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# Race and association of angiotensin converting enzyme/angiotensin receptor blocker exposure with outcome in heart failure

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***Purpose*** **Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been established as a mainstay of heart failure treatment. Current data are limited and conflicting regarding the consistency of ACE/ARB benefit across race groups in heart failure. This study aims to clarify this point.**

***Methods*** **This was a retrospective study of insured patients with a documented ejection fraction of less than 50%, hospitalized for heart failure between January 2000 and June 2008. Pharmacy claims data were used to estimate ACE/ARB exposure over 6-month rolling windows. The association between ACE/ARB exposure and all-cause hospitalization or death was assessed by proportional hazards regression, with adjustment for baseline covariates and β-blocker exposure. Further analyses were stratified by race, and included an ACE/ARB × Race interaction term.**

***Results*** **A total of 1095 patients met inclusion criteria (619 African-American individuals). Median follow-up was 2.1 years. In adjusted models, ACE/ARB exposure was associated with lower risk of death or hospitalization in both groups (African-Americans hazard ratio 0.47, $P<0.001$; whites hazard ratio 0.55, $P<0.001$). A formal test for interaction was consistent with similar effects in each group ($P=0.861$, $\beta=0.04$).**

***Conclusion*** **ACE/ARB exposure was equally associated with a protective effect in preventing death or rehospitalization among heart failure patients with systolic dysfunction in both African-American patients and whites.**

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**Keywords: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, heart failure, hospitalization, outcomes**

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## Introduction

Despite advances in its treatment, heart failure remains a substantial public health problem, afflicting over 500 000 Americans annually, with a US prevalence of five million people,[1] 1-year mortality estimates as high as 45%[2] and annual costs in the United States of $40 billion.[3] Heart failure also displays important racial disparities with respect to outcomes and response to treatment, with African-American patients bearing disproportionate burden.[4] A variety of explanations for these disparities have been explored, including differences in access to care,[5,6] but a portion may be related to differential effectiveness of drug therapies.[6] This portion remains unclear in part because of the fact that pivotal clinical trials often include insufficient numbers of African-American patients.[6,7] Neurohormonal antagonism via angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) remain a cornerstone of the treatment of heart failure with reduced ejection fraction[8–12] and accordingly are a quality metric and included in consensus guidelines.[13,14]

However, the data regarding whether the efficacy of ACE/ARB differs by race are still inconclusive. A review of racial differences in blood pressure response to renin–angiotensin–aldosterone system inhibition demonstrated less pressure-lowering effects of these agents (compared with thiazides and β blockers) among African-American individuals.[15] Despite this difference in effectiveness by race in the setting of hypertension, a similar effect in terms of clinical endpoints in heart failure patients treated with ACE/ARB remains unclear. Several studies have suggested that ACE/ARB therapy is less effective in African-Americans when compared with whites,[16–18] but another study showed similar efficacy regardless of race.[19] We attempted to help clarify this critical point by conducting a retrospective study of heart failure patients examining the correlation with ACE/ARB exposure over time with clinical outcomes and whether this association was different in African-American compared with white patients.

## Methods

### Study population

Individuals received their care through a large health system in southeastern Michigan, which is affiliated with


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a health maintenance organization (HMO). The system's large administrative database was queried for this study. Many patients are also enrolled in the affiliated HMO, and for these patients insurance claims data are also available. We included individuals that were more than or equal to 18 years of age with a primary hospital discharge diagnosis of heart failure between 1 January 2000 and 30 June 2008. The study population was limited to those that were continuously enrolled in the HMO for at least 1 year prior to the index hospitalization, which was defined as the first hospitalization during the observation period, and received their care through health system physicians. Including only those who were enrolled in the HMO allowed access to electronic data on all healthcare visits and prescriptions filled whether inside or outside the health system. Our group and others have assessed the use of primary hospital discharge diagnosis as a claim signature for heart failure, and it was found to be highly specific (95–100%).[20,21] Follow-up continued until participants either reached the study endpoint – that is, rehospitalization or death – reached the end of study follow-up on 31 December 2008, or were censored because of early disenrollment from the HMO. The Institutional Review Board at Henry Ford Hospital approved this study.

### Data sources

The health systems' electronic administrative databases, Michigan Department of Community Health and the Social Security Administration Death Master File (DMF), were the databases used to compile the study data. The health system administrative data provided claims data, including coded diagnoses, procedures, and prescription fills occurring both within and outside the health system. Demographic data (i.e., race, sex, and date of birth) is part of the master patient index. Race–ethnicity was mostly self-reported, but occasionally the registering health system employee would provide these data. A high agreement rate between self-reported and recorded race–ethnicity has been previously demonstrated.[22] Results of tests performed within the health system were also available. The patient's social security number was used to query the Michigan State Division of Vital Records and the National Technical information Service DMF identifying deaths. The left ventricular ejection fraction obtained from echocardiography, nuclear stress tests, angiography, or radionuclide pool imaging with the closest proximity to the time of patients' index admission was utilized in the study. The analysis included only those individuals with an ejection fraction less than 50%.

### Pharmacy claims and angiotensin converting enzyme/angiotensin receptor blocker exposure estimation

In order to assess the ACE/ARB exposure across the entire class and include all the different medications in the estimate equivalent doses of the medications were established. This was based on the target doses prescribed for systolic heart failure or the maximum daily dose in medications without a specific heart failure indication from the Food and Drug Administration. The ACE/ARB exposure estimate was calculated by the sum of the drug-equivalent dose of medication dispensed over the 180-day window, divided by 180. Thus, every individual had a calculated ACE/ARB exposure estimate for each day of observation, representing his or her average ACE/ARB exposure over the previous 6 months. The first day of estimated exposure (and hence the first day of analysis) was 180 days after discharge from the index hospitalization. The daily individual exposure measures varied and when appropriate included periods of no medication exposure. Both dose and adherence are accounted for in this method. Similarly, a β-blocker exposure variable was calculated and used in the analysis to account for adherence and other medications as confounders to the benefit with ACE/ARB use.

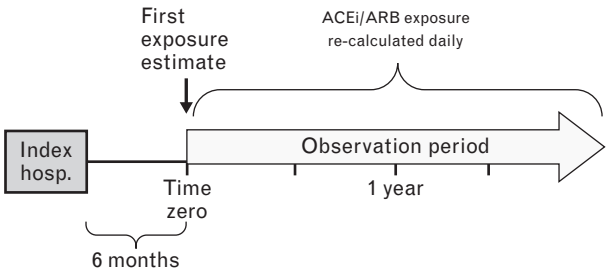
### Covariates

All multivariate models included race, sex, age, ejection fraction, and baseline comorbid conditions (diabetes, hypertension, atrial fibrillation, vascular disease, stroke, preexisting heart failure, coronary disease, and renal dysfunction) as covariates. A β-blocker exposure estimate was also included to adjust for the benefits of this therapy as well as to account for adherence. Adherence has been shown to affect outcomes even in the placebo arm of controlled trials.[23] With the exception of hypertension and diabetes, baseline characteristics were identified as having a primary or secondary International Classification of Diseases, Ninth Revision (ICD 9) diagnosis code or certain disease-specific procedure codes in the year prior to the index hospitalization. The definition of diabetes and hypertension required two claims from any clinical setting or at least one primary diagnosis in the baseline year with relevant ICD 9 codes. Diabetes could also be defined if a diabetic medication was filled at least once in the baseline year. Along with diagnostic codes, procedure codes related to treatment were used to define peripheral vascular disease, end stage renal disease, coronary artery disease, and stroke/transient ischemic attacks.

### Endpoint assessment

Time to death or all-cause rehospitalization was the composite primary endpoint. Claims data, which were available for affiliated HMO members, were used to identify hospital readmission. Separate analyses were performed for all-cause death and all-cause hospitalization. Other secondary analyses were performed on patients exposed to ACE or ARB separately. These included all-cause hospitalization or death, death, all-cause hospitalization, or heart failure hospitalization alone. The exposure metric required a 6-month window; therefore, the first day included in the analysis was 6 months after the index hospitalization (Fig. 1). Individuals who died or were rehospitalized in the first 6 months were excluded from the study analysis.

**Fig. 1**




Study timeline.

### Statistical analysis

Chi-squared tests for categorical variables, two sample Student's *t*-tests for normally distributed continuous variables, and two samples Mann–Whitney for continuous variables not normally distributed were used to identify significant differences in baseline characteristics. Multivariable proportional hazards regression models were used to evaluate the association between ACE/ARB exposure with the composite of all-cause rehospitalization or death. Models were also stratified by race. All models were adjusted for sex, age, comorbidities (diabetes, hypertension, atrial fibrillation, vascular disease, stroke, preexisting heart failure, coronary disease, and renal dysfunction), ejection fraction, sodium level, and β-blocker exposure variable. Survival curves were calculated from the Cox model evaluated at the average covariate value and a set value of ACE/ARB exposure. ACE/ARB exposure variable was set at the median value or the 75th percentile to demonstrate the independent effect of differing levels of exposure to the outcome within each race. Secondary analyses were performed for death, heart failure rehospitalization only, or all-cause rehospitalization. Primary effects were considered statistically significant for *P*-values $<0.05$. *P*-values $<0.1$ were considered significant for interactions.[24] SAS version 9.1.3 (SAS institute, Cary, North Carolina, USA) was used for all statistical analysis.

## Results

The total cohort meeting inclusion criteria consisted of 476 white and 619 (56.5%) African-American individuals, for a total of 1095 individuals. Median patient follow-up was 2.1 years, over which time there were 478 deaths and 890 hospitalizations. African-Americans were more likely to be younger females. They were also less likely to have preexisting heart failure, coronary artery disease, or atrial fibrillation (Table 1). The mean exposure estimates were similar between groups for both ACE/ARB and β adrenergic antagonists.

ACE/ARB exposure was associated with lower risk of death or rehospitalization in both groups (Table 2), with hazard ratio of 0.47 ($P<0.001$) and hazard ratio of 0.55 ($P<0.001$) for African-Americans and whites, respectively. A formal test for race interaction was not significant ($P=0.861$, $\beta=0.04$). Figure 2 depicts the survival curves by race and ACE/ARB exposure, based on the Cox model. The relative protection associated with more intense ACE/ARB exposure is represented by the space between similar colored lines, which grossly appears to be similarly protective across racial groups.

When examining the individual components of the primary endpoint, our findings also appeared consistent across race categories. In terms of all-cause mortality, ACE/ARB exposure was associated with a protective effect in African-Americans (hazard ratio 0.37, $P<0.001$) as well as whites (hazard ratio 0.34, $P<0.001$). For time to hospitalization, ACE/ARB exposure continued to be associated with a protective effect in both African-Americans (hazard ratio 0.47, $P=0.001$) and whites (hazard ratio 0.60, $P=0.005$).

We also performed a series of secondary analyses to better characterize the relationship of these medications to outcomes in African-Americans and whites. First, we examined heart failure-specific rehospitalizations. Similar to the primary analysis, this showed no significant difference in the protective association of ACE/ARB by race. Exposure to ACE/ARB decreased the risk of heart failure hospitalization among both white patients (hazard ratio

**Table 1 Baseline characteristics**

| Characteristic | African-American ($n=619$) | White ($n=476$) | *P*-value |
|---|---|---|---|
| Age (years) | 64.4 ± 14.1 | 71.5 ± 11.7 | 0.001 |
| Female, *n* (%) | 273 (44%) | 179 (38%) | 0.030 |
| Preexisting heart failure, *n* (%) | 290 (47.1) | 254 (53.4) | 0.037 |
| Diabetes, *n* (%) | 245 (40%) | 199 (42%) | 0.457 |
| Hypertension, *n* (%) | 391 (63.2) | 278 (58.4%) | 0.109 |
| Coronary disease, *n* (%) | 173 (28.%) | 175 (36.8%) | 0.002 |
| Atrial fibrillation, *n* (%) | 114 (18.5%) | 167 (35.1%) | 0.001 |
| PVD, *n* (%) | 72 (11.6%) | 68 (14.3%) | 0.192 |
| CVA, *n* (%) | 85 (17.7%) | 64 (13.5%) | 0.891 |
| EF | 27.5 ± 11 | 30.1 ± 11.4 | 0.001 |
| Creatinine | 1.31 ± 0.62 | 1.29 ± 0.51 | 0.27 |
| ACE/ARB exposure | 0.25 ± 0.26 | 0.28 ± 0.28 | 0.1 |
| BB exposure | 0.24 ± 0.27 | 0.25 ± 0.27 | 0.74 |

ACE/ARB, angiotensin converting enzyme/angiotensin receptor blocker; BB, β Blocker; CVA, cerebrovascular accident; EF, ejection fraction; PVD, peripheral vascular disease.

**Table 2 Effect of race on angiotensin converting enzyme/angiotensin receptor blocker exposure and all-cause rehospitalization or death**

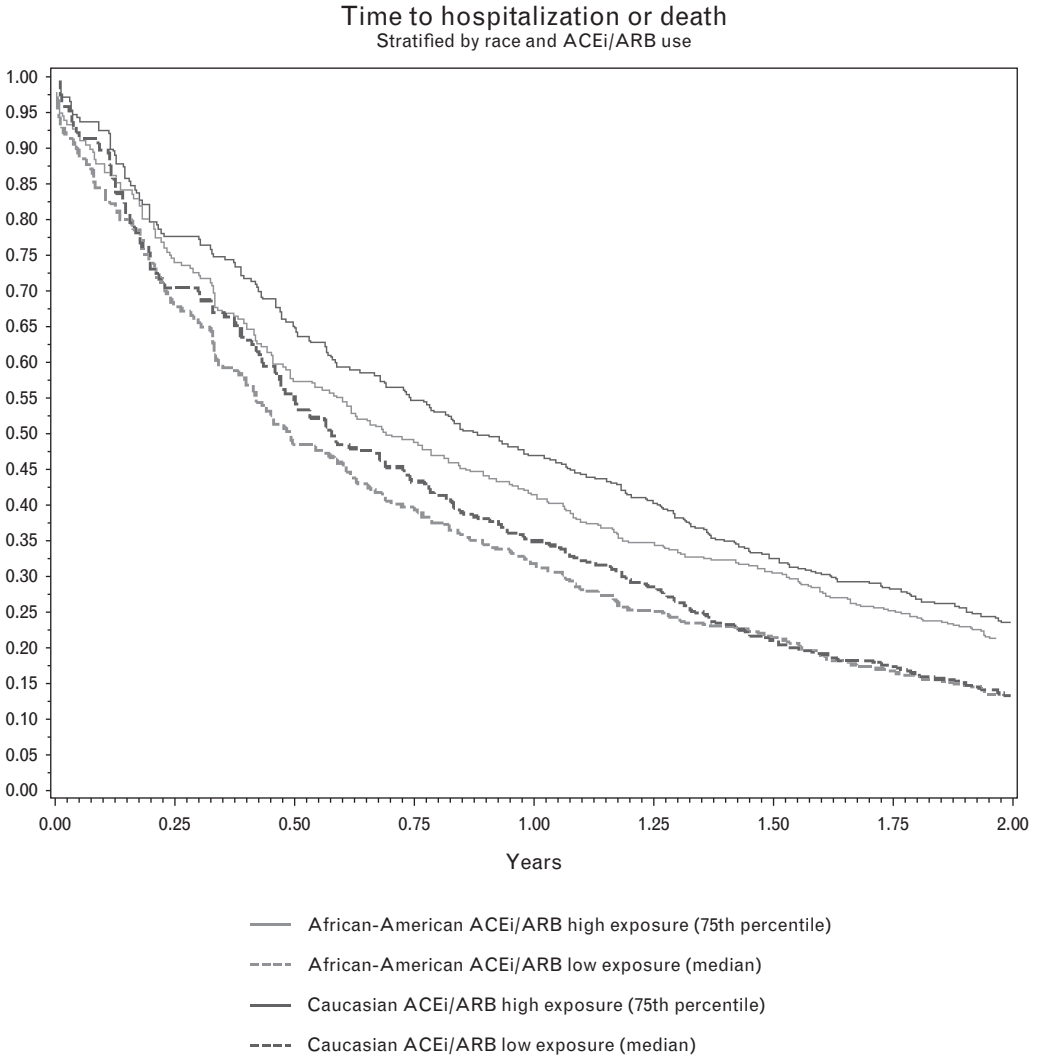
| Outcome | African-American (HR) | *P*-value | White (HR) | *P*-value |
|---|---|---|---|---|
| All-cause death or rehospitalization (1095) | 0.47 | <0.001 | 0.55 | <0.001 |
| All-cause death (1095) | 0.37 | <0.001 | 0.34 | <0.001 |
| All-cause hospitalization (1095) | 0.47 | 0.001 | 0.60 | 0.005 |
| Heart failure hospitalization (1093) | 0.48 | 0.035 | 0.66 | 0.001 |
| ACE/ARB exposure × race interaction (all-cause death + rehospitalization) | | $\beta = 0.04$ | | 0.861 |

ACE/ARB, angiotensin converting enzyme/angiotensin receptor blocker; HR, hazard ratio. Covariates included age, sex, atrial fibrillation, diabetes, hypertension, peripheral vascular disease, stroke, preexisting heart failure, chronic kidney disease, ejection fraction, and β-blocker exposure.

0.66, $P = 0.001$) and African-American patients (hazard ratio 0.48, $P = 0.035$). Interaction testing showed no significant difference ($P = 0.721$, $\beta = 0.08$).

We also examined ACE and ARB exposure separately, in case a race-associated difference was class specific. Again, we found no significant difference in the protective association of either agent class by race (Table 3). ACE exposure was associated with a decrease in time to death or hospitalization in each group of similar magnitude (white hazard ratio 0.27, $P = 0.001$; African-American hazard ratio 0.22, $P = 0.001$), and interaction was not significant ($P = 0.94$, $\beta = 0.02$). The improved outcomes associated with ARB exposure appeared less

**Fig. 2**




Time to hospitalization of death: stratified by race and angiotensin converting enzyme/angiotensin receptor blocker exposure.

**Table 3 Effect of race on angiotensin converting enzyme or angiotensin receptor blocker exposure and all-cause rehospitalization and/or death**

| | All | | White | | African-American | | Interaction |
|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | *P*-value |
| All-cause hospitalization or death | | | | | | | |
| ACE (674) | 0.25 (0.17, 0.36) | 0.001 | 0.27 (0.16, 0.45) | 0.001 | 0.22 (0.13, 0.37) | 0.001 | 0.943 |
| ARB (195) | 0.67 (0.52, 0.87) | 0.002 | 0.75 (0.53, 1.08) | 0.126 | 0.62 (0.43, 0.89) | 0.010 | 0.881 |
| Death | | | | | | | |
| ACE | 0.16 (0.09, 0.29) | 0.001 | 0.12 (0.05, 0.29) | 0.001 | 0.21 (0.009, 0.47) | 0.001 | 0.541 |
| ARB | 0.51 (0.34, 0.79) | 0.002 | 0.56 (0.31, 1.02) | 0.058 | 0.48 (0.26, 0.90) | 0.021 | 0.775 |
| All-cause hospitalization | | | | | | | |
| ACE | 0.27 (0.19, 0.39) | 0.001 | 0.31 (0.18, 0.52) | 0.001 | 0.22 (0.13, 0.38) | 0.001 | 0.818 |
| ARB | 0.69 (0.54, 0.90) | 0.005 | 0.78 (0.54, 1.13) | 0.196 | 0.64 (0.44, 0.91) | 0.014 | 0.950 |
| HF hospitalization | | | | | | | |
| ACE | 0.28 (0.20, 0.41) | 0.001 | 0.35 (0.21, 0.60) | 0.001 | 0.23 (0.13, 0.39) | 0.001 | 0.691 |
| ARB | 0.72 (0.55, 0.93) | 0.013 | 0.83 (0.57, 1.21) | 0.329 | 0.65 (0.45, 0.94) | 0.021 | 0.970 |

Covariates included age, sex, atrial fibrillation, diabetes, hypertension, peripheral vascular disease, stroke, preexisting heart failure, chronic kidney disease, ejection fraction, and β-blocker exposure.

robust (relative to ACE exposure), however, this represented a smaller subgroup ($n = 195$). Regardless, we found no evidence of a difference across race ($P = 0.88$, $\beta = 0.04$).

## Discussion

Our data help clarify the questions that still surround the issue of racial differences in the efficacy of heart failure therapies, specifically related to ACE inhibitors and ARBs. In this adequately powered, retrospective study, ACE/ARB exposure was associated with a similar protective effect in both whites and African-Americans with systolic heart failure. The effect of ACE/ARB exposure on death or rehospitalization and death alone was both significant and similar for both groups.

Previous analyses of other cohorts have demonstrated conflicting results. A retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) cohort ($n = 1196$; blacks = 800) suggested a differing effect of enalapril on preventing hospitalization between whites and African-Americans. Although placebo-matched white patients had a decrease in hospitalization when given enalapril (relative risk 0.51, confidence interval 0.37–0.7), a similar effect was absent in the African-American group.[18] However, a subsequent meta-analysis of the SOLVD trial ($n = 6797$; blacks = 800) showed no difference in mortality between blacks and whites with the prescription of enalapril.[25] Another analysis ($n = 4054$; blacks = 403) examining the progression to symptomatic heart failure also failed to show a significant difference between races.[19] Analysis of the Veterans Affairs Vasodilator-Heart Failure Trials (V-HeFT II) trial ($n = 804$; blacks = 215) suggested that there is a difference in the survival benefit of ACE inhibitors between whites and blacks.[16] The notable benefit was seen most clearly in whites ($P < 0.02$), and a race interaction variable reached statistical significance with ($P = 0.09$) in that study. Although this disagrees with our study, these data are limited by the relatively small number of African-Americans and the fact that only male patients were included in the study. In contrast, our study population was larger, including three times the number of self-identified African-Americans, included both sexes, and had a more equitable race distribution.

Furthermore, our methodology allows a more granular accounting of medication exposure, as well as accounting for medication adherence, which can differ with self-identified race. Thus, we are able to clearly show significantly reduced mortality and hospitalization associated with ACE or ARB exposure among African-Americans with systolic heart failure, who have been underrepresented in heart failure trials. Although the retrospective nature of our study prevents it from defining the absolute benefit of these medications in African-Americans, our data clearly support their effectiveness in this setting. Moreover, the retrospective nature does not mitigate the validity in terms of comparing effectiveness between African-American and white patients, which our data clearly indicate is similar in magnitude, which should put to rest any persisting concerns that ACE inhibitors are less effective or suboptimal treatment for African-Americans with heart failure.

Our study should be interpreted bearing in mind some potential limitations. As mentioned above, retrospective studies have inherent limitations, including potential selection bias or unidentified confounding factors. Some variables of possible interest were missing from our administrative data, including blood pressure and diuretic use. Despite these the primary comparison by race should be robust to most such factors, and we have diligently tried to adjust for potential confounding factors. The fact that our data are derived from a single center study may limit external validity, although our diverse study population reflects well the greater metropolitan population of our region.[26] Given the use of administrative data, diagnostic misclassification may have occurred, but when

evaluating heart failure as a primary discharge diagnosis, our group and others have found that ICD 9 codes were 95–100% specific in meeting Framingham heart failure Criteria.[20] Finally, the ACE/ARB exposure variable included a variety of medications within the classes and an estimated equivalent dose calculation which may be imperfect. However, one might expect that this would likely affect both races equally thus not impacting the racial effectiveness comparison.

## Conclusion

ACE/ARB exposure is associated with a similarly significant protective effect in both white and African-American patients with systolic heart failure, with very similar magnitude of effect in both groups. This supports the continued usage of these medication classes in African-Americans and alleviates any concern for decreased efficacy in African-Americans with heart failure.

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