Original Paper

Comparative Effectiveness of Renin-Angiotensin System Antagonists in Maintenance Dialysis Patients

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Key Words

Maintenance dialysis • Comparative effectiveness • ACE Inhibitors • ARBs • Cardiovascular outcomes • Mortality

Abstract

Background/Aims: Whether angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB) are differentially associated with reductions in cardiovascular events and mortality in patients receiving maintenance dialysis is uncertain. We compared outcomes between ACE and ARB users among hypertensive, maintenance dialysis patients. **Methods:** National retrospective cohort study of hypertensive, Medicare-Medicaid eligible patients initiating chronic dialysis between 1/1/2000 to 12/31/2005. The exposure of interest was new use of either an ACEI or ARB. Outcomes were all-cause mortality (ACM) and combined cardiovascular hospitalization or death (CV-endpoint). Cox proportion hazards models were used to compare the effect of ACEI vs ARB use on ACM and, separately, CV-endpoint. **Results:** ACM models were based on 3,555 ACEI and 1,442 ARB new users, while CV-endpoint models included 3,289 ACEI and 1,346 ARB new users. After statistical adjustments, ACEI users had higher hazard ratios for ACM (AHR = 1.22, 99% CI 1.05-1.42) and CV-endpoint (AHR = 1.12, 99% CI 0.99-1.27). **Conclusions:** Patients initiating maintenance dialysis who received an ACEI faced an increased risk for mortality and a trend towards an increased risk for CV-endpoints when compared to patients who received an ARB. Validation of these results in a rigorous clinical trial is warranted.

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Introduction

Cardiovascular disease is the leading cause of death in patients receiving maintenance dialysis. In the general population, renin-angiotensin system (RAS) antagonists reduce cardiovascular morbidity and mortality through primary or secondary prevention, as has been summarized in a number of meta-analyses [1-8]. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have demonstrated efficacy in reducing all-cause mortality and myocardial infarction in people with ischemic heart disease [1], hypertension [3, 4], heart failure [5], and diabetes [7]. Results for patients with heart failure are less consistent across study settings but are generally favorable toward RAS agents compared to controls [5, 8-10]. Several foundational trials in non-dialysis patients such as the Studies of Left Ventricular Dysfunction (SOLVD) [11], Survival and Ventricular Enlargement (SAVE) trial [12], and Trandolopril Cardiac Evaluation (TRACE) [13] demonstrated all-cause and cardiovascular mortality benefits in patients with reduced ejection fraction, although patients with preserved systolic function may not benefit from these therapies [14, 15].

Both subclasses have shown efficacy in chronic kidney disease (CKD) for prevention of kidney failure and cardiovascular events [16]. Overall, reductions in mortality associated with ACEI/ARB use range from 13% to 28% in CKD patients [1, 8, 17-21]. Comparable effects have been reported in patients receiving maintenance dialysis [22], although these findings are not consistent across observational studies [23]. The lone randomized clinical trial of an ACEI in maintenance dialysis patients found no significant impact on combined CV mortality and morbidity [24].

While the RAS inhibitors share important similarities in reducing preload and afterload, altering cardiac remodeling, improving endothelial function, and reducing sympathetic activity [25], they differ pharmacodynamically in important ways. ACEIs, but not ARBs, alter kinin synthesis, reduce angiotensin (AT) II formation, and affect AT2 sites [26]. In contrast, ARBs effect AT1 activity and may have better tolerability [26, 27]. There are also important differences with respect to dialyzability, with ACEIs more completely removed with dialysis relative to ARBs [28]. As such, the comparative effectiveness of these agents in specific populations remains an important area of study. In patients with essential hypertension, systematic reviews of RAS comparative effectiveness studies demonstrated no appreciable differences across most outcomes [29, 30]. In the context of non-dialysis CKD patients, a recent review showed that ACEIs or ARBs compared to controls reduced risk of kidney failure by 25-35% and cardiovascular events by 18-24% [16]. ACEIs had larger effects relative to controls than did ARBs compared to placebos or controls, but there were no direct comparisons between these two subclasses [16]. A single study comparing enalapril to losartan reported no significant differences in renal outcomes in non-dialysis CKD patients [31].

Whether these findings extend to dialysis patients is less well understood. A small crossover study in hemodialysis patients demonstrated that while the ARB valsartan had favorable effects on inflammation, the ACEI ramipril had a more pronounced benefit on endothelial dysfunction [32], but the relative magnitude of differential clinical benefits has not been established. A large retrospective cohort study comparing new users of ARBs and ACEIs in maintenance dialysis, from 1997-2003, reported no significant differences in cardiovascular outcomes or all-cause mortality [33], though they reported a trend toward more favorable outcomes with ARBs.

Given the lack of evidence on comparative effectiveness between ACEIs and ARBs in people receiving maintenance dialysis, we exploited a large observational cohort to compare the effects of these agents on all-cause mortality and cardiovascular morbidity and mortality in maintenance dialysis patients with hypertension. Findings could inform the decision as to whether to conduct a randomized clinical trial, since the utility of such a trial would likely be diminished in the absence of evidence from observational studies indicating differences between these classes of agents.

Subjects and Methods

Study Design

We conducted a retrospective, cohort analysis of people initiating maintenance dialysis identified through the United States Renal Data System (USRDS) core files from 2000 through 2005. For the present analysis, the observation window commenced when subjects received either an ACEI or an ARB with a minimum 90-day washout period to establish new use. New use also had to occur within 180 days of the initiation of dialysis so as to minimize substantial changes in underlying cardiovascular risk profiles. Subjects were followed until they accrued an event of interest or were censored if they reached the end of the observation window (12/31/2005) or dis-enrolled from Medicare or Medicaid fee-for-service coverage. The outcomes of interest were all-cause mortality and combined cardiovascular morbidity and mortality, as defined below. We have applied this general approach to several other studies [34-37].

Cohort construction

Our cohort was limited to individuals who were dually eligible for Medicaid and Medicare so as to have access to prescription medication records (Medicaid) along with claims for inpatient and outpatient care (Medicare), as this study was initiated before the formation of the Medicare Part D program. We further limited the cohort to individuals with hypertension documented as either their primary cause of ESRD or as a comorbidity in the USRDS core file [34-36]. We imposed the hypertension restriction so as to identify individuals with at least one significant indication for treatment. We did include individuals regardless of their primary cause of ESRD. Exclusions relevant to Medicaid were residence in more than one state, residence in Ohio (which does not reliably record a days supplied variable), and no prescription filled in their first 90 days on dialysis (a strong marker of Medicaid's spenddown status). Veterans Administration (VA) enrollment, continuous institutionalization, and prior kidney transplant were also exclusion criteria. Finally, patients who changed from an ACE to ARB or vice versa were excluded.

ACEI or ARB Exposure

Medication exposure was derived from pharmacy claims for new users (90-day wash out period). The first prescription filled between day 90 and 180 post-dialysis initiation for an ACEI (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, perindopril, ramipril, andtrandolapril) or an ARB (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) was recorded as the start of therapy. Combination products that included an ACEI or an ARB with another agent were included according to the parent RAS component. For the outcome analysis, we treated subclass assignment as an intent-to-treat variable. To ensure comparable exposure over time, we computed and compared the proportion of days covered (PDC) within each subclass during the observation window. The PDC was adjusted for hospital and skilled nursing home admissions with the relevant lengths of stay considered non-observable [36].

Outcomes

The outcomes of interest were time to all-cause mortality and time to cardiovascular morbidity and mortality. The Death Notification Form (CMS 2746), included in the USRDS Core CD, documents the date and primary cause of death as reported by a nephrologist, permitting ascertainment as to whether the death was cardiovascular-related. All-cause mortality included death attributed to any cause. Cardiovascular morbidity was captured as hospitalizations attributed, based upon the primary ICD-9 (International Classification of Disease, 9th Revision) codes, to myocardial infarction, ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular disease, or revascularization. Cardiovascular mortality included deaths attributed to cardiac arrest, myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, or cerebrovascular accident. Combined cardiovascular mortality and morbidity is hereafter referred to as the CV-endpoint.

Measurements

Baseline measures (demographic and clinical variables) were taken from the CMS 2728 Medical Evidence Form, a component of the USRDS Core CD. For demographic measures, we used age, sex, race by ethnicity (non-Hispanic African-Americans, non-Hispanic Caucasians, Hispanics, and Others), employment status (employed or unemployed), smoking status, substance abuse (alcohol or other drugs), and body mass

index (BMI). There were four categories of BMI: <20, 20-24.99, 25-29.99, and ≥ 30 kg/m². Functional status was captured as ability to ambulate and the ability to transfer. Other clinical variables included the primary cause of ESRD (diabetes, hypertension, glomerulonephritis, and other), comorbidities, time on dialysis (vintage) at the time of medication initiation, and dialysis modality (in-center hemodialysis versus self-care for home hemodialysis or peritoneal dialysis). We used our modification of the Liu comorbidity index [38, 39] specific for ESRD patients to measure overall disease burden. Specific baseline conditions recorded on the CMS 2728 Medical Evidence form were updated with claims-based diagnoses recorded during the first 90 days on maintenance dialysis.

Statistical analyses

We generated contingency tables using Pearson's chi-square test and assessed validity by examining expected cell counts for categorical measures to examine balance between ACEI/ARB subclasses. Descriptive statistics were generated, stratified histograms were examined, and two-sample t-tests performed for continuous measures. For within-class comparative effectiveness, we examined these data using Kaplan-Meier survival curves for an unadjusted comparison and then fit Cox proportional hazards regression models to compare these subgroups. We adjusted for other factors potentially associated with all-cause mortality and the CV-endpoint in separate models. Exponentiation of the parameter estimates obtained from these models using appropriate contrast statements allowed us to calculate the adjusted hazard ratios (AHRs) for evaluating ARBs relative to ACEIs. Cox proportionality assumptions were ascertained through visual assessment of the complementary log-log survival plots.

Statistical significance was inferred when $P < 0.01$ (99% confidence intervals, CI). Statistical analyses were done with SAS 9.2 (SAS Institute, Inc., www.sas.com).

Compliance and Research Participant Protection

The research protocol was approved by the institutional review board at the University of Kansas Medical Center. Data Use Agreements between the University and the USRDS and CMS permitted the data linking across the USRDS, Medicare and Medicaid files.

Results

The sample selection process, listing the exclusion criteria for the cohort, is shown in Figure 1. From the initial cohort of individuals with hypertension (n=52,922), 35.3% (n=18,714) received at least one ACEI/ARB prescription after dialysis initiation. Most of these were users with evidence of a prescription within the first 90 days, with 13,717 individuals eliminated from the all-cause mortality model and 14,079 eliminated from the CV-endpoint model. There were 81 (2.2%) individuals whose first prescription was an ACEI and went on to receive an ARB, while 57 (4.0%) individuals began with an ARB and switched to an ACEI; these individuals were removed from the cohort. The all-cause mortality model therefore included 3,555 ACEI and 1,442 ARB new users, while the CV-endpoint model included 3,289 ACEI and 1,346 ARB new users.

In the bivariate comparisons of ACEI versus ARB new users, baseline measures were generally balanced (Table 1). For both outcome models, subjects who initiated with an ARB were slightly older and more likely to be female. There were also small difference in the race/ethnicity distribution between ACE and ARB users in the all-cause mortality model here was a higher proportion of ARB users concurrently receiving a calcium channel blocker at baseline in the all-cause mortality model and less likely to receive a beta blocker in the cardiovascular morbidity and mortality model. Comorbidities, causes of ESRD, and most other baseline factors did not differ substantially between ACEI and ARB new users. The duration of follow up (days) did not different between treatment groups. The PDCs were clinically comparable between the two subclasses in both analytic cohorts (all-cause mortality model: ARB mean PDC = 0.55 versus ACEI mean PDC = 0.53, $p > 0.01$; CV-endpoint model: ARB mean PDC = 0.56 versus ACEI mean PDC = 0.54, $p = 0.006$). Visual inspection of the PDC histograms showed high comparability across the ranges. Coupled with comparable durations of follow-up, there would be consistent duration of treatment between the two drug classes.

Fig. 1. Flowchart demonstrating creation of the study cohort for new users of ACEI/ARBs. *Total individuals included differed in the models due to specific aspects of the study design. Thus some individuals could be in one model and not the other. For example, a person could be in the ACM model but not the CV-endpoint model if they started a ACEI/ARB prescription after a cardiovascular event; in distinction, as person could be in the CV-endpoint model but not the ACM model if they switched ACEI/ARBs classes between a cardiovascular event and death (thus causing elimination from the ACM model). Abbreviations: Rx, prescription; CMS, Centers for Medicare and Medicaid Services; ACM, all-cause mortality; CV, cardiovascular.

Unadjusted all-cause mortality occurred more often in the ACEI group, 34.4% versus 28.7% ($p = 0.0024$). The greater survival in ARB users was reflected in the Kaplan Meier curves (Figure 2a). In the CV-endpoint model, a similar pattern was present, with events occurring more frequently among the ACEI new users (49.3%) as compared to ARB new users (45.0%), ($p = 0.006$; Figure 2b). Visual inspection of the log-log survival plots were consistent with the proportional hazards assumption.

After adjustment for differences in baseline characteristics between groups (Table 2), ACEI users had a higher hazard ratio for all-cause mortality (AHR = 1.22, 99% CI 1.05-1.42). The difference in CV-endpoints was not statistically significant between ACEI and ARB users (AHR = 1.12, 99% CI 0.99-1.27), but strongly trended in the same direction as all-cause mortality. AHRs and 99% CIs for all parameters in the model are shown in Table 2. All-cause mortality and CV-endpoints increased with age (10-year increments, AHR (all-cause mortality) = 1.25, 99% CI 1.18-1.32; AHR (CV-endpoint) = 1.07, 99% CI 1.02-1.12), was higher for Caucasians (AHR (all-cause mortality) = 1.31, 99% CI 1.13-1.53; AHR (CV-endpoint) = 1.24, 99% CI 1.09-1.42), and increased with higher overall comorbidity (AHR (all-cause mortality) = 1.11, 99% CI 1.08-1.13; AHR (CV-endpoint) = 1.08, 99% CI 1.06-1.11). Individuals with lower BMI (< 20 kg/m²) had an increased hazard for mortality (AHR = 1.30, 99% CI 1.06-1.61) but no significant increased risk for the CV-endpoint. Individuals with BMI ≥ 30 kg/m² had lower mortality in the all-cause mortality model (AHR = 0.73, 99% CI 0.62-0.87), but not in the CV-endpoint model, as compared to their normal weight peers. None of the other variables were statistically significant.

Discussion

Using a large, national cohort, we examined the relative outcomes of initiation of ACEIs versus ARBs in newly initiated hemodialysis patients. In these patients, who were well-balanced across baseline characteristics, the initiation of an ACEI, compared to an ARB, was associated with a 22% increased risk for mortality. While the impact on cardiovascular

Table 1. Descriptive characteristics of new ACE inhibitor and ARB users within 90 days among chronic dialysis patients with hypertension for all-cause mortality and cardiovascular morbidity-mortality models

	All-Cause Mortality Model		CV-Endpoint Model	
	ACEI	ARB	ACEI	ARB
Number of cases	3,555 (100%)	1,442 (100%)	3,289 (100%)	1,346 (100%)
Age, mean years $\pm$ SD	58.8 $\pm$ 15.4*	60.1 $\pm$ 15.3*	58.2 $\pm$ 15.4*	59.9 $\pm$ 15.2*
Females, n (%)	2,003 (56.3%)*	879 (61.0%)*	1,846 (56.1%)*	812 (60.3%)*
Race/Ethnicity, n (%)				
African-American	2,589 (44.7%)*	603 (41.8%)*	1,486 (45.2%)	568 (42.2%)
Caucasian	1,120 (31.5%)	435 (30.2%)	1,015 (30.9%)	396 (29.4%)
Hispanic	647 (18.2%)	274 (19.0%)	1,359 (17.7%)	587 (19.2%)
Other	199 (5.6%)	130 (9.0%)	457 (6.0%)	282 (9.2%)
BMI category, n (%)				
< 20 kg/m ²	354 (10.0%)	146 (10.1%)	322 (9.8%)	135 (10.0%)
20-24.9 kg/m ²	1,083 (30.5%)	399 (27.7%)	1,004 (30.5%)	366 (27.2%)
25-29.9 kg/m ²	938 (26.4%)	372 (25.8%)	873 (26.5%)	347 (25.8%)
30+ kg/m ²	1,125 (31.7%)	511 (35.4%)	1,039 (31.6%)	484 (36.0%)
Missing	55 (1.6%)	14 (0.97%)	51 (1.6%)	141 (1.0%)
Smoker, n (%)	252 (7.1%)	81 (5.6%)	229 (7.0%)	75 (5.6%)
Substance abuser, n (%)	134 (3.8%)	35 (2.4%)	120 (3.7%)	32 (2.4%)
Unemployed, n (%)	3,443 (96.9%)	1,403 (97.3%)	3,181 (96.7%)	1,308 (97.2%)
Unable to ambulate, n (%)	180 (5.1%)	78 (5.4%)	169 (5.1%)	71 (5.3%)
Unable to transfer, n (%)	59 (1.7%)	23 (1.6%)	54 (1.6%)	21 (1.6%)
Cause of ESRD, n (%)				
Diabetes	1,917 (53.9%)	789 (54.7%)	1,759 (53.5%)	735 (54.6%)
Hypertension	1,035 (29.1%)	435 (30.2%)	961 (29.2%)	408 (30.3%)
Glomerulonephritis	285 (8.0%)	110 (7.6%)	270 (8.2%)	103 (7.7%)
Other	318 (9.0%)	108 (7.5%)	299 (9.1%)	100 (7.4%)
Comorbidities, n (%)				
Diabetes	2,289 (64.4%)	948 (66.4%)	2,104 (64.0%)	890 (66.1%)
Congestive heart failure	1,272 (35.8%)	470 (32.6%)	1,136 (34.5%)	431 (32.0%)
Coronary artery disease	889 (25.0%)	329 (22.8%)	782 (23.8%)	304 (22.6%)
Peripheral vascular disease	551 (15.5%)	213 (14.8%)	500 (15.2%)	203 (15.1%)
Cerebrovascular accident	363 (10.2%)	161 (11.2%)	333 (10.1%)	148 (11.0%)
β -blocker use, baseline	1,373 (38.6%)	532 (36.9%)	1,251 (38.0%)*	485 (36.0%)*
CCB use, baseline	1,989 (55.9%)*	900 (62.4%)*	1,856 (56.4%)	841 (62.5%)
In-center hemodialysis n (%)	3,390 (95.4%)	1,355 (94.0%)	3,133 (95.3%)	1,262 (93.8%)
Hemoglobin $\geq$ 11.0	769 (21.6%)	345 (23.9%)	696 (21.2%)	318 (23.6%)
Comorbidity index, mean $\pm$ SD	6.3 $\pm$ 3.6	6.3 $\pm$ 3.6	6.1 $\pm$ 3.6	6.2 $\pm$ 3.6
Vintage (years) when drug initiated, mean $\pm$ SD	0.10 $\pm$ 0.07	0.10 $\pm$ 0.07	0.10 $\pm$ 0.07	0.10 $\pm$ 0.07
Proportion days covered, mean $\pm$ SD	0.53 $\pm$ 0.28	0.55 $\pm$ 0.29	0.54 $\pm$ 0.29*	0.56 $\pm$ 0.29*
Days of follow-up, mean $\pm$ SD	625.0 $\pm$ 503.4	620.2 $\pm$ 501.4	625.8 $\pm$ 504.6	633.8 $\pm$ 509.2
Mortality, n (%)	1,224 (34.4%)*	414 (28.7%)*		
CV event, n (%)			1,622 (49.3%)	606 (45.0%)

BMI, body mass index; ESRD, end stage renal disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular. *Significant differences between subclasses within model, $p < 0.01$.

morbidity and mortality did not differ significantly between treatment groups, the trend was in the same direction, and the point estimate for the effect only slightly less in magnitude. This observational comparison of the comparative effectiveness of subclasses of RAS agents in maintenance dialysis patients suggests that, given patients who appear to be equally good candidates for drug, use of ARBs may be preferable to use of ACEIs.

Major guideline-forming organizations such as the American College of Cardiology Foundation/American Heart Association [40], the Eighth Joint National Committee [41], and the Kidney Disease Outcomes Quality Initiative [42] have suggested that ACEIs and ARBs can generally be used interchangeably for hypertension and heart failure. Relatively recent evidence of equivalence comes from the ONTARGET study (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) which studied patients at high risk of vascular events (specifically, those with established vascular disease or high-risk diabetes); rates of death plus cardiovascular events were no different between patients randomized to the ACEI compared to the ARB [43]. More generally, guidelines rest upon a large body of com-

Fig. 2. (A) Time to event, all-cause mortality (B) Time to event, CV-endpoint.

parative effectiveness research summarized in several meta-analyses. One such review of the treatment of hypertension, encompassing 160,000 patients from 20 studies, showed concluded that ACEIs, but not ARBs, were associated with a decrease in all-cause mortality relative to placebo [3]. Other meta-analyses show generally positive evidence for left ventricular remodeling, preservation of residual renal function, and improved vascular compliance translating into reductions in cardiovascular events and mortality irrespective of the RAS inhibitor agent evaluated [2, 25, 44, 45].

Relatively little work, however, has been done on comparative effectiveness in maintenance dialysis; most work in kidney disease patients has been confined to patients with non-dialysis-re-

Table 2. Comparative effectiveness of ACEI to ARB in persons on chronic dialysis with respect to mortality and cardiovascular endpoint models

	All-cause mortality		CV-Endpoint	
	AHR	99% CI	AHR	99% CI
ACEI (1) vs. ARB (0)	1.22	1.05-1.42	1.12	0.99-1.27
Age, per 10 years	1.25	1.18-1.32	1.07	1.02-1.12
Vintage, per year	1.14	0.46-2.80	0.62	0.28-1.35
Female sex	1.08	0.94-1.25	1.17	1.04-1.32
Race/Ethnicity				
Caucasian	1.31	1.13-1.53	1.24	1.09-1.42
African-American	1.0	--	1.0	--
Hispanic	0.98	0.82-1.18	1.07	0.92-1.25
Other	0.87	0.65-1.16	0.98	0.77-1.24
BMI category				
< 20 kg/m ²	1.30	1.06-1.61	1.13	0.93-1.39
20-24.9 kg/m ²	1.0	--	1.0	--
25-29.9 kg/m ²	0.87	0.73-1.03	0.94	0.81-1.09
30+ kg/m ²	0.73	0.62-0.87	0.92	0.80-1.07
Smoker	1.25	0.97-1.63	1.06	0.84-1.34
Substance abuser	0.99	0.67-1.48	1.09	0.78-1.51
Unemployed	1.38	0.77-2.49	1.12	0.76-1.64
Inability to ambulate	1.18	0.87-1.60	0.93	0.70-1.25
Inability to transfer	1.40	0.70-1.85	0.86	0.52-1.44
Comorbidities				
Diabetes	0.85	0.73-0.99	1.08	0.94-1.24
Congestive heart failure	0.94	0.80-1.09	0.99	0.86-1.13
Coronary artery disease	0.99	0.85-1.15	1.08	0.94-1.24
Cerebrovascular accident	1.08	0.89-1.30	0.92	0.77-1.11
Peripheral vascular disease	0.98	0.82-1.17	0.94	0.80-1.12
Modified Liu comorbidity index	1.11	1.08-1.13	1.08	1.06-1.11
Hemoglobin >=11, baseline	0.99	0.85-1.16	0.91	0.79-1.04
Self-care dialysis	1.05	0.77-1.43	0.84	0.64-1.10

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHR, adjusted hazards ratio; CI, confidence interval; BMI, body mass index; CV, cardiovascular. Missing values for BMI and hemoglobin were included in the model but results not shown.

quiring CKD. In a meta-analysis encompassing 119 trials enrolling nearly 65,000 CKD patients [16], there were only eight trials that explicitly tested ACEIs against ARBs. Using network analytic techniques, results from other trials (e.g., 2-arm trials testing ACEIs or ARBs to placebo or active control, or 3-arms trials involving both or one of these agents) were leveraged to inform the conclusion that ACEIs were superior to ARBs for all-cause mortality and may have been superior for cardiovascular events. However, in the subset of studies in which direct comparisons were made between two subclasses, ACEIs were not superior to ARBs for all-cause death, cardiovascular death, or cardiovascular events

There appears to be only one major study of the comparative effectiveness of ACEIs versus ARBs in maintenance dialysis patients who are new users of the drugs [33]. In this observational study designed primarily to examine the effect of dual RAS blockade on outcomes, the authors were nonetheless able to compare patients receiving ACEIs (alone) to those receiving ARBs (alone) [33]. They found no clear differences in outcomes between classes: the relative hazard ratios for ARBs compared to ACEI for cardiovascular death was 0.90 (95% CI 0.80-1.01), and for all-cause mortality was 0.95, (95% CI 0.88-1.03). These results are generally consistent with our findings, at least in terms of the point estimates for the effects, although we found statistically significant advantage for ARBs with respect to ACM. It is possible that differences between the two study cohorts allowed us to uncover significant differences. Our cohort was younger by approximately two years and included a

higher proportion of non-Caucasian subjects, a higher proportion of women, and patients with an earlier vintage as we included subjects within their first six months on dialysis. Another possible difference involves treatment selection, concerns about which have been raised previously in comparisons of ACEI and ARB users [46]. Our treatment groups appear to have been more well-balanced at baseline than those of the study by Chan et al [33]. Additionally, our treatment groups also had comparable survival curves early in the follow-up period, suggesting minimal selection bias, and we had a longer follow-up period, up to 6 years as compared with 2 years. Finally, we had a higher proportion of subjects initiating an ARB (29% versus 20%) [33].

While the body of work in maintenance dialysis appears to assume consistency in the effects of ACEIs relative to ARBs, there is reason to question this orthodoxy. A small but important crossover study which examined the relative benefits of ACEIs versus ARBs on inflammatory markers in 15 hemodialysis patients may provide insights into our findings [32]. Compared to valsartan, an ARB, ramipril, an ACEI, was associated with an increase in IL-1 β (a pro-inflammatory cytokine) and a decrease in IL-10 (an anti-inflammatory cytokine), suggesting that ARBs may exert a more anti-inflammatory effect in hemodialysis patients compared to ACEIs. This differential effect on inflammatory profile may be due to each medicine's effects on bradykinin, which is increased by ACE inhibition but which is unaffected by angiotensin receptor blockade. ACEIs increase the effect of IL-1 β [47-50], while blockage of bradykinin increases IL-10, in an animal model of ischemia [51] as well as in maintenance hemodialysis patients [52]. IL-10 levels appear to be decreased in hemodialysis patients with carotid atherosclerotic plaques [53], suggesting that the adverse outcomes we observed could be mediated by alteration in the inflammatory milieu via bradykinin, which may itself play a particularly important role in hemodialysis patients given the fact that its levels increase in response to exposure to dialyzers made of polyacrylonitrile, and perhaps dialyzers made of other materials [54]. One additional factor that comes into play is that ACEIs are removed during dialysis to a greater extent than ARBs [28]. In the context of our findings, ARBs would likely remain at therapeutic levels more consistently benefiting the subjects with respect to outcomes.

Our models adjusted for several variables derived from the USRDS standard data files. The relationships between age, race, comorbidity burden, and BMI are consistent with findings from other USRDS-based studies [35, 36, 55]. In particular, BMI and mortality or morbidity often demonstrates a U-shaped relationship [56-58], with lowest BMI (< 20 kg/m²) have higher mortality or worse outcomes and highest BMI levels appearing to be protective.

Limitations

As with any observational study, there are important limitations in contextualizing our findings. First, only a prospective, randomized clinical trial comparing ACEIs to ARBs could truly answer whether ARBs are superior to ACEIs in reducing all-cause mortality and cardiovascular events among people receiving maintenance dialysis; observational studies such as ours cannot definitively answer this question. Although such a trial would balance clinical measures which are unmeasured in our cohort study, it is reassuring that our large comparison groups were generally well-balanced in their characteristics and had comparable mortality early in the follow-up window. It is more likely that they were balanced in non-measured confounders as well. While we did contemplate explicit propensity adjustment, the distributions of the measured baseline factors were sufficiently well-balanced that such an approach seemed unnecessary and would not have afforded much benefit. Any unmeasured residual confounders, including clinical measures such as baseline blood pressure, would need to be both common and substantial to account for the effect size that we observed in this study. Second, although more subjects in our study were initiated on an ACEs, the selection of ACEIs over ARBs or vice versa did not appear to be differential in our population as evidenced by within class switching (excluded cases). Third, we limited the look-back period for prior RAS use to 90 days to establish new use; this may be an imperfect approach, since maintenance dialysis patients may well have been exposed to RAS agents in their

more distant medical history. While this would tend to overstate the degree of benefit of RAS medications, the bias would not be expected to be differential between the subclasses. Fourth, we also limited the ascertainment of new RAS use to persons in their first six months of dialysis treatment so as to limit changes in underlying cardiovascular risks. While this is actually a strength of our design, it is possible that clinical status might well have changed during this period. Our observations are relatively dated, going back to 2000-2005; however, there have not been any major therapeutic advances among ACEIs or ARBs since then. Finally, our cohort included Medicare-Medicaid (dually) eligible individuals; these individuals are generally younger, more likely to be women, and more likely to be racial or ethnic minorities compared to non-dually-eligible USRDS-Medicare only cohorts [37]. However, there is no a priori, physiologic reason why dually enrolled beneficiaries would experience a different response as compared to the overall maintenance dialysis population. Important strengths of our approach include use of a large sample size, employment of a design which focused on new users of the medications, demonstration of comparable levels of exposure between ACEIs and ARBs, and consistency in the results across sensitivity analyses.

Conclusion

In this observational study of comparative effectiveness in incident dialysis patients, ARBs, compared to ACEIs, were associated with a significant reduction in all-cause mortality of >20%. A similar pattern was observed for cardiovascular morbidity and mortality, although the results were not statistically significant at our conservative threshold. The reasons for this are uncertain, but they suggest that these agents may not be truly equivalent choices for initiation in incident dialysis patients. Given both the wide use and well-developed therapeutic rationale for use of RAS agents in both the dialysis and pre-dialysis CKD populations, a randomized controlled trial to validate the present findings appears warranted as does continued work differentiating the relevant pharmacodynamics properties among RAS agents.

Disclosure Statement

The authors have no conflicts of interest to declare. The data reported here have been supplied by the United States Renal Data System (DUA#2007-10, 2009-19, & 2015-02) and the Centers for Medicare & Medicaid Services (DUA#16977 & 19707). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

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