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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