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Angiotensin-Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease

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Objectives The study objective was to assess the association between angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) use and mortality in patients with chronic kidney disease (CKD).

Background There is insufficient evidence about the association of ACEI or ARBs with mortality in patients with CKD.

Methods A logistic regression analysis was used to calculate the propensity of ACEI/ARB initiation in 141,413 U.S. veterans with nondialysis CKD who were previously unexposed to ACEI/ARB treatment. We examined the association of ACEI/ARB administration with all-cause mortality in patients matched by propensity scores using the Kaplan-Meier method and Cox models in "intention-to-treat" analyses and in generalized linear models with binary outcomes and inverse probability of treatment weights in "as-treated" analyses.

Results The age of the patients at baseline was 75 ± 10 years, 8% of patients were black, and 22% were diabetic. ACEI/ARB administration was associated with a significantly lower risk of mortality both in the intention-to-treat analysis (hazard ratio: 0.81, 95% confidence interval: 0.78 to 0.84; $p < 0.001$) and the as-treated analysis with inverse probability of treatment weights (odds ratio: 0.37, 95% confidence interval: 0.34 to 0.41; $p < 0.001$). The association of ACEI/ARB treatment with lower risk of mortality was present in all examined subgroups.

Conclusions In this large contemporary cohort of nondialysis-dependent patients with CKD, ACEI/ARB administration was associated with greater survival. (J Am Coll Cardiol 2014;63:650–8) © 2014 by the American College of Cardiology Foundation

The incidence and prevalence of patients with nondialysis-dependent chronic kidney disease (CKD) have continuously increased during the last decades in the United States and other countries (1,2). Despite decreasing adjusted death rates in the past 2 decades, cardiovascular morbidity and mortality in patients with CKD remains substantially higher compared with populations without CKD (2,3). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are considered standard therapies in patients with certain comorbid conditions, such as coronary artery disease and congestive heart failure, because of their favorable impact on mortality and cardiovascular outcomes (4–6). Although these agents are also deemed beneficial toward delaying progression of kidney disease in patients with nondialysis-dependent CKD (7–13), their effects on mortality in this patient population remain unclear.

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Observational studies examining the effect of ACEI or ARB on mortality in CKD of various stages have yielded

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inconclusive results, with some (14–21) but not all (22) showing an association with lower mortality. Most of these studies enrolled patients from single centers (18,20,21) or limited geographic areas (14,17), and many were limited to patients with certain comorbid characteristics, such as congestive heart failure (CHF), coronary artery disease (CAD), and diabetes (14–16,18–20,22), making it difficult to generalize their results to the entire population with CKD. Moreover, randomized controlled trials (RCTs) of ACEI and/or ARB in CKD also do not offer a clear answer regarding their effect on mortality. A recent meta-analysis of RCTs that examined the effect of ACEI and ARB on all-cause mortality in patients with early-stage (stages 1 to 3) CKD (23) identified only 3 studies (11,24,25) and concluded that the evidence was insufficient to determine whether ACEI or ARB is beneficial in this population. Clinical trials of ACEI and/or ARB that included patients with CKD with more advanced stages examined primarily renal and composite renal outcomes (which sometimes included mortality), but not mortality alone (7–10,13,26). An earlier meta-analysis of smaller RCTs examining primarily the effect of ACEI on the progression of CKD in nondiabetic patients did not detect a significant effect on mortality, but there were only 29 deaths in the 10 studies included in this analysis (12).

Given the uncertainty surrounding the effect of ACEI/ARB administration on mortality in patients with CKD, we examined this question in a large, nationally representative cohort of U.S. veterans with nondialysis-dependent CKD. We hypothesized that ACEI/ARB administration is associated with a lower risk of mortality in this patient population.

Methods

Cohort definition. A detailed description of our nondialysis-dependent CKD cohort has been published (27,28). Briefly, glomerular filtration rate was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration equation (29), and CKD was defined on the basis of the presence of a stable estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or a stable eGFR ≥60 ml/min/1.73 m^2 and an elevated urine microalbumin measurement (30). We identified exposure to ACEI and/or ARB on the basis of VA Outpatient Pharmacy dispensation records (31). Patients who received at least 1 dispensation of ACEI or ARB in a calendar quarter were recorded as having been treated with these agents. Most patients received 90-day supplies of ACEIs/ARBs (81% of all pharmacy dispensations), and almost all received at least a 30-day supply (98% of dispensations). The algorithm for defining the cohort used for the present study is shown in Online Figure S1. Of a total of 659,546 patients with nondialysis-dependent CKD between October 1, 2004, and September 30, 2006 (27), we identified 194,175 patients who were not treated with an ACEI/ARB before entering the cohort, on the basis of a review of VA Outpatient Pharmacy dispensation records from October 1, 2002, to September 30, 2004. For our analysis, we defined de novo exposure as the initiation of ACEI or ARB in previously untreated patients within 1 year of entering the CKD cohort to minimize secular trends in prescribing practices. Patients were categorized as untreated if they did not receive any ACEI or ARB throughout the duration of the follow-up period. After excluding patients who initiated ACEI or ARB >1 year after entering the CKD cohort (n = 31,509) and patients with incomplete information on ACEI/ARB treatment (n = 21,253), our cohort consisted of 141,413 patients (26,051 in the treated group and 115,362 in the untreated group). To minimize confounding by indication (32), we generated from this group a propensity score-matched cohort of 40,494 patients (20,247 exposed and 20,247 unexposed to ACEI/ARB) for our primary analyses.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker
CHF = congestive heart failure
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
OR = odds ratio
RCT = randomized controlled trial

Sociodemographic characteristics, comorbidities, and laboratory characteristics. Data on patient age, sex, race, and blood pressure were obtained through the VA Corporate Data Warehouse. Information on race was complemented with data obtained from Medicare through the VA-Medicare data merge project (33). All blood pressure values available from the October 1, 2004, to October 1, 2009, time period were recorded and grouped by calendar quarters, and their quarterly averaged values were used for analyses (34). Data on comorbidities and the occurrence of episodes of acute kidney injury were collected from the VA Inpatient and Outpatient Medical SAS Datasets (35) using International Classification of Diseases, Ninth Revision diagnostic and procedure codes and Current Procedural Terminology codes recorded during the October 1, 2004, to September 30, 2006, time period. Prevalent cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, or myocardial infarction, or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We calculated the Charlson Comorbidity Index using the Deyo modification for administrative datasets, without including kidney disease (36,37). Data on select laboratory variables were collected from October 1, 2004, to September 30, 2009, using the Decision Support System National Data Extracts Laboratory Results file (38). To minimize random variability, all available laboratory values were grouped by calendar quarters, and their quarterly averaged values were used in analyses. We used Medicare and Medicaid definition for race categories (39).

Outcomes. Information about all-cause mortality was obtained from the VA Vital Status Files. The VA Vital Status Files is a registry containing dates of death or last

medical/administrative encounter from all available sources in the VA system with a sensitivity and specificity compared with the National Death index as the gold standard of 98.3% and 99.8%, respectively (40).

Statistical analyses. Descriptive analyses were performed, and skewed variables were log-transformed. In the cohort of 141,413 patients, data were missing for marital status (1.4%), blood pressure (4.5%), eGFR (1.5%), and serum potassium (1.7%), with 93% of patients having complete data. Missing values were not imputed in primary analyses and were substituted by using single imputation procedures in sensitivity analyses.

The start of the follow-up period for both treated and untreated patients was the date of cohort entry. Patients first exposed to an ACEI/ARB at a subsequent date were considered as part of the untreated group for the time period between cohort entry and ACEI/ARB initiation in all survival analyses. Patients were followed until death or were censored at the date of the last health care or administrative VA encounter or on September 30, 2009.

The propensity score method was used to account for the confounding arising from the differences in the clinical characteristics of patients initiating ACEI/ARB versus the untreated group. This method allows for the generation of a single variable representing the likelihood of an individual patient's ACEI/ARB use based on the presence or absence of defined clinical characteristics in each individual. Patients with and without exposure to ACEI/ARB can then be matched on the basis of similar propensity scores to ensure that the typical predictors of therapy with these agents are similar in the 2 groups, and are thus not confounding the association of ACEI/ARB therapy with the studied outcome. Variables associated with ACEI/ARB administration were identified using logistic regression and were used to calculate propensity scores of the likelihood of initiating ACEI/ARB (41). C-statistic and receiver-operating characteristic analysis was used to test the logistic regression model. A propensity score-matched cohort was generated by a 1-to-1 nearest neighbor matching without replacement using Stata's "psmatch2" command suite (StataCorp LP, College Station, Texas).

The association of ACEI/ARB administration with mortality was assessed using the Kaplan-Meier method. ACEI/ARB administration was modeled in both an "intention-to-treat" approach (with all de novo exposed patients kept in the treated group irrespective of subsequent discontinuation of ACEI/ARB) and an "as-treated" approach (with patients allowed to switch treatment groups in time-dependent analyses according to actual subsequent exposure status). We hypothesized that change in certain clinical characteristics arising as a result of ACEI/ARB therapy (e.g., hyperkalemia, low blood pressure, or decline in kidney function) could result in subsequent discontinuation of ACEI/ARB therapy. These clinical characteristics can thus be both time-dependent confounders in that they cause a change in initially assigned ACEI/ARB therapy and intermediate variables in that they could be the mediators of ACEI/ARB effect on outcomes. Simple adjustment for these characteristics in multivariable models results in biased estimates. Novel classes of statistical methods are marginal structural models, which address the problem of time-dependent confounding by inverse probability weighting for receipt of the intervention (42–43). Stabilized inverse probability of treatment weights for ACEI/ARB use were calculated using baseline covariate values (age, sex, race, marital status, type of insurance, presence of cardiovascular disease, CHF, hypertension, diabetes mellitus, liver disease, rheumatologic disease, lung disease, malignancy, depression, dementia, and Charlson Comorbidity Index) and time-varying covariate values (systolic and diastolic blood pressures, eGFR, and serum potassium). To account for selection bias, inverse probability of censoring weights was calculated and combined with the inverse probability of treatment weights. The mortality risk associated with time-dependent ACEI/ARB use was then assessed in a weighed generalized linear model with binary outcomes.

The association of ACEI/ARB administration with mortality was examined separately in subgroups of patients categorized by eGFR level, key sociodemographic characteristics, presence or absence of key comorbid conditions, and their levels of relevant laboratory and blood pressure values. Sensitivity analyses were performed by examining the entire cohort of 141,413 patients and calculating a propensity score that also included levels of microalbuminuria. Finally, we repeated our analyses after imputing missing independent variables (<7%).

Statistical analyses were performed using Stata MP version 11.1 (StataCorp LP). The study protocol was approved by the Research and Development Committee at the Memphis VA Medical Center.

Results

Baseline characteristics. The age of the cohort at baseline was 74.8 ± 9.8 years; 89% and 8% of patients were white and black, respectively; 22% of the patients were diabetic; and the mean eGFR was 50 ± 13 ml/min/1.73 m^2. During the first year after entering the cohort, 18% (n = 26,051) of patients started ACEI/ARB therapy. Baseline characteristics of patients categorized by ACEI/ARB use in the first year of follow-up are shown in Table 1. Patients treated with ACEI/ARB were younger, more likely to be black, and more likely to have diabetes, hypertension, congestive heart failure (CHF), cardiovascular disease, and higher eGFR and systolic and diastolic blood pressures. Online Table S1 shows the baseline characteristics of patients included in our final cohort versus those excluded for reason of prior exposure to ACEI/ARB or missing information regarding exposure to ACEI/ARB. Excluded patients were younger, more likely to be black and diabetic, and more likely to have hypertension, cardiovascular disease, CHF, and higher systolic blood pressure.

Table 1 Baseline Characteristics of Individuals Stratified by ACEI/ARB Exposure

	Total Cohort (N = 141,413)	ACEI/ARB Treated (n = 26,051)	Untreated (n = 115,362)	p Value*
Male	97%	97%	96%	<0.001
Age (yrs)	74.8 ± 9.8	73.1 ± 10.3	75.2 ± 9.7	<0.001
Deaths	39,556 (28%)	6,484 (25%)	33,072 (29%)	<0.001
Race				<0.001
White	89%	85%	90%	
African American	8%	10%	7%	
Hispanic	1%	1%	1%	
Other	2%	4%	2%	
Diabetes mellitus	22%	41%	17%	<0.001
eGFR (ml/min/1.73 m^2)	50 ± 13	52 ± 16	50 ± 12	<0.001
CKD				<0.001
Stage 1	1%	4%	1%	
Stage 2	3%	6%	2%	
Stage 3A	69%	62%	71%	
Stage 3B	21%	22%	20%	
Stage 4	5%	5%	5%	
Stage 5	1%	1%	1%	
Blood pressure (mm Hg)				
Systolic	133 ± 17	138 ± 18	132 ± 16	<0.001
Diastolic	72 ± 10	74 ± 11	72 ± 10	<0.001
BMI (kg/m^2)	27.9 ± 5.1	29.0 ± 5.5	27.5 ± 5.0	<0.001
Comorbidities				
Hypertension	71%	89%	67%	<0.001
Cardiovascular disease	34%	43%	32%	<0.001
Congestive heart failure	8%	14%	6%	<0.001
Cerebrovascular disease	12%	15%	12%	<0.001
Chronic lung disease	24%	25%	24%	0.005
Liver disease	1%	1%	1%	0.014
Rheumatologic disease	2%	2%	2%	<0.001
Cancer	20%	18%	21%	<0.001
Depression	7%	7%	7%	0.016
Charlson Comorbidity Index	3 (2–4)	3 (2–4)	3 (2–4)	<0.001
Laboratory values				
Serum potassium	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	0.932
Spot urine microalbumin/creatinine	33 (9–68)	41 (15–85)	29 (7–58)	<0.001
Serum albumin (g/dl)	3.97 ± 0.43	3.99 ± 0.42	3.97 ± 0.43	<0.001
Blood hemoglobin (g/dl)	14.1 ± 1.7	14.1 ± 1.7	14.1 ± 1.7	0.987
Serum cholesterol (mg/dl)	175 ± 38	174 ± 40	175 ± 37	<0.001
Serum calcium (mg/dl)	9.3 ± 0.5	9.3 ± 0.5	9.3 ± 0.5	0.389
Serum bicarbonate (mmol/l)	27.4 ± 3.0	27.4 ± 3.0	27.4 ± 2.9	0.287
WBC count (×10^3/l)	7.4 ± 5.3	7.4 ± 3.0	7.4 ± 5.7	0.991

Values are %, mean ± SD, n (%), or median (IQR). ACEI/ARB exposure was defined as de novo initiation of any ACEI or ARB during the first year of follow-up. Unexposed patients were defined as those not receiving any ACEI or ARB throughout the entire follow-up period. *p value compares the treated and untreated groups.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IQR = interquartile range; WBC = white blood cell.

Table 2 shows the baseline characteristics of the treated and untreated groups in the propensity score-matched cohort, which showed only clinically minor differences, albeit most of these were statistically significant because of the large sample size.

Likelihood of initial ACEI/ARB exposure. Table 3 shows the multivariable adjusted odds ratios (ORs) of initiating ACEI/ARB treatment during the first year of the follow-up period associated with various baseline characteristics. Diabetic and hypertensive patients and those with CHF were more than twice as likely to initiate treatment compared with patients without these conditions. Furthermore, each 10 ml/min/1.73 m^2 higher eGFR and 10 mm Hg higher systolic blood pressure were associated with a 13% and 22% higher likelihood of initiating treatment, respectively. The area under the receiver-operating characteristic of the predicted probability of ACEI/ARB administration in our logistic regression model was 0.74.

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Table 2 Baseline Characteristics of Propensity Score-Matched Cohort Stratified by ACEI/ARB Treatment Status During the First Year of the Cohort

	ACEI/ARB Treated	Untreated	p Value*
n	20,247	20,247	N/A
Male	97%	97%	0.277
Age (yrs)	73.1 ± 10.4	73.6 ± 10.2	<0.001
Deaths	5,028 (25%)	6,450 (32%)	<0.001
Race			0.007
White	84%	86%	
African American	11%	10%	
Hispanic	1%	1%	
Other	4%	3%	
Diabetes mellitus	41%	41%	0.425
eGFR (ml/min/1.73 m^2)	52 ± 16	51 ± 15	<0.001
CKD			
Stage 1	4%	3%	<0.001
Stage 2	6%	5%	
Stage 3A	62%	65%	
Stage 3B	22%	20%	
Stage 4	5%	6%	
Stage 5	1%	1%	
Blood pressure (mm Hg)			
Systolic	138 ± 18	138 ± 17	0.016
Diastolic	74 ± 11	73 ± 11	<0.001
Comorbidities			
Hypertension	89%	90%	<0.001
Cardiovascular disease	43%	44%	<0.001
Congestive heart failure	14%	15%	0.631
Cerebrovascular disease	15%	14%	<0.001
Chronic lung disease	26%	26%	0.786
Liver disease	1%	1%	<0.001
Rheumatologic disease	2%	2%	0.052
Malignancy	18%	21%	<0.001
Depression	7%	7%	0.336
Charlson Comorbidity Index	3 (2–5)	3 (2–5)	<0.001
Laboratory values			
Serum potassium (mmol/l)	4.3 ± 0.5	4.3 ± 0.5	0.133
Spot urine microalbumin/creatinine	42 (15–86)	34 (10–71)	<0.001
Serum albumin (g/dl)	3.98 ± 0.43	3.97 ± 0.45	0.058
Blood hemoglobin (g/dl)	14.0 ± 1.7	14.0 ± 1.8	<0.001
Serum cholesterol (mg/dl)	173 ± 40	172 ± 39	0.013
Serum calcium (mg/dl)	9.3 ± 0.5	9.3 ± 0.5	0.357
Serum bicarbonate (mmol/l)	27.4 ± 3.0	27.5 ± 3.0	0.021
WBC ($\times 10^3$/l)	7.4 ± 3.1	7.5 ± 4.7	0.004

Values are n (%), mean ± SD, or median (IQR). *p value compares the treated and untreated groups.
N/A = not applicable; other abbreviations as in Table 1.

Table 3 ORs (95% CIs) of ACEI/ARB Initiation During the First Year of the Cohort

	OR	95% CI	p Value
Age (each +10 yrs)	0.80	0.78–0.81	<0.001
Race			
White (reference)	1.00	1.00–1.00	N/A
African American	1.09	1.03–1.15	0.002
Hispanic	1.41	1.22–1.62	<0.001
Other race	1.20	1.04–1.38	0.01
Female (vs. male)	0.84	0.76–0.92	<0.001
Presence of diabetes mellitus (vs. absence of diabetes mellitus)	2.73	2.63–2.83	<0.001
eGFR (each +10 ml/min/1.73 m^2)	1.13	1.12–1.15	<0.001
Systolic blood pressure (each +10 mm Hg)	1.22	1.21–1.24	<0.001
Presence of cardiovascular diseases (vs. absence of cardiovascular disease)	1.44	1.39–1.49	<0.001
Presence of hypertension (vs. absence of hypertension)	3.15	3.00–3.30	<0.001
Presence of congestive heart failure (vs. absence of congestive heart failure)	2.27	2.15–2.39	<0.001
Serum potassium (each +1 mmol/l)	1.11	1.07–1.15	<0.001

The ORs of ACEI/ARB initiation are calculated from a multivariable logistic regression model.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Mortality. The median cohort time was 4.7 years (interquartile range: 3.6 to 5.2 years). In the propensity score-matched cohort, there were 5,028 deaths (25%, mortality rate [95% CI] 22.6 [22.0 to 23.2]/1,000 patient-years) in the treated group and 6,450 deaths (32%, 26.5 [25.9 to 27.2]/1,000 patient-years) in the untreated group. Of 20,247 patients initiating ACEI/ARB, 1,705 (8.4%), 3,385 (17%), and 13,353 (66%) received their medication 100%, >90%, and >50% of time during follow-up visits, respectively.

Figure 1 shows the survival probability of treated and untreated patients in the propensity score-matched cohort, with ACEI/ARB treatment showing an association with lower mortality in both intention-to-treat and as-treated models. Similar associations are shown in Online Figure S2, which shows the cumulative hazards of treated and untreated patients in the propensity score-matched cohort. ACEI/ARB administration was associated with a lower risk of mortality in both the intention-to-treat analysis (hazard ratio: 0.81, 95% confidence interval [CI]: 0.78 to 0.84) and the as-treated analysis (OR: 0.37, 95% CI: 0.34 to 0.41). The estimated mortality risk associated with ACEI/ARB treatment was lower in all examined subgroups, but a lower magnitude of benefit was observed in nondiabetic patients (Fig. 2). The benefit associated with ACEI/ARB use was independent of eGFR level.

We performed a sensitivity analysis using the cohort of 172,922 patients (the 141,413 patients in the original analysis and 31,509 patients who started ACEI/ARB >1 year after the cohort entry). By using this cohort, ACEI/ARB administration was associated with a lower risk of mortality in both the intention-to-treat analysis (hazard ratio: 0.66, 95% CI: 0.64 to 0.68) and the as-treated analysis (OR: 0.48, 95% CI: 0.44 to 0.52). Hazard ratios and ORs of mortality associated with ACEI/ARB administration were similar when analyzing the entire cohort of 141,413 patients and when matching patients by a propensity score that included microalbuminuria (results

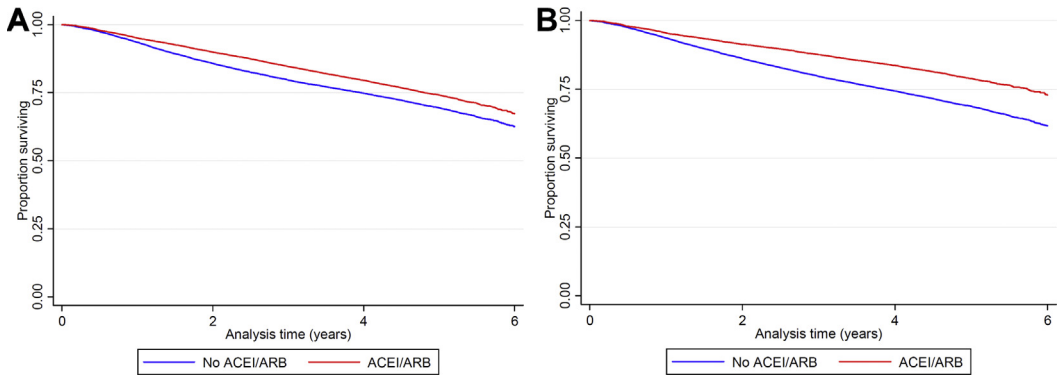

Figure 1 **Kaplan-Meier Survival Curves of 20,247 Patients Treated With ACEIs/ARBs and 20,247 Untreated Patients Matched by Propensity Scores**

Kaplan-Meier survival curves of 20,247 angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)-treated and 20,247 untreated patients matched by propensity scores. Exposure modeled in intention-to-treat **(A)** and as-treated manner **(B)**.

not shown). We also found qualitatively similar results when repeating our analyses after imputing missing variables (not shown).

Discussion

We examined characteristics of de novo ACEI/ARB initiation and their effect on all-cause mortality in a large cohort of U.S. veterans with all stages of nondialysis-dependent CKD. We found that traditional indications for ACEI/ARB administration, such as higher blood pressure and congestive heart failure, were associated with therapy initiation. Administration of ACEI/ARB was associated with lower all-cause mortality in various statistical analyses that adjusted for bias by indication and for selective discontinuation of ACEI/ARB therapy. In these nondialysis-dependent patients with CKD, discontinuation rates of ACEI/ARB were high: only 66% of treated patients received renewed prescriptions on >50% of their follow-up visits, and only <10% of patients remained on ACEI/ARB therapy throughout all follow-up visits. Because of such high discontinuation rates, it is possible that the 19% lower mortality associated with ACEI/ARB administration in intention-to-treat analyses (in which all patients are considered as receiving treatment throughout follow-up irrespective of discontinuation of the drug) is underestimating the true effect of these medications. Consistent with this hypothesis, the benefit of ACEI/ARB appeared larger in as-treated exposure models. Our result remained qualitatively unchanged even when using marginal structural models to account for the selective discontinuation of these agents due to hyperkalemia, hypotension, or change in kidney function. In addition, patients treated with ACEI/ARB in our study were more likely to be black and to have diabetes, hypertension, congestive heart failure, cardiovascular disease, and higher systolic and diastolic blood pressures. As a result, the risk of mortality is expected to be higher in these patients. The fact that ACEI/ARB use was associated with lower mortality despite this imbalance further strengthens our conclusion that ACEI/ARB treatment might be protective. However, the main reason for using a propensity score-matched analysis is to eliminate this type of bias by creating 2 groups for comparison with similar comorbid and other relevant conditions. The fact that even after propensity score matching, patients treated with ACEI/ARB reported better outcomes also supports our conclusions.

The uncertainty surrounding the effects of ACEI/ARB on mortality in nondialysis-dependent CKD stems from the paucity of clinical trials with a mortality endpoint in this patient population. Previous large RCTs of ACEI/ARB in CKD primarily explored renal endpoints (8–10,24,26), and other studies initiated to determine the effects of ACEI/ARB on mortality have typically excluded patients with moderate or advanced CKD (23). Extrapolating the results of studies from the general population to patients with CKD may be inappropriate given potentially harmful CKD-specific effects of ACEI/ARB, such as hyperkalemia or acute kidney injury (44). Given the paucity of clinical trial evidence, the association of ACEI/ARB administration with mortality in CKD has been explored in a number of observational studies, with most (14–21) but not all (22) showing beneficial trends. However, to the best of our knowledge, our study is the only one that examines a large cohort of patients with nondialysis-dependent CKD with de novo exposure to ACEI/ARB without restricting enrollment on the basis of geographic location, hospitalization, or other preexisting comorbid conditions. Our study suggests a substantial survival benefit from ACEI/ARB administration in nondialysis-dependent patients with CKD even when applying novel statistical techniques that can better control for confounding, such as propensity score matching and inverse probability treatment weighing (42,45).

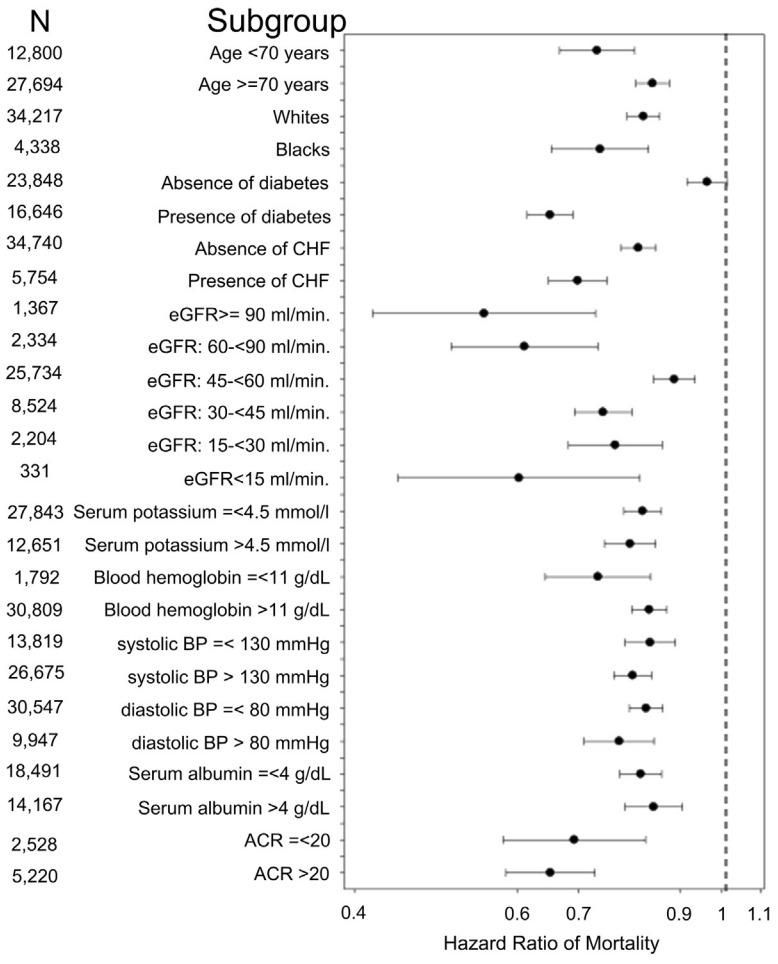

Figure 2 **Hazard Ratios (95% CIs) of All-Cause Mortality Associated With ACEI/ARB Administration in Various Subgroups of 40,494 Propensity Score-Matched Patients With Nondialysis-Dependent CKD**

Results are from unadjusted time-dependent Cox analyses modeling ACEI/ARB exposure in intention-to-treat manner. ACR = urine albumin creatinine ratio; BP = blood pressure; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; other abbreviations as in Figure 1.

Several potential mechanisms can explain the association between ACEI/ARB administration and decreased risk of mortality. ACEI/ARB treatment decreases the severity of left ventricular hypertrophy (46), dilation (47), remodeling, and heart failure (48) commonly seen in CKD, and their treatment could contribute to lower cardiovascular risk. In addition, ACEIs/ARBs are renoprotective in patients with CKD, which could indirectly provide survival benefits (8–10,24). ACEI/ARB administration was associated with a substantially larger survival benefit in diabetic patients compared with nondiabetic patients. Patients with cardiovascular disease, heart failure, and hypertension may overpopulate the diabetic cohort, thus resulting in the larger apparent benefit from ACEI/ARB treatment in this subgroup.

Another potential mechanism is the anti-inflammatory effect of renin-angiotensin system modulation, which could be especially important in this group of patients in whom inflammation is likely more prevalent than in non-CKD populations (49–51).

It is important to note that approximately 30% of our original cohort had not been exposed to an ACEI/ARB. Our data cannot provide definitive answers to why these patients were not treated with ACEIs/ARBs, but some potential explanations can be proposed. Patients previously exposed to ACEIs/ARBs were younger, more likely to be black and diabetic, and more likely to have hypertension, cardiovascular disease, CHF, and higher systolic blood pressure. These patients were "sicker" and more likely to have comorbidities, such as CHF and diabetes, which are well-documented indications of ACEI/ARB initiation. It is possible that patients who were previously unexposed to an ACEI/ARB and were subsequently administered these agents developed such indications de novo, which then led to the initiation of these medications. It is also possible

that patients never exposed to such agents did not have a solid indication for them or had contraindications to them.

Study strengths and limitations. Our study is notable for its large sample size and event numbers, and for being representative of veterans in the entire geographic United States. Our study also has limitations that need to be acknowledged. A limitation of observational studies such as ours is that they cannot prove causal associations between predictors and outcomes, and therefore we cannot claim that the administration of ACEI/ARB was indeed the primary reason for the better survival observed in the group exposed to these agents (32). We used relatively novel statistical methods, such as propensity score matching and marginal structural modeling, to minimize the effects of bias by indication and time-dependent confounding (42,45), but even these methods do not address unmeasured confounders. Full endorsement of the clinical use of ACEIs/ARBs toward decreasing mortality will thus be possible only if our results are corroborated by clinical trials. The study population consisted mostly of male patients; thus, the results may not apply to female patients. In addition, our results cannot be applied to patients receiving renal replacement therapy. We used data obtained during the course of clinical practice, making selection bias by medical indication possible. However, we used serum creatinine-based equations for cohort definition, which is part of routine panels that are measured in most patients receiving health care; it is thus less likely that a large proportion of actively enrolled veterans were excluded. We defined CKD using the Chronic Kidney Disease Epidemiology Collaboration equation because it is more accurate than other estimating equations (e.g., Modification of Diet in Renal Disease equation) in patients with normal and mildly decreased glomerular filtration rate (52). We did not collect information about other clinically relevant outcomes, such as end-stage renal disease and hospitalizations; thus, we could not test the association of ACEI/ARB with such outcomes, and we could not determine whether their effect on mortality is different before or after initiating dialysis therapy. In addition, we did not have information about the causes of death; therefore, we cannot analyze associations with cardiovascular mortality, and we did not collect information about smoking history. Nevertheless, by examining overall (pre- and post-dialysis) mortality, we eliminated the potential bias imparted by the competing risk of end-stage renal disease as an endpoint. We did not examine the effects of other antihypertensive agents; thus, we cannot determine to what extent the observed effects of ACEIs/ARBs were related to blood pressure lowering, to some other physiologic effect of this drug class, or merely to the fact that patients administered such medications may have received better care in general. However, we were able to match treated and untreated patients closely for their blood pressure levels, which would partially alleviate this concern. Last, we used diagnostic codes to define comorbid conditions that could act as confounders in the association of ACEI/ARB initiation with lower mortality risk, which may have resulted in underestimation of their prevalence.

Conclusions

In our large and contemporary cohort of 141,413 nondialysis-dependent patients with CKD, ACEI/ARB administration was associated with improved survival. Given the high mortality rates observed in patients with nondialysis-dependent CKD, the paucity of interventions available to lower these mortality rates, and the difficulties associated with conducting properly powered RCTs in this population, our results may have important clinical and public health implications by suggesting that ACEIs/ARBs may hold benefits beyond renoprotection in this vulnerable population and by re-emphasizing the need for RCTs with a mortality endpoint.

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Key Words: angiotensin-converting enzyme inhibitors ■ angiotensin receptor blockers ■ chronic kidney disease ■ mortality.

APPENDIX

For supplemental figures and a table, please see the online version of this article.