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ORIGINAL RESEARCH

Angiotensin Receptor Neprilysin Inhibition and Associated Outcomes by Race and Ethnicity in Patients With Heart Failure With Reduced Ejection Fraction: Data From CHAMP-HF

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BACKGROUND: There are limited data on the use of angiotensin receptor neprilysin inhibitors (ARNIs) in minority populations with heart failure (HF) with reduced ejection fraction. We used data from the CHAMP-HF (Change the Management of Patients With Heart Failure) registry to evaluate ARNI initiation and associated changes in health status and clinical outcomes across different races and ethnicities.

METHODS AND RESULTS: CHAMP-HF was a prospective, observational registry of US outpatients with chronic HF with reduced ejection fraction. We compared patients starting ARNI with patients not starting ARNI using a propensity-matched analysis. Patients were grouped as Hispanic, non-Hispanic Black, non-Hispanic White, or non-Hispanic other individuals, where "non-Hispanic other" consists of all patients who did not identify as Hispanic, Black, or White. Health status was assessed using the 12-item Kansas City Cardiomyopathy Questionnaire. Outcomes were analyzed with multivariable models that included race and ethnicity, ARNI initiation, and an interaction term between race and ethnicity and ARNI initiation. Cox proportional hazards models were used for death/HF hospitalization, and multiple regression was used for change in Kansas City Cardiomyopathy Questionnaire score. The analysis included 1516 patients, with 758 patients in each group (ARNI and no ARNI). Changes in Kansas City Cardiomyopathy Questionnaire score after ARNI initiation were similar among all race and ethnicity groups (mean [SD], non-Hispanic White individuals, 3.5 [19.0]; non-Hispanic Black individuals, 2.0 [17.0]; non-Hispanic other individuals, 5.5 [20.3]; and Hispanic individuals, 3.2 [20.1]), with no statistically significant interaction between race and ethnicity and ARNI initiation (P=0.21). There was similarly no statistically significant interaction between race and ethnicity and ARNI initiation for HF hospitalization (P=0.82) or all-cause mortality (P=0.92).

CONCLUSIONS: In a large registry of outpatients with HF with reduced ejection fraction, the association between ARNI initiation and outcomes did not differ by race and ethnicity. These data support the use of ARNI therapy for chronic HF with reduced ejection fraction irrespective of race and ethnicity.

Key Words: angiotensin receptor neprilysin inhibitor ■ heart failure ■ population groups ■ registries ■ sacubitril/valsartan

See Editorial by Luo

Heart failure with reduced ejection fraction (HFrEF) remains an important public health issue with variable impact based on race, ethnicity, and other social and demographic differences.[1] Variability has been found in both the severity of heart failure (HF) clinical presentation and in HF outcomes by race.[2,3] However,

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CLINICAL PERSPECTIVE

What Is New?

- A propensity score–matched secondary analysis of the CHAMP-HF (Change the Management of Patients With Heart Failure) outpatient registry of patients with heart failure with reduced ejection fraction did not reveal a difference in the association between aldosterone receptor neprilysin inhibitor initiation and clinical outcomes for patients among different racial and ethnic groups.
- Association between aldosterone receptor neprilysin inhibitor initiation and health status outcomes, as measured by Kansas City Cardiomyopathy Questionnaire score, was similar for patients of all racial and ethnic groups.

What Are the Clinical Implications?

- Aldosterone receptor neprilysin inhibitor therapy should be used in all patients with chronic heart failure with reduced ejection fraction irrespective of race and/or ethnicity.

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor neprilysin inhibitor
HFrEF	heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire

randomized clinical trials are frequently limited in size for subgroup analyses and may involve enrollment criteria that focus on a more selected population. This, among other factors, has contributed to the underenrollment of certain patient populations in HFrEF clinical trials.[4] In minority demographic populations, there are limited data on the use of many medications for HFrEF, including angiotensin receptor neprilysin inhibitors (ARNIs).

Although limited, there are hypothesis-generating data on use and efficacy of ARNIs in patients of various races and ethnicities. In data from the PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial, investigators found that among Black patients admitted with acute HF, the in-hospital initiation of sacubitril/valsartan was more effective than enalapril in reducing natriuretic peptide levels and the composite of cardiovascular death or HF rehospitalization, and was both safe and well tolerated without differential effect by race.[5] Although these data are intriguing, they are from a trial population and these patients may differ in important ways from those who are represented in registries.[6] To provide insight into this clinical question in a larger cohort of registry patients, we used the CHAMP-HF (Change the Management of Patients With Heart Failure) registry of US outpatients with chronic HFrEF to assess the tolerability and effectiveness of ARNIs on clinical and functional outcomes by race and ethnicity.

METHODS

Data for this study were obtained from the CHAMP-HF registry, and the data that support the findings of this study are available within the article. CHAMP-HF was a prospective observational cohort study of outpatients with chronic HFrEF. The design of CHAMP-HF was described previously.[7] In brief, patients enrolled in the registry had a left ventricular ejection fraction ≤40% on the most recent study in the 12 months before enrollment and were treated with at least one oral therapy for HFrEF. At the time of study enrollment, site coordinators interviewed participants to collect their self-identified race and ethnicity. There were 152 sites across the United States that participated in patient enrollment, and postenrollment clinical data, including data on mortality and HF hospitalization, were reported by the sites at designated time points: 30 days and 3, 6, 12, 18, and 24 months. Safety events were reported at any time throughout the duration of study follow-up.

Statistical Analysis

Our analysis began with all patients in the CHAMP-HF registry. We excluded patients if race or ethnicity was missing or if the patient did not have sufficient follow-up data, including at least 2 assessments for the Kansas City Cardiomyopathy Questionnaire (KCCQ). A propensity model for medication use with matching was used for the primary analysis. Because propensity matching was based in part on the timing of ARNI initiation, patients were excluded from this analysis for any of the following: (1) if they were already taking an ARNI at the time of enrollment, (2) if the start date of ARNI could not be determined, or (3) if they had documented intolerance or contraindication to ARNI. The timing of angiotensin-converting enzyme inhibitor (ACEI) or aldosterone receptor blocker (ARB) therapy was similarly important in the matched analyses, and thus patients were excluded from this analysis if ACEI or ARB start time could not be determined. Patients were then classified as either new ARNI starts, defined as patients who began ARNI therapy at or after enrollment, or as no ARNI, defined as patients who did not begin ARNI therapy. All patients who met inclusion criteria and began ARNI therapy at or after enrollment in the CHAMP-HF registry were included in the matched analysis. For race and ethnicity, patients were grouped as Hispanic, non-Hispanic Black, non-Hispanic White,

or non-Hispanic other individuals. For brevity, race and ethnicity subgroups will hereafter be referred to as "Hispanic," "Black," "White," and "other" patients.

To account for the longitudinal nature of ARNI initiation during registry follow-up, we then performed time-dependent propensity matching to account for differences between patients who initiated ARNI over longitudinal follow-up and those who did not, and to improve balance of covariates across treatment groups and within racial subgroups.[8,9] We created 2 propensity models: one to address initiating ARNI as a switch from ACEI/ARB (the ACEI/ARB model) and one to address de novo ARNI starts (the no-ACEI/ARB model). The comparison of interest was ARNI versus no ARNI, while adequately accounting for initial ACEI/ARB status. Each patient was included in only one model. Each propensity model was a time-dependent Cox model in which time to ARNI start (calculated as days from enrollment to medication start) was used as the outcome with time-independent covariates (race, age, and sex) and time-dependent covariates (systolic blood pressure, heart rate, left ventricular ejection fraction, creatinine, comorbid coronary disease, ischemic HF cause, New York Heart Association class, duration of HF, presence of implantable cardioverter-defibrillator, prior coronary revascularization, β blocker use, and mineralocorticoid receptor antagonist use).

ARNI patients were then matched longitudinally, on the day of ARNI start, 1:1 with no-ARNI patients with the closest time-dependent propensity score, among those of the same race and ethnicity group and same ACEI/ARB status, on the same day of registry follow-up at which the ARNI patient initiated treatment. This method keeps time-dependent confounders "in order" as measured before the matched comparison, and follow-up begins afterward.[9] It also allows for subsequent models to account for time elapsed since registry baseline, which can be an important confounder because of changes attributable to entering the registry. To preserve sample size, all ARNI patients were matched. The quality of the match was assessed using standardized differences. Standardized differences >0.1 are generally considered mild imbalance, and those >0.2 are considered meaningful imbalance. To account for remaining imbalances, the covariate values at the time of the match were further adjusted for in models described below.[9]

Change in KCCQ score was summarized as mean (SD) change, where a positive value indicates an improvement. For clinical outcomes, descriptive event rates were calculated as events per 100 patient-years by race and ARNI status postmatch. Association of race and ethnicity and ARNI initiation with change was assessed in the matched cohort using Cox proportional hazard models, beginning at the time of the match. All models included race and ethnicity subgroup, ARNI initiation, and a term for the interaction between them. In addition, models included matched set as a random effect, time of match, ACEI/ARB status, and all matching variables to account for any remaining imbalances. The KCCQ change model also included the prematch KCCQ score. Robust sandwich variance estimators were used to account for clustering within site. Analysis of adverse effects was performed in the same manner as the clinical outcomes assessment, but within the ARNI group only, and examined race and ethnicity.

In separate sensitivity analyses, we repeated the analyses using the full cohort. The matching algorithm for this was modified so that for each no-ARNI patient, the most similar ARNI patient was identified and assigned that ARNI patient's medication start time as the start time for the no-ARNI patient. Given the differences in cohort size, each ARNI patient's start time was assigned to between 2 and 6 no-ARNI patients. Thus, in the full analysis cohort, ARNI and no-ARNI patients were matched in terms of start times for similar patients only. All covariates were included for adjustment in models of KCCQ change and clinical events.

Institutional Review Board approval was obtained, and patients signed written informed consent before enrollment into the study. The CHAMP-HF registry was sponsored by the Novartis Pharmaceuticals Corporation (East Hanover, NJ). Data were managed by the United BioSource Corporation (Blue Bell, PA), and the Duke Clinical Research Institute (Durham, NC) was the data analytic center for this analysis.

RESULTS

Among 4969 patients in the CHAMP-HF registry, 8 were excluded for missing race and ethnicity and 250 missing for insufficient follow-up data. Of the remaining cohort, 573 were already taking ARNI at enrollment, 116 had a documented intolerance or contraindication to ARNI, and 127 had an unclear ACEI/ARB/ARNI initiation date. There were 3895 patients remaining after exclusions. Patients were then classified as either new ARNI starts (n=758) or as no-ARNI (n=3137).

Compared with the no-ARNI subgroup, patients in the ARNI subgroup were younger, more likely to have an implantable cardioverter-defibrillator, and more likely to be taking a β blocker and mineralocorticoid receptor antagonist (Table S1). For the primary analysis involving 1:1 matching, 1516 patients were included in the analysis, with 758 patients in the ARNI subgroup and 758 patients in the no-ARNI subgroup. After matching, most standardized differences were <10%. Prior differences in age, left ventricular ejection fraction, medication use, and implantable cardioverter-defibrillator presence were not present after matching (Table 1 and Figure S1).

Over half of patients included in the postmatch analysis were White race (67.8%), with Black (17.3%) race and Hispanic (11.5%) ethnicity constituting most of the

Table 1. Patient Characteristics After Matching, by ARNI Subgroup

Patient characteristic at the time of the match	ARNI (N=758)	No ARNI (N=758)	Standardized difference, %
Sociodemographic			
Age, y	63.9 (13.0)	66.4 (11.7)	20.5
Female sex	220 (29)	193 (25)	8.0
Hispanic ethnicity	87 (11)	87 (11)	0.0
Non-Hispanic Black race and ethnicity	131 (17)	131 (17)	0.0
Non-Hispanic White race and ethnicity	514 (68)	514 (68)	0.0
Non-Hispanic other race and ethnicity	26 (3)	26 (3)	0.0
Clinical measures			
Systolic BP (mm Hg)	120.5 (17.7)	120.9 (15.5)	2.6
Heart rate (beats per minute)	74.4 (12.9)	74.0 (11.1)	3.4
LVEF (%)	28.0 (8.2)	30.0 (8.3)	24.5
Creatinine (mg/dL)	1.2 (0.4)	1.2 (0.4)	5.7
Medical history			
Coronary artery disease	467 (62)	478 (63)	3.0
Ischemic HF cause	293 (39)	297 (39)	1.1
NYHA class III/IV	216 (28)	195 (26)	6.2
Duration of HF, y	5.5 (5.4)	5.2 (5.2)	6.2
Presence of ICD	415 (55)	385 (51)	7.9
Prior revascularization	281 (37)	282 (37)	0.3
Medication			
ACEI/ARB	472 (62)	472 (62)	0.0
β Blocker	735 (97)	735 (97)	0.0
MRA	390 (51)	350 (46)	10.6
Patient-Reported Outcomes (PRO)			
KCCQ-OS	67.7 (22.8)	69.1 (23.7)	6.0

Data are given as mean (SD) or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; ARNI, aldosterone receptor neprilysin inhibitor; BP, blood pressure; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary Score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; and PRO, patient-reported outcomes.

rest of the patients (Table S2). The non-Hispanic other cohort was a small (N=52) and heterogeneous population, although their data are included in analyses and data tables for completeness. Black patients were younger (mean [interquartile range] age, 58 [50–65] years) than White (mean [interquartile range] age, 68 [60–75] years) and Hispanic (mean [interquartile range] age, 66 [59–75] years) patients, and were less likely to have coronary disease (Black patients, 42.4%; White patients, 66.8%; Hispanic patients, 68.4%) compared with the other groups. Patients in the White race group had higher baseline KCCQ scores (White patients, 74.0 [55.2–89.3]; Black patients, 68.8 [50.0–87.5]; Hispanic patients, 65.6 [46.4–83.3]) and fewer HF hospitalizations before enrollment (White patients, 31.8%; Black patients, 44.7%; Hispanic patients, 35.1%) compared with the other groups.

In the matched sample, changes in KCCQ score from before to after ARNI initiation were similar among race and ethnicity groups, as reported in Table 2 (mean [SD], White patients, 3.5 [19.0]; Black patients, 2.0 [17.0]; Hispanic patients, 3.2 [20.1]). Overall, there was a borderline statistically significant association between ARNI group and change in KCCQ score, as reflected in Table 2 (parameter estimate [95% CI], 1.65 [–0.02 to 3.31]; P=0.05) with a signal that patients on ARNI therapy had more improvement in KCCQ score compared with their no-ARNI counterparts. There was no significant evidence that this association varied by race and ethnicity (interaction P=0.21).

Patients of White race had the highest mortality in the ARNI (White patients, 6.0; Black patients, 3.8; Hispanic patients, 1.7) and no-ARNI groups (White patients, 10.0; Black patients, 5.6; Hispanic patients, 3.6). Patients of Black race had the highest rates of HF hospitalization in the ARNI (Black patients, 24.2; White patients, 17.4; Hispanic patients, 16.3) and no-ARNI groups (Black patients, 18.7; White patients, 13.6; Hispanic patients, 12.9). Overall, there was a statistically significant association between ARNI group

Table 2. KCCQ-OS Values Before and After ARNI Initiation

Variable	All patients (N=758)	Hispanic patients (N=87)	Non-Hispanic White patients (N=514)	Non-Hispanic Black patients (N=131)	Non-Hispanic other patients (N=26)
ARNI patients					
Prematch	67.9 (22.9)	63.4 (25.8)	69.1 (22.1)	65.7 (23.7)	68.4 (21.4)
Postmatch	71.2 (21.9)	66.7 (23.8)	72.7 (21.0)	67.7 (23.0)	73.9 (24.4)
Change in score (postmatch-prematch)	3.3 (18.8)	3.2 (20.1)	3.5 (19.0)	2.0 (17.0)	+5.5 (20.3)
No-ARNI patients					
Prematch	69.7 (23.2)	64.3 (22.6)	71.1 (22.8)	67.6 (24.5)	71.0 (24.4)
Postmatch	71.1 (23.0)	66.1 (23.5)	72.1 (22.8)	71.0 (22.8)	70.3 (24.6)
Change in score (postmatch-prematch)	1.4 (16.1)	1.8 (14.1)	1.0 (16.2)	3.4 (17.4)	−0.7 (13.3)
Adjusted model					
ARNI vs no ARNI	1.65 (−0.02 to 3.31)	1.35 (−3.40 to 6.11)	2.36 (0.36 to 4.36)	−1.80 (−5.68 to 2.07)	5.65 (−2.93 to 14.22)
P value	0.053*		0.21†		

Prematch and postmatch scores and changes in score are reported as mean (SD). Model results are reported as parameter estimate (95% CI) and can be interpreted as the expected difference in change in KCCQ-OS for ARNI patients compared with the change in no-ARNI patients. ARNI indicates aldosterone receptor neprilysin inhibitor; and KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary Score.

*Reported *P* value is for overall association of ARNI use with change in KCCQ-OS.

†Reported *P* value is for interaction between ARNI use and race and ethnicity.

and mortality (hazard ratio [HR] [95% CI], 0.62 [0.41–0.96]; *P*=0.03), although there was no such similar association between ARNI group and HF hospitalization (HR [95% CI], 1.19 [0.92–1.53]; *P*=0.20), as reflected in Table 3. There was no statistically significant interaction between race and ethnicity and ARNI use with regard to clinical outcomes, with interaction term *P*=0.92 for mortality and *P*=0.82 for HF hospitalization (Table 3). ARNI tolerability was similar across all races and ethnicities (Table 4).

The sensitivity analyses using the full cohort are reported in Tables S3 and S4. We observed similar results to the primary analysis. There was again an association between ARNI group and change in KCCQ score (parameter estimate [95% CI], 1.72 [0.39–3.05]; *P*=0.01), with patients on ARNI therapy having more improvement in KCCQ score compared with the no-ARNI group. However, we again observed no evidence that this association varied by race and ethnicity (interaction *P*=0.58). Similarly, there was also an association between ARNI group and mortality (HR [95% CI], 0.46 [0.33–0.65]; *P*<0.001), but no statistically significant variation by race and ethnicity (interaction *P*=0.95).

DISCUSSION

In this study, we evaluated whether the association between ARNI initiation and outcomes in outpatients with HFrEF differed by patient racial and ethnic group. After matching to account for measured differences, we observed that changes in health status and clinical outcomes were similar for patients of all races and ethnicities when comparing patients starting ARNI therapy with those who did not. There was a statistically significant association between ARNI group and both change in KCCQ score as well as mortality, although no evidence of interaction with race and ethnicity. This indicates that although patients on ARNI therapy may have more improvement in KCCQ score and may have lower rates of mortality, as has been previously published, there is no signal that this improvement is significantly modified by patient race and ethnicity. ARNI tolerability was also similar among race and ethnicity subgroups. These data together are indicative that the tolerability and efficacy of ARNI is similar for patients with HFrEF of all races and ethnicity, and that ARNI therapy should not be withheld on the basis of race and ethnicity alone.

There are prior studies that focused on the tolerability and efficacy of ACEI and ARNI specifically in patients of Black race. For instance, early studies identified higher rates of angioedema with ACEIs.[10,11] In addition, in the SOLVD (Studies of Left Ventricular Dysfunction) clinical trials comparing enalapril with placebo, enalapril was more likely to reduce the risk of HF hospitalization in patients of White race compared with those of Black race, although outcomes for all-cause mortality were similar by race.[12,13] Similarly, in a study that used data from the OptumLabs Data Warehouse and Social Security Death Master File, authors found that ARNI use was associated with a reduced hazard of all-cause death or all-cause hospitalization in patients of White but not Black race.[14] The reasons for these findings were not clear from the analysis and

Table 3. Clinical Outcomes by Race and Ethnicity and ARNI Initiation

Variable	All patients (N=1516)	Hispanic patients (N=87)	Non-Hispanic White patients (N=514)	Non-Hispanic Black patients (N=131)	Non-Hispanic other patients (N=26)
Mortality					
Entire cohort	6.66 (134)	2.64 (6)	7.95 (108)	4.70 (17)	4.59 (3)
ARNI patients	5.05 (52)	1.72 (2)	6.01 (42)	3.84 (7)	3.08 (1)
No-ARNI patients	8.35 (82)	3.61 (4)	10.01 (66)	5.58 (10)	6.08 (2)
Adjusted model					
ARNI vs no ARNI	0.62 (0.41–0.96)	0.47 (0.08–2.94)	0.62 (0.37–1.03)	0.80 (0.31–2.06)	0.35 (0.03–3.93)
P value	0.03*		0.92†		
HF hospitalization					
Entire cohort	16.16 (289)	14.66 (30)	15.53 (189)	21.38 (65)	8.03 (5)
ARNI patients	18.29 (164)	16.34 (17)	17.44 (107)	24.18 (36)	13.40 (4)
No-ARNI patients	14.02 (125)	12.92 (13)	13.58 (82)	18.69 (29)	3.08 (1)
Adjusted model					
ARNI vs no ARNI	1.19 (0.92–1.53)	1.22 (0.70–2.14)	1.13 (0.84–1.53)	1.24 (0.70–2.18)	3.57 (0.33–39.18)
P value	0.20*		0.82†		

All event rates are reported as events per 100 patient-years (number of events). All risk relationships are reported as hazard ratio (95% CI). ARNI indicates aldosterone receptor neprilysin inhibitor; and HF, heart failure.

*Reported *P* value is for overall association of ARNI use with risk of mortality or HF hospitalization.

†Reported *P* value is for interaction between ARNI use and race and ethnicity.

were limited in part by the lack of granularity of clinical detail, although it was theorized that baseline natriuretic peptide levels may differ on the basis of race and ethnicity, and could explain differential response to ARNI therapy.[15,16] Despite this theoretical concern, heterogeneity in response to ARNI therapy by race was not observed in either the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in HF) or PIONEER-HF (Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute HF Episode) clinical trials.[17,18] Our data also observed no interaction between patient race and ARNI initiation for clinical outcomes, including patients of Black race and Hispanic ethnicity.

Our data support current recommendations for the use of guideline-directed medical therapy for HFrEF, regardless of race and ethnicity.[19,20] These data are especially relevant given ongoing disparities in HF outcomes by race and ethnicity.[21] For example, among patients with HF, patients of Black race have higher rates of HF hospitalization compared with White patients and other

Table 4. Medication Tolerability Among Patients on ARNI Therapy by Race and Ethnicity

Variable	Hispanic patients	Non-Hispanic Black patients	Non-Hispanic White patients	Non-Hispanic other patients
New or worsening cough	2.35 (2)	3.83 (5)	4.43 (21)	5.47 (1)
Renal failure	0.00 (0)	2.11 (3)	0.38 (2)	4.96 (1)
Worsening renal function	2.23 (2)	5.13 (7)	4.84 (24)	15.24 (3)
Clinically significant hyperkalemia	1.09 (1)	0 (0)	2.33 (12)	5.84 (1)
Angioedema	1.05 (1)	0 (0)	0.19 (1)	0 (0)
Dizziness/lightheadedness	7.44 (6)	6.54 (7)	16.88 (62)	0 (0)
Other adverse effects	7.94 (7)	6.20 (9)	10.30 (51)	5.09 (1)
Any adverse effect	17.97 (15)	17.88 (24)	30.36 (129)	36.86 (6)
HR (95% CI) for any adverse effect	0.56 (0.31–1.00)	0.57 (0.36–0.92)	Reference	1.17 (0.53–2.61)
No. of different adverse effects, N (%)				
0	72 (82.8)	107 (81.7)	385 (74.9)	20 (76.9)
1	11 (12.6)	17 (13.0)	94 (18.3)	5 (19.2)
2	4 (4.6)	7 (5.3)	26 (5.1)	1 (3.8)
3	0	0	9 (1.8)	0

All values reported as events per 100 patient-years (N) unless otherwise specified. ARNI indicates aldosterone receptor neprilysin inhibitor; and HR, hazard ratio.

groups.[2] Black patients also have higher rates of age-adjusted HF-related mortality compared with White patients.[3] Ultimately, disparities may be improved by increased use of guideline-directed medical therapy, including use of ARNI therapy for patients with HFrEF.[22]

Our study has potential limitations. Although it included a diverse population of patients from across the Unites States, the number of patients from various races and ethnicities and the number of safety events and outcomes were limited. Also, CHAMP-HF was composed of voluntary participating sites and included patients who signed informed consent and had the ability to complete multiple surveys over time. Thus, the patient population may differ from the general population of patients with HFrEF by unstudied characteristics. In addition, medication adverse effects and tolerability were primarily captured via medical record review at specified data abstraction points.[7] This differs from scheduled study visits in traditional clinical trials where patients receive standardized queries on potential medication adverse effects. Finally, we were only able to adjust for variables collected in the registry, and associations between race and ethnicity groups and outcomes may be confounded by other measured or unmeasured variables.

CONCLUSIONS

After propensity score matching patients with HFrEF enrolled in the CHAMP-HF registry, there was no observed difference in association of ARNI initiation in the outpatient setting with outcomes among race and ethnicity subgroups. These data support the use of ARNI therapy in all patients with chronic HFrEF regardless of race and ethnicity and highlight the need for continued improvements in guideline adherence, particularly for patients who belong to racial and ethnic minorities.

ARTICLE INFORMATION

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Disclosures

Dr Thomas reports research funding from Novartis. Dr Albert reports consulting for Amgen, AstraZeneca, Boston Scientific, Merck, and Novartis. Dr Butler is a consultant to Abbott, Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squib, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, and Vifor. Dr Patterson reports research support from Novartis, serves as a consultant to Novartis and Otsuka, and serves on the Advisory Board for Alnylam and SQ Innovations. Dr Hernandez has received research support from the American Heart Association, AstraZeneca, Merck, National Heart, Lung, and Blood Institute, Luitpold, and Novartis, and honorarium from Bayer, Boston Scientific, and Novartis. Dr Shen reports employment by Novartis Pharmaceuticals Corporation. Dr Spertus reports providing consulting services on PROs to Novartis, Bayer, Myokardia, Pfizer, Amgen, Janssen, and Merck. He serves as principal investigator of a research grant from Myokardia and Abbott Vascular and serves on the scientific advisory board for United Healthcare and the Board of Directors of Blue. Dr Fonarow reports consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Edwards, Janssen, Medtronic, Merck, and Novartis. Dr DeVore reports research funding through his institution from the American Heart Association, Amgen, Bodyport, Cytokinetics, American Regent, Inc, the National Heart, Lung, and Blood Institute, and Novartis. He also provides consulting services for and/or receives honoraria from Amgen, AstraZeneca, InnaMed, LivaNova, Novartis, Procyrion, Story Health, Vifor, and Zoll. He has also received nonfinancial support from Abbott for educational activities. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4
Figure S1

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743. doi: 10.1161/CIR.0000000000000950
2. Ziaeian B, Kominski GF, Ong MK, Mays VM, Brook RH, Fonarow GC. National differences in trends for heart failure hospitalizations by sex and race/ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003552. doi: 10.1161/CIRCOUTCOMES.116.003552
3. Glynn P, Lloyd-Jones DM, Feinstein MJ, Carnethon M, Khan SS. Disparities in cardiovascular mortality related to heart failure in the United States. *J Am Coll Cardiol*. 2019;73:2354–2355. doi: 10.1016/j.jacc.2019.02.042
4. Maddox TM, Januzzi JL, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, Masoudi FA, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2021;77:772–810. doi: 10.1016/j.jacc.2020.11.022
5. Berardi C, Braunwald E, Morrow DA, Mulder HS, Duffy CI, O'Brien TX, Ambrosy AP, Chakraborty H, Velazquez EJ, DeVore AD. Angiotensin-neprilysin inhibition in black Americans: data from the PIONEER-HF trial. *JACC Heart Fail*. 2020;8:859–866. doi: 10.1016/j.jchf.2020.06.019
6. Greene SJ, DeVore AD, Sheng S, Fonarow GC, Butler J, Califf RM, Hernandez AF, Matsouaka RA, Samman Tahhan A, Thomas KL, et al. Representativeness of a heart failure trial by race and sex: results from ASCEND-HF and GWTG-HF. *JACC Heart Fail*. 2019;7:980–992. doi: 10.1016/j.jchf.2019.07.011
7. DeVore AD, Thomas L, Albert NM, Butler J, Hernandez AF, Patterson JH, Spertus JA, Williams FB, Turner SJ, Chan WW, et al. Change the management of patients with heart failure: rationale and design of the CHAMP-HF registry. *Am Heart J*. 2017;189:177–183. doi: 10.1016/j.ahj.2017.04.010
8. Lu B. Propensity score matching with time-dependent covariates. *Biometrics*. 2005;61:721–728. doi: 10.1111/j.1541-0420.2005.00356.x
9. Thomas LE, Yang S, Wojdyla D, Schaubel DE. Matching with time-dependent treatments: a review and look forward. *Stat Med*. 2020;39:2350–2370. doi: 10.1002/sim.8533
10. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension*. 2008;51:1624–1630. doi: 10.1161/HYPERTENSIONAHA.108.110270

11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240–e327. doi: 10.1161/CIR.0b013e31829e8776
12. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med*. 2001;344:1351–1357. doi: 10.1056/NEJM200105033441802
13. Shekelle PG, Rich MW, Morton SC, Atkinson CW, Tu W, Maglione M, Rhodes S, Barrett M, Fonarow GC, Greenberg B, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol*. 2003;41:1529–1538. doi: 10.1016/S0735-1097(03)00262-6
14. Tan NY, Sangaralingham LR, Sangaralingham SJ, Yao X, Shah ND, Dunlay SM. Comparative effectiveness of sacubitril-valsartan versus ACE/ARB therapy in heart failure with reduced ejection fraction. *JACC Heart Fail*. 2020;8:43–54. doi: 10.1016/j.jchf.2019.08.003
15. Gupta DK, de Lemos JA, Ayers CR, Berry JD, Wang TJ. Racial differences in natriuretic peptide levels: the Dallas Heart Study. *JACC Heart Fail*. 2015;3:513–519. doi: 10.1016/j.jchf.2015.02.008
16. Gupta DK, Daniels LB, Cheng S, deFilippi CR, Criqui MH, Maisel AS, Lima JA, Bahrami H, Greenland P, Cushman M, et al. Differences in natriuretic peptide levels by race/ethnicity (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol*. 2017;120:1008–1015. doi: 10.1016/j.amjcard.2017.06.030
17. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077
18. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548. doi: 10.1056/NEJMoa1812851
19. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807
20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509
21. Nayak A, Hicks AJ, Morris AA. Understanding the complexity of heart failure risk and treatment in black patients. *Circ Heart Fail*. 2020;13:e007264. doi: 10.1161/CIRCHEARTFAILURE.120.007264
22. Giblin EM, Adams KF Jr, Hill L, Fonarow GC, Williams FB, Sharma PP, Albert NM, Butler J, DeVore AD, Duffy CI, et al. Comparison of hydralazine/nitrate and angiotensin receptor neprilysin inhibitor use among black versus nonblack Americans with heart failure and reduced ejection fraction (from CHAMP-HF). *Am J Cardiol*. 2019;124:1900–1906. doi: 10.1016/j.amjcard.2019.09.020

SUPPLEMENTAL MATERIAL

Table S1. Patient characteristics before matching, by ARNI subgroup*

Patient Characteristic at the time of enrollment	ARNI N=758	No-ARNI N=3,137	Standardized difference (%)
Sociodemographic			
Age	63.3 (13.0)	67.3 (12.3)	31.7
Female	220 (29%)	910 (29%)	0.0
Hispanic	87 (11%)	646 (21%)	25.0
Non-Hispanic Black	131 (17%)	492 (16%)	4.3
Non-Hispanic White	514 (68%)	1,866 (59%)	17.4
Non-Hispanic Other	26 (3%)	133 (4%)	4.2
Clinical Measures			
Systolic BP	119.8 (17.2)	121.9 (17.8)	12.2
Heart rate	73.9 (12.7)	74.0 (12.4)	0.6
LVEF	27.9 (7.8)	30.2 (7.7)	30.7
Creatinine	1.2 (0.4)	1.2 (0.5)	9.0
Medical History			
Coronary artery disease	465 (61%)	2,071 (66%)	9.7
Ischemic HF etiology	287 (38%)	1,278 (41%)	5.9
NYHA Class III/IV	224 (30%)	923 (29%)	0.3
Duration of HF, years	5.0 (5.3)	4.7 (5.7)	5.0
Presence of ICD	375 (49%)	1,139 (36%)	26.8
Prior revascularization	275 (36%)	1,131 (36%)	0.5
Medication			
ACEI/ARB	499 (66%)	2,495 (80%)	31.1
Beta-Blocker	730 (96%)	2,808 (90%)	26.7
MRA	354 (47%)	1,000 (32%)	30.7
PRO			

Patient Characteristic at the time of enrollment	ARNI N=758	No-ARNI N=3,137	Standardized difference (%)
KCCQ-OS	64.0 (23.5)	64.8 (23.6)	3.5

ARNI = Aldosterone receptor-neprilysin inhibitor; BP = blood pressure; LVEF = left ventricular ejection fraction; HF = heart failure; NYHA = New York Heart Association; ICD = implantable cardiac defibrillator; ACEI = angiotensin converting enzyme inhibitor; ARB = aldosterone receptor blocker; MRA = mineralocorticoid receptor antagonist; PRO = patient reported outcomes; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score

*Mean (SD) is shown for continuous variables and N (%) for categorical.

Table S2. Patient characteristics at the time of match (ARNI initiation), by race/ethnicity, among the matched cohort*

Patient Characteristic	Hispanic N=174	Non-Hispanic White N=1,028	Non-Hispanic Black N=262	Non-Hispanic Other N=52
Sociodemographic				
Age, years	66 (59, 75)	68 (60, 75)	58 (50, 65)	65 (58-71)
Female	48 (27.6%)	267 (26.0%)	96 (36.6%)	13 (25.0%)
Clinical measures				
Systolic BP	122 (110, 132)	120 (110, 130)	122 (112, 135)	122 (110, 132)
Heart rate	71 (66, 79)	72 (66, 81)	77 (68, 85)	72 (66, 81)
LVEF, %	30.0 (25.0, 37.0)	30.0 (23.0, 35.0)	28.0 (20.0, 33.0)	33.0 (28.0, 36.0)
Serum creatinine, mean (SD)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)
eGFR, ml/min/1.73 m^2				
< 30	8 (4.6%)	35 (3.4%)	7 (2.7%)	2 (3.8%)
30 - <45	17 (9.8%)	140 (13.6%)	24 (9.2%)	5.8% (3)
45 - <60	41 (23.6%)	252 (24.5%)	53 (20.2%)	17 (32.7%)
≥ 60	108 (62.1%)	601 (58.5%)	178 (67.9%)	30 (57.7%)
Medical history				
Coronary artery disease	119 (68.4%)	687 (66.8%)	111 (42.4%)	27 (51.9%)
Ischemic HF etiology	79 (45.4%)	444 (43.2%)	48 (18.3%)	20 (38.5%)
NYHA Class				
I	24 (13.8%)	146 (14.2%)	28 (10.7%)	8 (15.4%)
II	82 (47.1%)	604 (58.8%)	167 (63.7%)	33 (63.5%)
III	66 (37.9%)	270 (26.3%)	66 (25.2%)	11 (21.2%)
IV	2 (1.1%)	8 (0.8%)	1 (0.4%)	0
HF hospitalization prior to enrollment	61 (35.1%)	327 (38.1%)	117 (44.7%)	12 (23.1%)
Duration of HF, years	3.9 (2.1, 7.0)	3.8 (1.4, 8.1)	3.3 (1.5, 7.7)	4.3 (1.5, 9.3)
ICD	92 (52.9%)	571 (55.5%)	125 (47.7%)	23 (44.2%)
CRT	9 (5.2%)	127 (12.4%)	17 (6.5%)	4 (7.7%)
Prior revascularization	67 (38.5%)	425 (41.3%)	49 (18.7%)	18 (34.6%)
Atrial fibrillation	63 (36.2%)	455 (44.3%)	62 (23.7%)	25 (48.1%)
COPD	54 (31.0%)	296 (28.8%)	88 (33.6%)	11 (21.2%)

Patient Characteristic	Hispanic N=174	Non-Hispanic White N=1,028	Non-Hispanic Black N=262	Non-Hispanic Other N=52
Diabetes mellitus	90 (51.7%)	390 (37.9%)	109 (41.6%)	26 (50.0%)
Hypertension	155 (89.1%)	818 (79.6%)	238 (90.8%)	41 (78.8%)
Medications				
ACEI/ARB	128 (73.6%)	626 (60.9%)	159 (60.3%)	32 (61.5%)
ARNI	87 (50.0%)	514 (50.0%)	131 (50.0%)	26 (50.0%)
Beta blocker	161 (92.5%)	967 (94.1%)	254 (96.9%)	49 (94.2%)
MRA	66 (37.9%)	427 (41.5%)	140 (53.4%)	23 (44.2%)
Hydralazine/ISDN	18 (10.3%)	115 (11.2%)	65 (24.8%)	5 (9.6%)
Digoxin	27 (15.5%)	170 (16.5%)	39 (14.9%)	10 (19.2%)
KCCQ				
Overall summary score	65.6 (46.4, 83.3)	74.0 (55.2, 89.3)	68.8 (50.0, 87.5)	71.9 (53.0, 90.1)
Physical limitation score	58.3 (37.5, 83.3)	75.0 (50.0, 91.7)	75.0 (50.0, 100)	75.0 (54.2, 100)
Symptom frequency score	82.3 (52.1, 95.8)	77.1 (58.3, 91.7)	75.0 (50.0, 93.8)	81.3 (60.4, 91.7)
Quality of life score	50.0 (37.5, 75.0)	62.5 (50.0, 87.5)	62.5 (37.5, 75.0)	62.5 (37.5, 87.5)
Social limitation score	75.0 (50.0, 100)	83.3 (50.0, 100)	75.0 (50.0, 100)	75.0 (50.0, 100)

*Continuous variables represented as median (IQR) unless otherwise specified

ARNI = Aldosterone receptor-neprilysin inhibitor; BP = blood pressure; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; NYHA = New York Heart Association; ICD = implantable cardiac defibrillator; CRT = cardiac resynchronization therapy; ACEI = angiotensin converting enzyme inhibitor; ARB = aldosterone receptor blocker; MRA = mineralocorticoid receptor antagonist; ISDN = isosorbide dinitrate; KCCQ = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score

Table S3. KCCQ Overall Summary Scores before and after ARNI initiation using the full cohort[*]

	All patients	Hispanic	Non-Hispanic White	Non-Hispanic Black	Non-Hispanic Other
ARNI patients	**N=758**	**N=87**	**N=514**	**N=131**	**N=26**
Pre-match	67.9 (22.9)	63.4 (25.8)	69.1 (22.1)	65.7 (23.7)	68.4 (21.4)
Post-match	71.2 (21.9)	66.7 (23.8)	72.7 (21.0)	67.7 (23.0)	73.9 (24.4)
Change in score (post–pre)	+3.3 (18.8)	+3.2 (20.1)	+3.5 (19.0)	+2.0 (17.0)	+5.5 (20.3)
No-ARNI patients	**N=3137**	**N=646**	**N=1866**	**N=492**	**N=133**
Pre-match	68.5 (22.9)	62.6 (20.1)	70.6 (22.8)	67.6 (24.6)	70.2 (24.6)
Post-match	69.5 (23.0)	63.4 (20.8)	71.5 (23.3)	69.0 (23.7)	72.2 (21.8)
Change in score (post–pre)	+1.0 (16.7)	+0.7 (15.8)	+0.9 (17.0)	+1.3 (17.1)	+2.0 (15.4)
Adjusted model					
ARNI vs. No-ARNI	1.72 (0.39-3.05)	2.35 (-1.31-6.00)	2.01 (0.41-3.61)	-0.21 (-3.29-2.88)	3.04 (-3.51-9.60)
P-value	0.011[α]		0.58[β]		

[*]Pre- and post-match scores and changes in score are reported as mean (SD). Model results are reported as parameter estimate (95% CI) and can be interpreted as the expected difference in change in KCCQ Overall Summary Score for ARNI patients compared to the change in No-ARNI patients.

[α]Reported P value is for overall association of ARNI use with change in KCCQ Overall Summary Score.

[β]Reported P value is for interaction between ARNI use and race/ethnicity.

KCCQ = Kansas City Cardiomyopathy Questionnaire; ARNI = aldosterone receptor-neprilysin inhibitor;

Table S4. Clinical outcomes by race/ethnicity and ARNI initiation using the full cohort*

	All patients (N=3895)	Hispanic (N=733)	Non-Hispanic White (N=2380)	Non-Hispanic Black (N=623)	Non-Hispanic Other (N=159)
Mortality					
Entire Cohort	9.85 (468)	5.40 (46)	11.59 (344)	8.48 (63)	8.01 (15)
ARNI patients	5.05 (52)	1.72 (2)	6.01 (42)	3.84 (7)	3.08 (1)
No-ARNI patients	11.18 (416)	5.98 (44)	13.31 (302)	9.98 (56)	9.04 (14)
Adjusted model					
ARNI vs. No-ARNI	0.46 (0.33-0.64)	0.33 (0.07-1.49)	0.47 (0.31-0.70)	0.48 (0.23-1.01)	0.30 (0.04-2.34)
P-value	<0.001[α]		0.95[β]		
HF Hospitalization					
Entire cohort	16.00 (682)	11.03 (87)	16.21 (432)	22.77 (144)	10.75 (19)
ARNI patients	18.29 (164)	16.34 (17)	17.44 (107)	24.18 (36)	13.40 (4)
No-ARNI patients	15.39 (518)	10.22 (70)	15.85 (325)	22.34 (108)	10.21 (15)
Adjusted model					
ARNI vs. No-ARNI	1.01 (0.84-1.22)	1.39 (0.75-2.56)	0.95 (0.77-1.19)	1.03 (0.67-1.58)	1.22 (0.38-3.96)
P-value	0.90[α]		0.70[β]		

*All event rates are reported as events per 100 patient-years (number of events). All risk relationships are reported as HR (95% CI).

[α] Reported P value is for overall association of ARNI use with risk of mortality or HF hospitalization.

[β]Reported P value is for interaction between ARNI use and race/ethnicity. ARNI = aldosterone receptor-neprilysin inhibitor

Figure S1. Patient Demographics Before and After Matching, Entire Cohort.