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Survival Association of Angiotensin Inhibitors in Heart Failure With Reduced Ejection Fraction: Comparisons Using Self-Identified Race and Genomic Ancestry

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ABSTRACT

Background: It remains unclear whether there is a racial disparity in the response to angiotensin inhibitors in patients with heart failure with reduced ejection fraction (HFrEF) and whether the role of genomic ancestry plays a part. Therefore, we compared survival rates associated with angiotensin inhibitors in patients with HFrEF by self-identified race and proportion of West African genomic ancestry.

Methods: Three datasets totaling 1153 and 1480 self-identified Black and White patients, respectively, with HFrEF were meta-analyzed (random effects model) for race-based analyses. One dataset had genomic data for ancestry analyses (416 and 369 self-identified Black and White patients, respectively). Cox proportional hazards regression, adjusted for propensity scores, assessed the association of angiotensin inhibitor exposure with all-cause mortality by self-identified race or proportion of West African genomic ancestry.

Results: In meta-analysis of self-identified race, adjusted hazard ratios (95% CI) for exposure to angiotensin inhibitors were similar in self-identified Black and White patients with HFrEF: 0.52 (0.31–0.85) $P = 0.006$ and 0.54 (0.42–0.71) $P = 0.001$, respectively. Results were similar when the proportion of West African genomic ancestry was $> 80\%$ or $< 5\%$: 0.66 (0.34–1.25) $P = 0.200$ and 0.56 (0.26–1.23) $P = 0.147$, respectively.

Conclusions: Among self-identified Black and White patients with HFrEF, reduction in all-cause mortality associated with exposure to angiotensin inhibitors was similar regardless of self-identified race or proportion of West African genomic ancestry. (*J Cardiac Fail* 2021;00:1–11)

Key Words: Race, ancestry, Heart failure, Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, Survival, Disparity.

Introduction

Black Americans are disproportionately burdened by heart failure (HF). The relative incidence of HF is 50% higher in Black Americans, and they present with HF at significantly younger ages. Black Americans also have significantly higher rates of both hospitalizations and mortality due to HF.¹ Although racism and socioeconomic disparities

contribute to health care disparities,^{2,3} differences in drug response could also contribute to poorer outcomes in Black Americans with HF. The landmark clinical trials of angiotensin inhibitors, which included angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and angiotensin receptor-neprilysin inhibitors (ARNIs), enrolled few Black patients with HF and reduced ejection fraction (HFrEF); the number ranged from 1% to 17% of participants.^{4–10} Thus definitive evidence for the efficacy of angiotensin inhibitors in Black Americans with HFrEF is limited.

Post hoc analyses of some of the landmark trials of angiotensin inhibitors in patients with HFrEF suggest a racial disparity in drug responses.^{7,11,12} Neither the subgroup nor the meta-analyses of the landmark trials found a statistically significant benefit for angiotensin inhibitors in Black patients with HFrEF.^{7,12,13} One study even found a statistically significant treatment-by-race interaction, in which Black patients received significantly less benefit from an ACEI in regard to HF hospitalizations compared to White patients.¹² These findings are concerning because it is well known that a significant racial disparity exists in the

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response to angiotensin inhibitors in the treatment of hypertension.¹⁴ Thus, angiotensin inhibitors are *not* recommended as a first-line therapy for Black patients with hypertension (in the absence of chronic kidney disease).¹⁴ Angiotensin inhibitors are still recommended as a first-line therapy in patients with HFrEF regardless of race,¹⁵ but the racial disparity in hypertension has led to doubts about the efficacy of angiotensin inhibitors in Black patients with HFrEF.¹⁶

Whether the significant racial disparity in the response to angiotensin inhibitors for the treatment of hypertension also exists for the treatment of HFrEF has been strongly debated.^{11,16–20} A major limitation of the previous studies of this potential disparity in patients with HFrEF was the reliance on self-identified race. Race is a social, not a scientific construct.² Thus, using race alone may convolute genetic, social and environmental contributions to drug outcomes. Analyzing drug outcomes according to biogeographic ancestry may help to parse the genomic component from other, nongenomic factors.^{21–24} This may be particularly important for Black Americans, who can have substantial differences in the proportion of African ancestry due to admixture.^{25,26} Therefore, for the first time, this study compared long-term survival benefit resulting from angiotensin inhibitors by both self-identified race and genomic ancestry in patients with HFrEF.

Methods

Patient Data

Three datasets were used to compare the survival benefit of angiotensin inhibitors between self-identified Black and White race: (1) patients with HFrEF enrolled in the Henry Ford HF Pharmacogenomic Registry (HFGR) at Henry Ford Health System (HFHS) in Detroit, MI²⁷; (2) a retrospective analysis of electronic health records (EHR) and insurance claims data of patients with HFrEF at HFHS (who were not enrolled in the HFGR) (HFHS-EHR); and (3) data from the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial.²⁸ Only the HFGR had genomic data available, so it was the only dataset available for ancestry analyses.

Patients with HF were enrolled into the prospective HFGR between October 2007 and March 2015. The methods of this HF registry have been published previously.²⁷ Briefly, patients were enrolled if they were 18 years of age or older, insured by the HFHS-affiliated plan (Health Alliance Plan [HAP]) and met the definition of HF as defined by the Framingham Heart Study.²⁹ Only patients insured by HAP were included because that allowed access to their pharmacy claims data. Unlike medication data from the EHR, which provides only the drugs the patients have been prescribed, pharmacy claims provide additional information regarding medication adherence, such as whether the patient picked up a prescription from the pharmacy, when

the patient picked up the prescription and how many tablets/capsules were dispensed. Patients were excluded if they were dependent on supplemental oxygen or dialysis. Patients on supplemental oxygen were excluded because that could signify severe chronic obstructive pulmonary disease. If patients had chronic obstructive pulmonary disease but did not require supplemental oxygen, they could be enrolled. Detailed phenotypic information (eg, demographics, physical examination, medical history, laboratory values, functional status, medications) were collected upon enrollment. Records of patients' deaths were collected from the Social Security Administration Death Master File, National Death Index, Michigan State Division of Vital Records, and the Henry Ford Health System administrative data, through December 31, 2018. Blood samples were collected at enrollment into the HFGR and were immediately processed and stored at -70°C . Each sample was genotyped using the Axiom Biobank array (Affymetrix; ThermoFisher Scientific, Cambridge, MA), which includes the following $\sim 600\text{K}$ genetic variants: (1) $\sim 300\text{K}$ genome-wide variants with minor allele frequencies $> 1\%$; (2) $\sim 250\text{K}$ low-frequency ($< 1\%$) coding variants from global exome sequencing projects; and (3) an additional $\sim 50\text{K}$ variants to improve West African ancestry coverage (Yoruba in Ibadan, Nigeria [YRI] booster). The proportion of West African genetic ancestry was estimated for each patient using ANCESTRYMAP2.0.³⁰ Briefly, the software program uses a Hidden Markov Model to combine data across unlinked single nucleotide polymorphisms and incorporates information from many neighboring markers to infer ancestry. All patients enrolled into the HFGR were eligible for the current study, except for the patients with HF with preserved ejection fraction (HFpEF) enrolled in the HFGR. Only patients with left ventricular ejection fraction (LVEF) $\leq 40\%$, verified by echocardiography, nuclear stress tests or radionuclide blood pool imaging, were included in this analysis.

The HFHS-EHR dataset is a retrospective analysis of HFHS EHR and insurance claims data. This dataset is more recent than the HFGR because the data were collected from January 1, 2014 to December 31, 2018. Data for all patients at HFHS within that time period who were diagnosed with HF in the inpatient setting or in at least 2 outpatient visits were collected. Patients who were already enrolled in the HFGR were excluded from the HFHS-EHR cohort. Only patients that were HAP members and those with a documented LVEF $\leq 40\%$ were included in this analysis. Information concerning patients' deaths was collected from the Michigan State Division of Vital Records through December 31, 2018.

Detailed methods from GUIDE-IT have been previously published.²⁸ Briefly, GUIDE-IT was a multicenter, randomized controlled trial (RCT) conducted between January 2013 and September 2016 at 45 sites in the United States and Canada. The study planned to randomize 1100 patients with HFrEF (ejection fraction $\leq 40\%$), elevated natriuretic

peptide levels within the prior 30 days and histories of prior HF events (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care. However, enrollment was stopped prematurely at 894 patients because of futility. The primary endpoint was the composite of time-to-first HF hospitalization or cardiovascular mortality. Pre-specified secondary endpoints included all-cause mortality, total hospitalizations for HF, days alive and not hospitalized for cardiovascular reasons, the individual components of the primary end point, and adverse events. The intervention did not significantly affect the any of the endpoints. Only patients with Black or White race were included in this analysis, and only all-cause mortality was used as the outcome. The insurance status of the patients in GUIDE-IT was not available.

Calculation of Angiotensin Inhibitor Exposure

Time-varying drug exposure was calculated using pharmacy claims data in the HFHS datasets as previously described.³¹ We demonstrated that this approach is superior to the typical use of a single time point and dichotomous classification of drug exposure (eg, discharge medication status) for association with clinical outcomes.³² Briefly, doses of angiotensin inhibitors were standardized into dose equivalents by the percentage of the target dose used in HFREF clinical trials, or for angiotensin inhibitors not tested in HFREF clinical trials, by the maximum daily dose (Supplementary Table 1). Exposure was calculated by multiplying the standardized dose equivalent by the quantity of medication dispensed in a 6-month time block, divided by the total number of days in the 6-month time block. This was calculated for each patient for each day of observation, so this method accounts for both dose and adherence over a rolling period of time (6 months). For example, the total daily target dose of candesartan is 32 mg. If a patient were prescribed 16 mg of candesartan daily, and had picked up the prescription from the pharmacy so that there was continuous availability over the previous 6 months, then the calculated angiotensin inhibitor exposure would be 0.5. Exposure was calculated for every day over the course of follow-up in the HFGR and HFHS-EHR datasets. The data from the GUIDE-IT trial did not include pharmacy claims, so exposure was calculated based on the medication data collected at each study visit over the course of follow-up: at baseline, 2 weeks, 6 weeks, and every 3 months through 24 months.

Statistical Analysis

The overall analytic approach used Cox proportional hazards regression models to test the association of time-varying angiotensin inhibitor exposure with all-cause mortality by self-identified race or proportion of West African genomic ancestry. For the continuous variables, a normal distribution was determined by the Kolmogorov-Smirnov test and visual inspection of distribution plots. Continuous baseline variables were summarized by the median (interquartile range) and compared by self-identified race or

proportion of West African ancestry (> 80% vs < 5%) by the Mann-Whitney U test. The proportion of West African ancestry in Black and White Americans is a continuous distribution, and we and others have shown that there is more genomic admixture in Black Americans than in White Americans.^{27,33} Therefore, the cutoffs of > 80% and < 5% of West African ancestry were chosen in order to compare the extremes of the ancestry distributions, while still maintaining comparable sample sizes in the groups with high and low West African ancestry. Categorical baseline variables were summarized by counts and percentages and compared by using χ^2 tests or Fisher exact tests when appropriate. Angiotensin inhibitor exposure was modeled as a continuous variable with values ranging from 0 to 1. Exposure was modeled as a time-varying continuous variable, so the hazard ratios for the association between angiotensin inhibitor exposure and all-cause mortality were scaled as 0 exposure vs target exposure.¹⁵ Average exposure over time was dichotomized only when plotting survival curves (high exposure was defined as the 3rd quartile of average angiotensin exposure over the course of follow-up, and low exposure was defined as the 1st quartile). Two separate sets of models were made, 1 for self-identified race (dichotomous variable) and another for West African ancestry (continuous variable); that is, both factors were not in models together. The models were otherwise similar (ie, had the same covariates and endpoints). Interaction between either self-identified race or proportion of West African ancestry and angiotensin inhibitor exposure was tested by incorporating a multiplicative interaction term within the models for time to all-cause mortality (eg, self-identified race*angiotensin inhibitor exposure). Models stratified by self-identified race and West African ancestry > 80% and < 5% were also developed. For the datasets from the Henry Ford Health System (HFGR and HFHS-EHR), the time dependency of angiotensin inhibitor exposure varied by each day of follow-up in the Cox proportional hazards models. For GUIDE-IT, the time dependency of exposure varied at each follow-up visit when medication data were collected. Patients were not randomized to treatment by angiotensin inhibitors, so the models were adjusted for a propensity score based on the use of angiotensin inhibitors. The propensity score was calculated by using logistic regression of all baseline characteristics in Table 1 (ie, not length of follow-up or death data), and the output was separated into quartiles and used as an ordinal adjuster in the Cox regression models.³⁴ The logistic model for the propensity score used a binary outcome of angiotensin inhibitor exposure (yes/no) at baseline. In addition to using the propensity score as a covariate, propensity matching was also performed, and analyses were repeated in propensity-matched subgroups. Results of the 3 datasets with self-identified race were meta-analyzed using a random effects model. Survival curves were generated from the adjusted Cox proportional hazards models with time-varying angiotensin inhibitor exposure. That approach was used instead of Kaplan-Meier plots because Kaplan-Meier plots use only

Table 1. Baseline Characteristics and Outcomes of the Three Datasets Used to Compare Angiotensin Inhibitor-Associated Survival Benefit by Self-Identified Race

	HFGR			HFHS-EHR			GUIDE-IT		
	Black n = 416 (53%)	White n = 369 (47%)	<i>P</i> ^a	Black n = 415 (40%)	White n = 623 (60%)	<i>P</i> ^a	Black n = 322 (40%)	White n = 488 (60%)	<i>P</i> ^a
Female	155 (37%)	113 (31%)	0.050	180 (43%)	211 (34%)	0.002	127 (39%)	128 (26%)	<.001
Age (years)	63 (56–73)	72 (63–80)	<.001	65 (55–77)	74 (63–83)	<.001	57 (50–65)	66 (58–75)	<.001
LVEF (%)	30 (20–35)	33 (25–37)	<.001	30 (24–35)	30 (24–36)	0.520	20 (15–30)	25 (20–30)	<.001
Ischemic etiology	149 (36%)	214 (58%)	<.001	165 (40%)	358 (58%)	<.001	117 (36%)	291 (60%)	<.001
Hypertension	383 (92%)	307 (83%)	<.001	351 (85%)	486 (78%)	0.009	281 (87%)	364 (75%)	<.001
COPD	84 (20%)	88 (24%)	0.217	144 (35%)	251 (40%)	0.069	73 (23%)	108 (22%)	0.869
Chronic kidney disease	118 (28%)	69 (19%)	0.002	39 (9%)	38 (6%)	0.047	130 (40%)	176 (36%)	0.224
Atrial fibrillation	81 (19%)	143 (39%)	<.001	77 (19%)	238 (38%)	<.001	98 (30%)	229 (47%)	<.001
Stroke	55 (13%)	44 (12%)	0.585	93 (22%)	154 (25%)	0.392	34 (11%)	54 (11%)	0.813
Diabetes	182 (44%)	141 (38%)	0.116	180 (43%)	260 (42%)	0.601	149 (46%)	223 (46%)	0.872
Body mass index (kg/m ²)	29 (26–35)	29 (25–34)	0.428	29 (24–34)	28 (24–33)	0.080	30 (26–37)	28 (24–32)	<.001
SBP (mmHg)	128 (112–143)	122 (109–138)	0.015	126 (112–140)	120 (107–132)	<.001	118 (105–136)	110 (100–123)	<.001
HR (bpm)	72 (63–82)	69 (62–77)	0.001	82 (72–94)	76 (65–90)	<.001	80 (69–90)	74 (66–83)	<.001
NT pro-BNP (pg/mL)	226 (25–579)	278 (129–558)	0.069	-	-	-	241 (135–503)	352 (197–682)	<.001
BNP (pg/mL)	-	-	-	594 (221–1220)	563 (263–1280)	0.761	-	-	-
Serum creatinine (mg/dL)	1.15 (0.90–1.58)	1.09 (0.89–1.40)	0.008	1.17 (0.93–1.47)	1.10 (0.89–1.41)	0.008	1.35 (1.10–1.80)	1.27 (1.01–1.70)	0.062
^b MAGGIC risk score	19 (14–24)	20 (15–25)	0.002	23 (17–28)	26 (21–30)	<.001	21 (17–25)	23 (18–28)	<.001
^c Angiotensin inhibitor exp.	5 (0–37)	3 (0–19)	0.011	1 (0–20)	0 (0–16)	0.164	25 (6–50)	25 (6–50)	0.127
Beta-blocker treatment	266 (64%)	204 (55%)	0.014	219 (53%)	328 (53%)	0.969	302 (94%)	461 (95%)	0.861
Length of follow-up (days)	1414 (860–1996)	1436 (840–2028)	0.898	760 (345–1264)	637 (275–1126)	0.008	497 (258–726)	442 (197–725)	0.042
Deaths	109 (26%)	96 (26%)	0.953	116 (28%)	228 (37%)	0.004	37 (11%)	91 (19%)	0.006

COPD, chronic obstructive pulmonary disease; EHR, electronic health record; exp., exposure (% of HFREF target dose or maximum dose); GUIDE-IT, Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure trial;²⁸ HFHS, Henry Ford Health System; HR, heart rate; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure risk score;²⁷ NT pro-BNP, N-terminal pro b-type natriuretic peptide; SBP, systolic blood pressure.

NOTES. ^a*p* values are for the comparison between self-identified Black vs White race within each dataset. All of the *p*-values < 0.05 in the table need to be made boldface.

^bMAGGIC risk score was calculated without angiotensin inhibitors as input variables.

^cAngiotensin inhibitor exposure at baseline was the percentage of the target dose used in HFREF clinical trials, or the angiotensin inhibitors not tested in HFREF clinical trials, the percentage of the maximum daily dose used by the patient at study entry. (See Supplementary Table 1 for standardized dose equivalents.)

the values of variables at baseline, and they would not allow angiotensin inhibitor exposure to vary over time. For main effects, $P < 0.05$ was considered statistically significant, and for interactions, $P < 0.1$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics by Self-identified Race and West African Ancestry

Table 1 compares baseline characteristics between the self-identified Black and White patients within the 3 datasets used to compare self-identified race: HFGR (n = 416 Black and n = 369 White); HFHS-EHR (n = 415 Black and 623 White); and GUIDE-IT (n = 322 Black and 488 White). The self-identified Black and White patients differed significantly in many ways, such as self-identified Black patients were consistently more female, younger, had lower LVEF, less ischemic etiology, and more hypertension. The mean angiotensin inhibitor exposure at baseline (expressed as % of HFrEF target dose or, in the absence of an established HFrEF dose, the maximum dose) was consistently higher in the self-identified Black patients than in the White patients. The difference was statistically significant in the HFGR (21% \pm 29% and 14% \pm 22% in Black and White patients, respectively; $P < 0.011$). The HFGR had the longest mean

follow-up, nearly 1500 days, and the GUIDE-IT trial had the shortest mean follow-up, approximately 450 days. Follow-up was significantly longer in the Black patients in both the HFHS-EHR and GUIDE-IT datasets, which is probably due to the significantly lower mortality rate for self-identified Black patients in those datasets: 28% vs 37% for Black and White patients in HFHS-EHR ($P = 0.004$) and 11% vs 19% ($P = 0.006$) in GUIDE-IT.

Table 2 summarizes the characteristics of the HFGR stratified by self-identified race and by West African ancestry. Although 416 and 369 patients self-identified their race as Black and White, respectively, only 309 and 353 patients had $> 80\%$ and $< 5\%$ West African ancestry, respectively. The mean proportion of West African ancestry in the self-identified Black and White patients was $85\% \pm 19\%$ and $0.9\% \pm 5.6\%$ ($P < 0.001$), respectively. The significant differences between self-identified Black and White race, such as sex, age, LVEF, comorbidities, etc., were also significantly different when compared by $> 80\%$ and $< 5\%$ West African ancestry.

Association of Angiotensin Inhibitor Exposure With Survival by Self-identified Race

Fig. 1 shows the adjusted association of time-varying angiotensin inhibitor exposure with all-cause mortality in the Cox proportional hazards models in the 3 datasets and the meta-

Table 2. Baseline Characteristics and Outcomes of the HFGR Stratified by Self-Identified Race and West African Ancestry.

Characteristic	Self-identified Race			West African Ancestry		
	Black n = 416 (53%)	White n = 369 (47%)	P^a	$> 80\%$ n = 309 (47%)	$< 5\%$ n = 353 (53%)	P^a
Female	155 (37%)	113 (31%)	0.050	117 (38%)	106 (30%)	0.033
Age (years)	63 (56–73)	72 (63–80)	$< .001$	63 (56–72)	72 (63–80)	0.001
Left ventricular ejection fraction (%)	30 (20–35)	33 (25–37)	$< .001$	30 (20–35)	34 (25–38)	0.001
Ischemic etiology	149 (36%)	214 (58%)	$< .001$	102 (33%)	211 (60%)	0.001
Hypertension	383 (92%)	307 (83%)	$< .001$	287 (93%)	293 (83%)	0.001
Chronic obstructive pulmonary disease	84 (20%)	88 (24%)	0.217	65 (21%)	85 (24%)	0.351
Chronic kidney disease	118 (28%)	69 (19%)	0.002	95 (31%)	63 (18%)	0.001
Atrial fibrillation	81 (19%)	143 (39%)	$< .001$	61 (20%)	135 (38%)	0.001
Stroke	55 (13%)	44 (12%)	0.585	42 (14%)	40 (11%)	0.378
Diabetes	182 (44%)	141 (38%)	0.116	142 (46%)	137 (39%)	0.063
Body mass index (kg/m ²)	29 (26–35)	29 (25–34)	0.428	31 (26–34)	29 (25–34)	0.603
Systolic blood pressure (mmHg)	128 (112–143)	122 (109–138)	0.015	128 (112–144)	122 (108–138)	0.004
Heart rate (beats per minute)	72 (63–82)	69 (62–77)	0.001	72 (63–82)	69 (62–77)	0.001
NT pro-BNP (pg/mL)	226 (25–579)	278 (129–558)	0.069	230 (85–564)	277 (128–558)	0.196
Serum creatinine (mg/dL)	1.15 (0.90–1.58)	1.09 (0.89–1.40)	0.008	1.20 (0.91–1.60)	1.10 (0.88–1.40)	0.002
^b MAGGIC risk score	19 (14–24)	20 (15–25)	0.002	19 (14–24)	20 (15–25)	0.013
^c Angiotensin inhibitor exposure	5 (0–37)	3 (0–19)	0.011	4 (0–36)	3 (0–19)	0.065
Beta-blocker treatment	266 (64%)	204 (55%)	0.014	195 (63%)	197 (56%)	0.057
Proportion West African ancestry	90 (81–96)	0 (0–0)	0.001	93 (88–97)	0 (0–0)	0.001
Length of follow-up (days)	1414 (860–1996)	1436 (840–2028)	0.898	1385 (856–1990)	1441 (844–2058)	0.802
Deaths	109 (26%)	96 (26%)	0.953	80 (26%)	88 (25%)	0.777

MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure risk score²⁷; NT pro-BNP, N-terminal pro b-type natriuretic peptide.

NOTE. all of the p-values < 0.05 in the table need to be made boldface.

^a P values are for the comparison between self-identified Black vs White race or $> 80\%$ vs $< 5\%$ West African ancestry.

^bMAGGIC risk score was calculated without angiotensin inhibitors as input variables.

^cAngiotensin inhibitor exposure at baseline was the percentage of the target dose used in HFrEF clinical trials or the angiotensin inhibitors not tested in HFrEF clinical trials, the percentage of the maximum daily dose used by the patient at study entry. (See Supplementary Table 1 for standardized dose equivalents.)

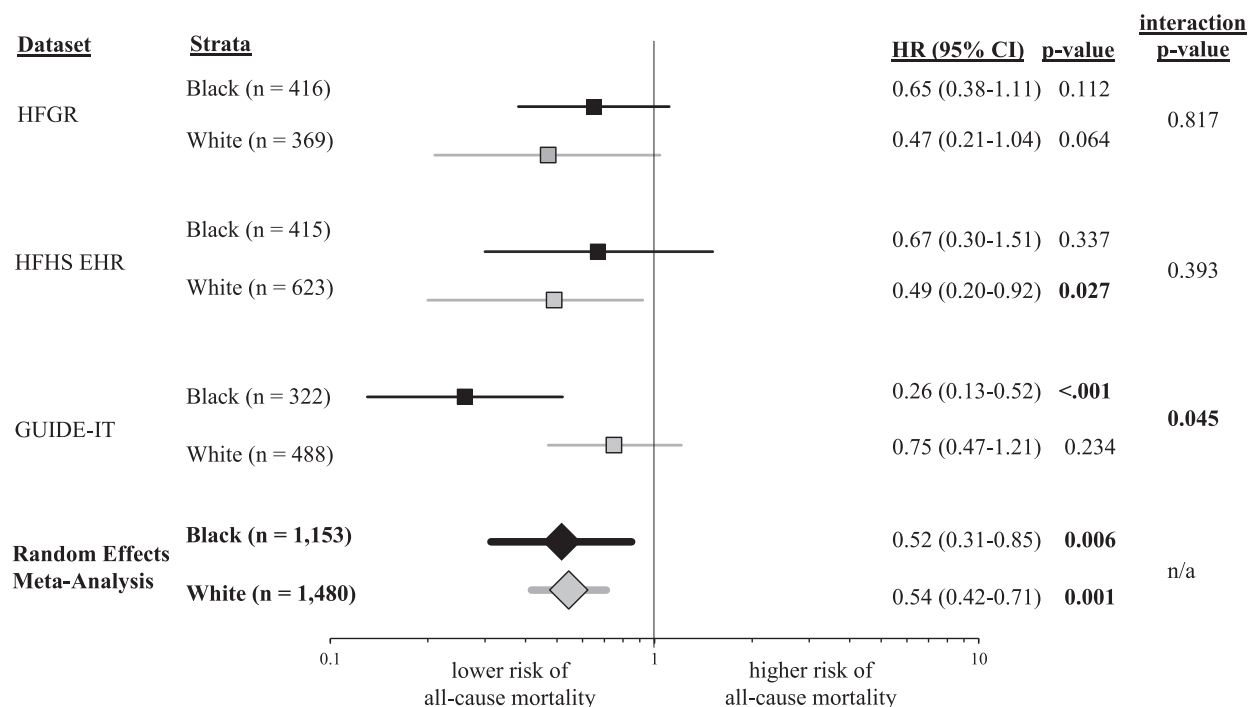


Fig. 1. Forest plot of adjusted association of time-varying exposure to angiotensin inhibitors with all-cause mortality in Cox proportional hazards models stratified by self-identified race. All models were adjusted for angiotensin inhibitor propensity score, which was calculated based on all baseline characteristics in Table 1. The x-axis is the hazard ratios and 95% confidence intervals plotted on a logarithmic scale. The y-axes are the 3 different datasets stratified by self-identified race, GUIDE-IT, Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure trial; HFGR, Henry Ford Heart Failure Pharmacogenomic Registry; HFHS-EHR, retrospective analysis of electronic health records (EHR) & insurance claims data of HFREF patients at Henry Ford Health System (who were not enrolled in the HFGR).

analysis stratified by self-reported race. The point estimates for the adjusted hazard ratios in White patients were lower than those in Black patients in the HFGR (0.47 vs 0.65, respectively) and the HFHS-EHR datasets (0.49 vs 0.67, respectively). However, the 95% confidence intervals (CI) mostly overlapped, so there was no significant difference between the Black and White patients in those datasets (both interaction P values > 0.3). In the GUIDE-IT dataset, angiotensin inhibitor exposure was significantly associated with more survival benefit in the self-identified Black patients than in White patients (interaction P value = 0.045). The adjusted hazard ratio (95% CI) was 0.26 (0.13–0.52); $P < 0.001$ in the self-identified Black patients, and it was 0.75 (0.47–1.21); $P = 0.234$ in the self-identified White patients. In the random effects meta-analysis of the 3 datasets, the adjusted hazard ratios (95% CI) were almost identical in the Black and White patients: 0.52 (0.31–0.85) $P = 0.006$ and 0.54 (0.42–0.71) $P = 0.001$, respectively. To visualize these results, survival curves for the association of time-varying angiotensin inhibitor exposure with all-cause mortality, stratified by self-identified race and high and low angiotensin inhibitor exposure, were constructed from the adjusted model data (Fig. 2). Consistent with the above data, the survival curves largely overlapped among self-identified Black and White patients with HFREF. The results were similar in the propensity-matched subgroups (Supplementary Material).

Association of Angiotensin Inhibitor Exposure With Survival According to West African Ancestry

When comparing patients according to West African ancestry in the HFGR, the associations were similar to the comparisons according to self-identified race (Fig. 3). In patients with $> 80\%$ West African ancestry, the adjusted hazard ratio (95% CI) was 0.66 (0.34–1.25; $P = 0.200$), and in patients with $< 5\%$ West African ancestry, it was 0.56 (0.26–1.23; $P = 0.147$). Again, the 95% confidence intervals mostly overlapped, so there was not a significant difference in the association according to proportion of West African ancestry (interaction P value = 0.772). Survival curves stratified by proportion of West African ancestry and high and low angiotensin inhibitor exposure are displayed in Fig. 2B. These parallel the curves stratified by self-identified race, such that patients with African ancestry $> 80\%$ and those with $< 5\%$ had substantial overlap. In almost all of the groups, the survival curves for high exposure to angiotensin inhibitors are higher than those for low angiotensin inhibitor exposure, regardless of race or ancestry. The exception is the self-identified Black patients in the HFHS-EHR dataset, in which the curves for high and low angiotensin inhibitor exposure are almost completely superimposed.

Discussion

To our knowledge, this is the first study to compare survival benefit associated with angiotensin inhibitors by both

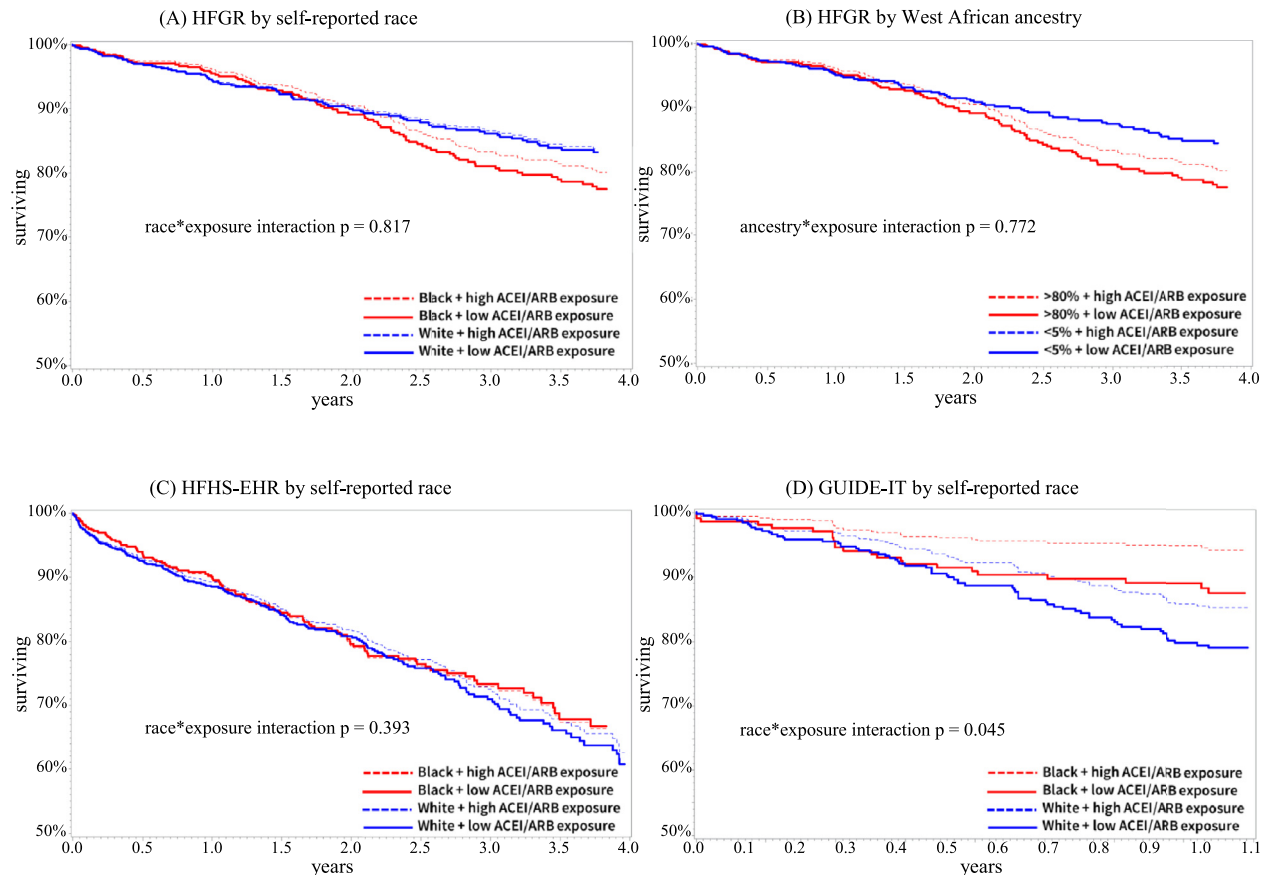


Fig. 2. Survival curves generated from adjusted Cox proportional hazards models for the association of time-varying angiotensin inhibitor exposure with all-cause mortality in (A) HFGR stratified by self-identified race (Black: HR [95% CI] 0.65 [0.38–1.11] $P = 0.112$; White: 0.47 [0.21–1.04] $P = 0.064$). (B) HFGR stratified by proportion of West African ancestry ($> 80\%$ West African ancestry: 0.66 [0.34–1.25] $P = 0.200$; $< 5\%$ West African ancestry: 0.56 [0.26–1.23] $P = 0.147$). (C) HFHS-EHR stratified by self-identified race (Black: 0.67 [0.30–1.51] $P = 0.337$; White: 0.49 [0.20–0.92] $P = 0.027$). (D) GUIDE-IT stratified by self-identified race (Black: 0.26 [0.13–0.52] $P < .001$; White: 0.75 [0.47–1.21] $P = 0.234$). All models were adjusted for angiotensin inhibitor propensity score, which was calculated based on all baseline characteristics in Table 1. In (A), (B), and (C), Red lines are self-identified Black patients; blue lines are self-identified White patients. In (D), the red lines indicate patients with $> 80\%$ West African ancestry, and the blue lines indicate patients with $< 5\%$ West African ancestry. High angiotensin inhibitor exposure was defined as the 3rd quartile of average angiotensin exposure over the course of follow-up (dashed lines), and low angiotensin inhibitor exposure was defined as the 1st quartile (solid lines). These plots are generated from the adjusted Cox proportional hazards models, so it is important to note that they are solely for illustrative purposes of showing the adjusted Cox proportional hazards model results, and they should not be interpreted as the more commonly used Kaplan-Meier plots. The nonsignificant interaction P values ($P > 0.1$) in (A), (B) and (C) indicate that although there is separation of the curves visually, those differences were not statistically significant. The interaction P value in (D) ($P = 0.045$) indicates that angiotensin inhibitor exposure was associated with a significantly greater reduction in the risk for all-cause mortality in the patients who identified as Black in GUIDE-IT (data from the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure trial.²⁸ HFGR, the Henry Ford Heart Failure Pharmacogenomic Registry²⁷; HFHS-EHR, retrospective analysis of electronic health records (EHR) and insurance claims data of patients with HFrEF at Henry Ford Health System (who were not enrolled in the HFGR).

self-identified race and genomic ancestry in patients with HFrEF. Despite a significant racial disparity in the response to angiotensin inhibitors for the treatment of hypertension,¹⁴ and previous data suggesting differential efficacy in regard to hospitalization in HFrEF,¹² we did not find a significant racial disparity in survival benefit for the treatment of HFrEF. The results of the ancestry-based analysis were similar to those of the race-based analysis. Previous studies analyzed racial differences among the few hundred Black patients enrolled in the landmark HFrEF clinical trials of angiotensin inhibitors,^{7,12,13} but the findings were equivocal, and those trials were performed more than 20 years

ago. As a result, we sought out additional and more contemporary datasets with enrollment of a large proportion of Black patients with HFrEF. The location of the Henry Ford Health System in Detroit, Michigan, is uniquely advantageous for this research; nearly 80% of the population of Detroit identifies as Black.³⁵ However, in order to improve the generalizability of our findings from this single center, we sought out additional data from other locations. The GUIDE-IT trial had much higher enrollment of patients with HFrEF who identified as Black (40%) than most other HFrEF landmark trials, and it included patients from 45 clinical sites across North America. Therefore, we were

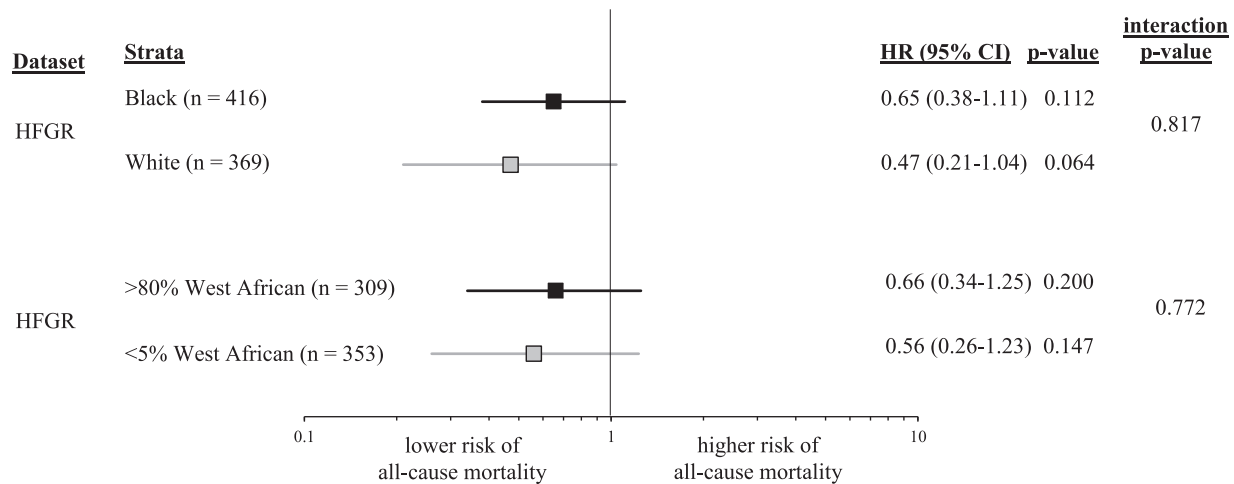


Fig. 3. Forest plot of adjusted association of time-varying exposure to angiotensin inhibitors with all-cause mortality in Cox proportional hazards models in the HFGR stratified by self-identified race and proportion of West African genomic ancestry. All models were adjusted for angiotensin inhibitor propensity score, which was calculated based on all baseline characteristics in Table 1. The x-axis shows the hazard ratios and 95% confidence intervals plotted on a logarithmic scale. The y-axes are the HFGR stratified by self-identified race and proportion of West African genomic ancestry. GUIDE-IT, data from the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure trial²⁸; HFGR, the Henry Ford Heart Failure Pharmacogenomic Registry²⁷; HFHS-EHR, retrospective analysis of electronic health records (EHR) and insurance claims data of patients with HFREF at Henry Ford Health System (who were not enrolled in the HFGR)

able to extend our findings from the 2 datasets at Henry Ford Health System to a multicenter clinical trial.

Our findings contrast with certain previous observations, but these data fit well when examined in full context and may help to clarify what may otherwise seem inconsistent. Noteworthy was a post hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials by self-identified Black and White race by Exner et al.¹² They found a significant race interaction in HF hospitalization (adjusted HR [95% CI] for Black patients: 0.86 [0.64–1.16]; White patients: 0.51 [0.37–0.70]; *P*value for interaction = 0.005). However, when testing all-cause mortality, angiotensin inhibitor benefit was similar between Black and White patients (adjusted HR for Black patients 0.85; White patients 0.92; *P*value for interaction = 0.68). Shekelle et al. performed a meta-analysis of Black and non-Black patients in the SOLVD prevention and treatment trials and the SAVE trial.¹³ The outcome analyzed was mortality due to HF and, similar to our findings, benefit from ACEIs did not differ by race (RR in Black patients: 0.89 [95% CI 0.74–1.06], and RR in White patients: 0.89 [95% CI 0.82–0.97]). A subgroup analysis of the Black population in the Valsartan Heart Failure (Val-HeFT) trial,⁷ which included 344 African American and South African patients, found that the relative risk was 1.11 (95% CI 0.77–1.61) for valsartan compared to placebo. In contrast, in the overall trial, which was composed predominantly of White patients, the relative risk for valsartan was 0.87 (95% CI 0.77–0.97). Of note, the primary endpoint was a composite, including death, cardiac arrest, hospitalization due to HF, or administration of intravenous inotropic or vasodilator drugs for 4 hours or more without hospitalization. Our group had previously performed a retrospective analysis of Black and

White patients by using older EHR data from HFHS (from 2000 to 2008).³⁶ Similar to the present study, when the outcome was all-cause mortality alone, the hazard ratios for angiotensin inhibitor benefit were almost identical in Black and White patients (0.37 and 0.34, respectively). For hospitalization due to HF, the point estimate for the hazard ratio in Black patients was lower when compared with that of white patients (0.48 and 0.66, respectively), although these differences did not reach statistical significance.

Taken together, when previous investigations focused on mortality benefit, they appear to be consistent across race, with which our current data agree. The contrasting data suggesting a difference in drug effect by race seems often focused on other endpoints, particularly hospitalization. It may be worth considering, given documented racial disparities in access to and quality of health care,³⁷ that using hospitalization as the endpoint may be more susceptible to confounding when trying to assess differences in drug efficacy by race.³⁸ For example, hospitalizations due to HF are 229% and 240% higher for Black men and women compared to White men and women, respectively.³⁹ Black Americans use the emergency department for health care significantly more than other racial groups.⁴⁰ These different patterns in health care use by race make it more difficult to draw conclusions regarding the impact of the medication itself.

Another potential limitation of previous studies was categorizing patients by race alone and not also assessing genomic ancestry. That was by necessity because the previous studies were conducted in the early 2000s, prior to the completion of the Human Genome Project and the wider availability of ancestry estimation. The recent and rapid increase in the availability and affordability of genomic arrays

should facilitate increased use of genomic ancestry in future research. A common misconception is that race can be used as a proxy for genetic ancestry, and this is especially problematic admixed populations.²⁴ Race can reflect multiple important factors, including genomic ancestry, socioeconomic status, cultural beliefs and practices, and local or regional environmental exposures, making it a variable with great associative power but poor resolution as to which components are causative. In order to distinguish genetic differences in drug outcomes from extrinsic determinants, we evaluated differences by ancestry and self-reported race. Indeed, Iniesta et al. found that differences in antihypertensive responses (including the ACEi lisinopril) were more closely associated with genetically defined ancestry than with self-defined ethnicity in admixed subjects.²² They also found that a relatively small number of genetic variants explained a large proportion of the difference in response to the ARB candesartan in Black and White hypertensive patients. Rao et al. compared outcomes of hypertensive patients in the Systolic Pressure Interventional Trial (SPRINT) by race and West African ancestry²¹ and, similar to our study, they did not find significant differences by West African ancestry. These findings and others suggest that the use of genomic ancestry, in addition to race, may be a better way of distinguishing pharmacological differences versus social determinants of health in precision medicine.²⁴ While pointing out the potential value of genomics in race-disparity research, it is also critically important to identify and quantify the other factors contributing to race associations, particularly the role of social determinants of health in drug outcomes.²³ Regardless of pharmacological responses, social determinants of health can nullify beneficial drug outcomes. For example, if patients with HFrEF are unable to obtain prescriptions, access pharmacies or afford their medications, they will not benefit from any drug therapy.³

It remains unclear why there is a significant racial disparity in the response to angiotensin inhibitors in hypertension/blood pressure, yet this does not translate into HFrEF. In addition to blood pressure lowering, angiotensin inhibitors also have other beneficial effects in the treatment of HFrEF, such as left ventricular remodeling, renal protection, improved endothelial function, regulated sympathetic activity, and antiproliferative and antimigratory effects.⁴¹ Indeed, patients with HFrEF still experience improvement in clinical outcomes resulting from angiotensin inhibitors independent of their effects on blood pressure.⁴² Therefore, it is possible that these other intermediate mechanisms, rather than simply blood pressure lowering, provide clinical outcome benefits in HFrEF and not in hypertension.

Limitations

Our study has some limitations. The datasets were observational as far as angiotensin inhibitor therapy. We attempted to overcome the limitation of using observational data by developing a propensity score for treatment by

angiotensin inhibitors, and we adjusted for it as a covariate in our models and in propensity-matched subgroup analysis. Ideally, this analysis would be performed using data from randomized clinical trials of angiotensin inhibitors but, as previously stated, enrollment of Black patients in the landmark randomized clinical trials has been low. Moreover, analyses of the landmark randomized clinical trials have been limited to self-identified race. Another limitation is that we did not assess specific social determinants of health in our analysis because these data were not available in all datasets. Our meta-analysis was not based on a systematic review of prior trials but, rather, on the convenience of the data available to us, which could be a source of bias. Finally, the survival plots were not the more commonly used Kaplan-Meier plots; rather, they were generated from the adjusted Cox proportional hazards models. Therefore, the survival plots are solely for illustrative purposes of the results of the adjusted Cox proportional hazards models, and they should not be interpreted as Kaplan-Meier plots.

Conclusions

In conclusion, we did not identify a significant racial disparity in survival benefit associated with angiotensin inhibitors in patients with HFrEF. Our findings were similar when examining this in terms of proportion of West African genomic ancestry. These data support current HF guidelines and may provide some reassurance concerning the benefits of angiotensin inhibitor treatment in Black Americans.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.cardfail.2021.08.007](https://doi.org/10.1016/j.cardfail.2021.08.007).

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