We also could not control for physician effects; it is possible that ACEIs/ARBs were prescribed more often by physicians who were more experienced with PD, and that this is driving the association with better outcomes rather than the actual drug use. We tried to mitigate this effect by controlling for the size of the PD program (larger programs have been shown to have better outcomes) [56]. 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. As always, the limitations must be balanced against the strengths of the study, which include a large, national cohort, the use of IPTW to minimize indication bias and results that were consistent across ITT and AT analyses as well as sensitivity analyses restricted to patients with a LIS, new users and those with residual renal function information available.

CONCLUSIONS

In a large, nationally representative cohort of patients on PD, we found ACEI/ARB use to be associated with a decreased risk of fatal CV outcomes. Further clinical trials are warranted to show whether this is a causal association, as it could change clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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