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see commentary on page 911

Combined angiotensin-converting enzyme inhibition and receptor blockade associate with increased risk of cardiovascular death in hemodialysis patients

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To compare the relative effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in reducing cardiovascular mortality in chronic hemodialysis patients, we conducted an observational analysis of all patients initiated on ACEI or ARB therapy undergoing chronic hemodialysis at a large dialysis provider. Survival curves with mortality hazard ratios (HRs) were generated using the Kaplan–Meier method and Cox regression. Outcomes were compared using inverse probability of treatment weighting and propensity score matching. Over 6 years, 22,800 patients were newly initiated on an ACEI and 5828 on an ARB after at least 60 days of chronic hemodialysis. After adjustment for baseline cardiovascular risk factors, there was no significant difference in the risk of cardiovascular, all-cause, or cerebrovascular mortality in patients initiated on an ARB compared with an ACEI (HR of 0.96). A third of 28,628 patients, newly started on an ACEI or ARB, went on to another antihypertensive medication in succession. After adjustment for risk factors, 701 patients initiated on combined ACEI and ARB therapy (HR of 1.45) or 6866 patients on ACEI and non-ARB antihypertensive agent (HR of 1.27) were at increased risk of cardiovascular death compared with 1758 patients initiated on an ARB and non-ACEI antihypertensive therapy. Thus, an ARB, in combination with another antihypertensive medication (but not an ACEI), may have a beneficial effect on cardiovascular mortality. As observational studies may be confounded by indication, even when adjusted, randomized clinical trials are needed to confirm these findings.

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More than 20,000 patients on maintenance dialysis are expected to die from cardiovascular disease this year. The risk of cardiovascular events in end-stage renal disease (ESRD) is 3.4-fold higher than that of the general population.[1] Although risk factors for coronary artery disease (CAD), such as diabetes and hypertension, are prevalent among ESRD patients, conventional risk factors alone fail to explain all of the excess cardiovascular mortality in epidemiological studies.[2] Furthermore, modification of these risk factors has not been shown so far to be effective in reducing cardiovascular risk in ESRD.[3–5] Consequently, there is a need to evaluate alternate therapies that could potentially moderate cardiovascular disease progression in the dialysis population.

Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin type 1 (AT_1) receptor blockers (ARBs) reduce cardiovascular events within the general population.[6–14] The comparative effectiveness of ACEIs and ARBs in reducing cardiovascular mortality in patients at risk for cardiovascular disease is currently controversial,[10] as is the efficacy of combined ACEI and ARB therapy.[10,14]

Even less is known about the relative efficacy and safety of ACEIs and ARBs in ESRD, as only a few studies have examined the individual efficacy of ACEIs or ARBs versus no treatment.[15–18] There have been no comparative effectiveness studies between ACEIs and ARBs in the ESRD patient population to date, despite the widespread prescription of these drugs among dialysis patients.[19,20]

To compare the effects of ACEIs and ARBs on cardiovascular mortality in chronic hemodialysis (CHD) patients, we conducted an observational analysis of outcomes in all patients undergoing CHD at a large dialysis provider, who were initiated on therapy with an ACEI, ARB, or both an ACEI and an ARB.

RESULTS

We surveyed 291,607 ESRD patients who received chronic dialysis at Fresenius Medical Care America over a 6-year period. Among this population, 22,800 CHD patients were newly initiated on an ACEI and 5828 patients on an ARB

after at least 60 days of CHD (9.8% of the population). Patients were followed up for an average of 1.26 years (ACEI users: 1.27 years; ARB users: 1.24 years).

When compared with ARB users, the ACEI group was more likely to be male, black, and diabetic, and more likely to have documented CAD, congestive heart failure, or history of stroke (Table 1). Baseline blood pressures were 2 mm Hg systolic and 1 mm Hg diastolic lower in the ACEI group when compared with the ARB group ($P<0.0001$); however, blood pressure responses to ACEI and ARB initiation were not different. These differences were successfully balanced after propensity score adjustment (see propensity score *P*-value in Table 1). The number of events for the three mortality outcomes (cardiovascular, all-cause, and cerebrovascular death) and for adverse events (hyperkalemia, orthostatic hypotension, risk of fall) is listed in Table 2.

In unadjusted models, initiation of an ARB (versus ACEI) was associated with a significantly decreased risk of cardiovascular death (hazard ratio (HR) = 0.87; 95% confidence interval 0.80–0.95) and death due to any cause (HR = 0.90; 95% confidence interval 0.85–0.95), but not with cerebrovascular mortality (Figure 1a and Table 2). After adjustment for baseline covariates and weighting for the inverse probability of treatment, there was no significant difference in the risk of cardiovascular, all-cause, or cerebrovascular mortality in patients initiated on an ARB versus ACEI (Figure 1b). There were also no statistical interaction effects by patient characteristic on mortality (Supplementary Figure S1 online). In a matched propensity score cohort, 4880 patients treated with ACEI were compared with 4880 patients treated with ARB. Baseline characteristics were similar in the matched cohort (Supplementary Table S1 online), and HRs were not different from those obtained after covariate adjustment and weighted for the inverse probability of treatment (Table 2).

Combination (ACEI+ARB) versus (ACEI+other antihypertensive) versus (ARB+other antihypertensive)

Overall, 33% of patients (9325 of 28,628) who were newly started on an ACEI or ARB went on to initiate another antihypertensive medication in succession (Table 3). Within this subgroup, the second drug in 701 patients also inhibited the renin–angiotensin axis such that these patients took combination therapy (ACEI + ARB). A total of 8624 patients were initiated on a non-renin–angiotensin-blocking agent in the setting of continued ACEI (ACEI + non-ARB, $n = 6866$) or ARB (ARB + non-ACEI, $n = 1758$) use. Patients were followed up for an average of 1.46 years (ACEI + ARB users: 1.46 years; ACEI + non-ARB users: 1.47 years; ARB + non-ACEI users: 1.43 years).

Patients initiated on combination ACEI and ARB therapy were older, were more likely to be black, diabetic, have had congestive heart failure, have CAD, and to take antiplatelet drugs, and took more antihypertensive medication than did patients initiated on an ACEI or ARB with another class of antihypertensive therapy. No statistically significant

Table 1 | Baseline characteristics of end-stage renal disease (ESRD) patients initiated on treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB)

	ACEI	ARB	*P*-value	Propensity score adjusted *P*-value[a]
N	22,800	5828		
Age (years)	61.0 (0.1)	61.1 (0.1)	0.68	0.90
Vintage (years)	2.7 (0.02)	2.8 (0.04)	0.03	0.82
Gender (% male)	52.4 (0.2)	48.1 (0.2)	<0.0001	0.84
Race				
Black (%)	38.2 (0.2)	36.4 (0.2)	0.003	0.64
White (%)	53.2 (0.2)	53.8 (0.2)		
Other (%)	8.6 (0.1)	9.8 (0.1)		
Access				
AVF (%)	25.3 (0.2)	24.5 (0.2)	0.53	0.42
Catheter (%)	27.2 (0.2)	27.9 (0.2)		
Graft (%)	42.8 (0.2)	42.9 (0.2)		
Unknown (%)	4.7 (0.1)	4.7 (0.1)		
Blood pressure (mm Hg)				
Pre-HD SBP	160.5 (0.1)	162.9 (0.2)	<0.0001	0.65
Pre-HD DBP	82.4 (0.08)	83.3 (0.1)	<0.0001	0.53
Post-HD SBP	148.4 (0.1)	150.1 (0.2)	<0.0001	0.63
Post-HD DBP	76.1 (0.08)	76.9 (0.1)	<0.0001	0.64
BMI (kg/m^2)	27.3 (0.05)	27.9 (0.1)	<0.0001	0.54
Laboratory				
Hemoglobin (g/dl)	11.4 (0.01)	11.5 (0.02)	<0.0001	0.39
Albumin (g/dl)	3.8 (0.003)	3.8 (0.006)	<0.0001	0.96
Potassium (mequiv./l)	4.8 (0.005)	4.8 (0.01)	0.02	0.98
Dialysate potassium (mequiv./l)	2.1 (0.003)	2.1 (0.007)	0.87	0.97
Dialysis adequacy (eKt/V)	1.41 (0.01)	1.40 (0.007)	0.74	0.88
Comorbidity				
Charlson's comorbidity	4.6 (0.01)	4.5 (0.02)	<0.0001	0.96
Diabetic (%)	53.2 (0.2)	50.9 (0.2)	0.001	0.67
CAD or past MI (%)	20.0 (0.2)	18.1 (0.2)	0.001	0.90
PVD (%)	18.4 (0.2)	17.4 (0.2)	0.08	0.66
CHF (%)	27.7 (0.3)	25.1 (0.3)	<0.0001	0.58
Past stroke (%)	6.2 (0.1)	5.0 (0.2)	0.0002	0.69
Medications				
EPO (1000 Units per session)	5.7 (0.03)	6.0 (0.08)	0.003	0.82
Vitamin D (% use)	74.6 (0.2)	75.5 (0.2)	0.13	0.59
Antiplatelet (% use)	33.8 (0.2)	32.1 (0.2)	0.01	0.52
Warfarin (% use)	10.1 (0.1)	10.0 (0.1)	0.95	0.93
Statin (% use)	21.2 (0.2)	22.6 (0.2)	0.02	0.71
Antihypertensive drugs				
1 drug (%)	36.5 (0.2)	33.7 (0.2)	<0.0001	0.96
2 drugs (%)	35.7 (0.2)	34.7 (0.2)		
⩾3 drugs (%)	27.8 (0.2)	31.7 (0.2)		

Abbreviations: AVF, arteriovenous fistula; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; EPO, erythropoietin; MI, myocardial infarction; post-HD, post-dialysis; pre-HD, pre-dialysis; PVD, peripheral vascular disease; SBP, systolic blood pressure.

[a]*P*-value between the ACEI and ARB groups with propensity score adjustment; components of the propensity score include age, gender, vintage, race (black, white, other), cause of ESRD (diabetic, hypertension, glomerulonephritis, other), access (fistula, graft, catheter, unknown), BMI, blood pressure (pre- and post-dialysis, systolic, and diastolic), dialysis adequacy (eKt/V), laboratory values (albumin, calcium, phosphorus, hemoglobin, white blood cell count, creatinine, ferritin, parathyroid hormone, bicarbonate, transferrin saturation, potassium), dialysate potassium, residual renal function (yes versus no), entry date, Charlson's comorbidity score, diabetic status, other comorbidities (documented myocardial infarction, CAD, peripheral vascular disease, stroke, transient ischemic attack, malnutrition, other cardiac disease, atrial fibrillation, menopause, family history of CAD), high-density lipoprotein-C >35 mg/dl, facility standardized mortality ratio, EPO dose, medication use (vitamin D, digoxin, nitroglycerin, warfarin, statin, antiplatelet agent), number of antihypertensive drugs prescribed at baseline.