RESEARCH ARTICLE

Circulation: Heart Failure

ORIGINAL ARTICLE

Racial and Ethnic Differences in Biomarkers, Health Status, and Cardiac Remodeling in Patients With Heart Failure With Reduced Ejection Fraction Treated With Sacubitril/Valsartan

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BACKGROUND: Among patients with heart failure and reduced ejection fraction (left ventricular (LV) ejection fraction ≤40%), sacubitril/valsartan (S/V) treatment is associated with improved health status and reverse cardiac remodeling. Data regarding racial and ethnic differences in response to S/V are lacking.

METHODS: This was an analysis from the PROVE-HF study (Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure). Longitudinal changes in NT-proBNP (N-terminal pro-B-type natriuretic peptide), cardiac reverse remodeling, and health status scores were compared between groups using multivariate latent growth curve modeling.

RESULTS: Among the 782 patients included in this study, 22.7% were non-Hispanic Black (from here referred to as Black), 14.9% were Hispanic, and 62.4% were non-Hispanic White (from here referred to as White). At baseline, compared with White patients, Black and Hispanic patients had lower NT-proBNP (g=0.34) and differences between groups in baseline values for LV end-diastolic volume index and LV end-systolic volume index were negligible (g<0.10). Following S/V initiation, NT-proBNP decreased in all 3 groups (P<0.0001) associated with improvements in LV ejection fraction, LV end-diastolic volume index, and LV end-systolic volume index. Although total improvement in LV measures was similar between groups, Black patients averaged larger gains in the first half of the trial while White patients averaged larger gains in the second half. Improvements in Kansas City Cardiomyopathy Questionnaire-23 Total Symptom scores were seen in all 3 groups. Treatment with S/V was well-tolerated.

CONCLUSIONS: Among Black, Hispanic, and White patients with heart failure and reduced ejection fraction, treatment with S/V was associated with similar reduction in NT-proBNP, improvement in health status, and reverse remodeling. More data regarding racial and ethnic responses to heart failure and reduced ejection fraction treatment are needed.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02887183.

Key Words: biomarker ■ health status ■ heart failure ■ ventricular remodeling

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WHAT IS NEW?

- Sacubitril/valsartan is given a class I indication by clinical guidelines for the treatment of heart failure and reduced ejection fraction (≤40%) and has benefit on health status and cardiac reverse remodeling; however, benefit in chronic heart failure and reduced ejection fraction stratified by race or ethnicity has not been previously examined.
- We examined the benefits of sacubitril/valsartan on health status and cardiac reverse remodeling in Black, Hispanic, and White patients with chronic heart failure and reduced ejection fraction to examine if benefit derived is consistent across these racial and ethnic groups.

WHAT ARE THE CLINICAL IMPLICATIONS?

- We demonstrated that Black, Hispanic, and White patients derive similar benefit from sacubitril/valsartan with respect to improvement in health status, cardiac reverse remodeling, and reduction in N-terminal pro-B-type natriuretic peptide concentrations.
- Importantly, sacubitril/valsartan is safe and well-tolerated among Black, Hispanic, and White patients and should be prescribed in all patients where clinically indicated.

Nonstandard Abbreviations and Acronyms

HF	heart failure
HFrEF	heart failure with reduced ejection fraction
KCCQ-23	Kansas City Cardiomyopathy Questionnaire
NT-proBNP	N-terminal pro-B-type natriuretic peptide
S/V	sacubitril/valsartan
TS	Total Symptom

Mechanisms for racial and ethnic differences in heart failure (HF) epidemiology are multifactorial; yet, continued underrepresentation of non-Hispanic Black (here referred to as Black) and Hispanic patients of all races and origins (herein referred to as Hispanic) in HF clinical trials contributes to ongoing and substantial gaps in our understanding about the role and effects of these mechanisms in HF with reduced ejection fraction (HFrEF). HF is more prevalent and is associated with higher mortality and morbidity in Black individuals than in non-Hispanic White (here referred to simply as White) individuals.[1] Once HF has developed, Black patients have a worse course, more events, and worse health status compared with White patients.[2] Notably, despite their higher risk, NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations are lower in Black individuals compared with White individuals.[3,4] The landscape of available studies on HFrEF in Hispanic patients is also scant. Among Hispanic individuals, the incidence and prevalence of HF is higher compared with White individuals,[5] and Hispanic individuals also generally present with NT-proBNP concentrations lower than White individuals, although this too can vary.[6] Similar to Black patients, Hispanic patients with HFrEF report worse health status compared with White patients.[2]

Sacubitril/valsartan (S/V), an angiotensin receptor blocker/neprilysin inhibitor is among the newest guideline supported options for treatment of HFrEF[7,8] reducing risk in patients affected by chronic HFrEF.[9] Most recently, the PROVE-HF study (Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure)[10] provided insight into a potential mechanism of benefit of S/V in chronic HFrEF by demonstrating cardiac reverse remodeling improvement in treated patients; reverse remodeling was associated with the reduction in NT-proBNP that occurred after S/V initiation. A major advantage of the PROVE-HF study is robust racial/ethnic balance with a substantial percentage of Black and Hispanic patients. Accordingly, we sought to explore differences in NT-proBNP concentrations, health status, and characteristics in reverse cardiac remodeling in Black, Hispanic, and White patients with HFrEF treated with S/V.

METHODS

The authors declare that all supporting data are available within the article and in the Data Supplement. All study procedures were approved by each center's Institutional Review Board and carried out in accordance with the Declaration of Helsinki.

PROVE-HF Study Design and Participants

PROVE-HF was a 52-week, multicenter, open-label, single-arm study that enrolled 794 patients with chronic HFrEF who were initiated and titrated on S/V to the target dose of 97 out of 103 mg twice daily where possible.[10,11] Echocardiographic assessments were performed at baseline and months 6 and 12 and interpreted by readers who were unaware of echocardiogram sequence at a core laboratory. Cardiac reverse remodeling was defined by changes in left ventricular (LV) ejection fraction (LVEF), LV end-diastolic volume index, and LV end-systolic volume index.[10]

Blood samples were collected from participants at each study visit and sent to a central laboratory for measurement of plasma NT-proBNP using a commercially available electrochemiluminescence immunoassay (proBNP II, Roche Diagnostics).

The Kansas City Cardiomyopathy Questionnaire (KCCQ-23) was used to assess health status and health-related quality of life.[11] The Total Symptom (TS) score, Clinical Summary score, and Overall Summary scores were recorded. Safety measures included monitoring for suspected cases of angioedema, which were evaluated by a central adjudication panel.[10]

Present Analysis

Race/ethnicity was self-assigned by study participants. For the purposes of this article, we aligned reporting of racial and ethnic categories with Federal data standards[12] such that Black refers to non-Hispanic Black patients, Hispanic refers to Hispanic patients of all races, and White refers to non-Hispanic White patients. This alignment was meant to ensure comparability with other studies.

Our aims for this differences-based subgroup analysis were 2-fold. First, we aimed to explore the magnitude of race and ethnicity-based differences, if any, in concentrations of NT-proBNP, cardiac reverse remodeling, and health status in response to treatment with S/V. Second, we set out to determine whether Black, Hispanic, and White patients had similar response to S/V treatment with respect to changes in NT-proBNP concentrations, cardiac reverse remodeling, and health status.

Statistical Analysis

From the original cohort of 794, we excluded 12 patients due to unknown race or ethnicity, yielding a final cohort size of 782.

Patient demographics, clinical biomarkers, and echocardiogram data were compared between Black, Hispanic, and White patients using counts or percentages for categorical variables and means with SD or medians (25th–75th percentile) for continuous variables as appropriate depending on normality. Due to non-normal distribution, log-transformed values for NT-proBNP were used.

Given the post hoc nature of the analysis, in support of recent recommendations, standardized mean differences were used to compare characteristics between racial/ethnic groups rather than hypothesis testing with *P* values. Standardized mean differences provide a more meaningful way to assess the balance of covariates between groups; here, we used the Hedges *g* for interval-scaled variables and the Phi coefficient (φ) for categorical variables. standardized mean differences values are interpreted in ranges that include large (>0.80); moderate-to-large (0.60–0.79); moderate (0.40–0.59); small-to-moderate (0.20–0.39); small (<0.20); and negligible (<0.10).[13,14] For these calculations, non-Hispanic Whites were the reference group and the *g* reported for interval-scaled variables was the average of paired gs between non-Hispanic Black versus non-Hispanic White patients, and Hispanic versus non-Hispanic White patients.

For our second study aim, we employed multivariate latent growth curve modeling to account for fixed and random effects in longitudinal change patterns in NT-proBNP, cardiac remodeling parameters, and KCCQ-23 TS scores over time; these methods have been similarly used in other recent studies.[15–17] Longitudinal estimates of change were adjusted for any baseline covariate that was imbalanced (defined as a Hedges *g* of >0.20) to account for its potential effect on estimates; additionally, using multivariate models allowed us to adjust for simultaneous changes across multiple measures. Missingness was handled using maximum likelihood due to the autocorrelation between repeated measures and the inability to meet the assumption of independently and identically distributed associated with multiple imputation techniques. Differences between median slope values were assessed using a nonparametric test of medians. We used the KCCQ TS score given colinearity with the other summary scores. Association between variables was assessed using Pearson correlations (*r*) on log-transformed values.

Growth parameter SE, estimates, and residuals were bootstrapped using 99% CIs using 1000 subsamples. All *P* values are 2-sided, with values ≤0.05 considered significant. All analyses were conducted using R v3.6.

RESULTS

Baseline Characteristics

Baseline characteristics for patients in each racial and ethnic group are detailed and compared with the overall PROVE-HF cohort in Table 1. Of the 782 patients included in this analysis, 178 (22.7%) were Black, 117 (14.9%) were Hispanic, and 487 (62.3%) were White.

Black patients tended to be younger and heavier than Hispanic or White patients. More Black patients had a hypertension and more White patients had a history of myocardial infarction and an ischemic cause of HF. Black patients had a more recent diagnosis of HF compared with Hispanic and White patients and more Hispanic patients were angiotensin-converting enzyme inhibitor/angiotensin receptor blocker naive. More White patients had cardiac resynchronization therapy/cardiac resynchronization therapy–defibrillator and more Black patients had internal cardioverter defibrillator alone.

NT-proBNP concentrations at baseline were moderately lower in Black patients (567 pg/mL) compared with White patients (863 pg/mL; g=0.32); differences between Black patients and Hispanic patients (735 pg/mL) were small (g=0.17). Differences in baseline values for LVEF, LV end-diastolic volume index, and LV end-systolic volume index varied between racial and ethnic groups. Generally, Hispanic patients had moderately higher values for LVEF (31.4±9.3%) than Black patients (LVEF: 27.8±6.7%, g=0.52) and small-to-moderately higher values than White patients (LVEF: 28.8±5.9%, g=0.33). Differences between groups in baseline values for LV end-diastolic volume index and LV end-systolic volume index were negligible (g<0.10). At baseline, differences in KCCQ-23 Clinical Summary score, TS, and Overall Summary scores were negligible (g<0.10) between racial and ethnic groups.

Following initiation and titration of S/V, Black patients reached the target dose (97/103 mg twice daily) by month 12 at slightly higher rates (73.0%) than White (62.2%) or Hispanic (52.1%) patients (φ=0.12). Following introduction and intensification of S/V, from baseline to follow-up, generally similar cross-sectional changes were noted in NT-proBNP concentrations, LVEF, and KCCQ-23 scores across the 3 groups (Table I in the Data Supplement). Treatment with S/V was well-tolerated in all racial and ethnic groups included in this analysis (Table 2).

Table 1. Baseline Demographics in Black, Hispanic, and White Patients Enrolled in PROVE-HF With Standardized Mean Differences (Hedges *g* for Interval-Scaled Variables and φ for Categorical Variables)

Parameter	All patients, N (%)	Black patients, N (%)	Hispanic patients, N (%)	White patients, N (%)	Standardized Mean Differences	
					Black vs White	Hispanic vs White
Age, y, mean (±SD)	65.2 (±12.3)	59.2 (±12.3)	66.3 (±13.3)	67.1 (±11.4)	0.69	0.08
Male sex, N (%)	559 (71.5)	118 (66.3)	71 (60.7)	370 (76.0)	0.13*	…
NYHA symptom severity, N (%)					0.07*	…
Class II	547 (69.9)	124 (69.7)	94 (80.3)	329 (67.6)		
Class III	221 (28.3)	50 (28.1)	22 (18.8)	149 (30.6)		
Class IV	14 (1.8)	4 (2.2)	1 (.9)	9 (1.8)		
Body-mass index, kg/m^2, mean (±SD)	31.3 (±6.9)	32.6 (±7.8)	30.4 (±6.6)	31.1 (±6.5)	0.23	0.10
Past medical history, N (%)						
Hypertension	689 (88.1)	166 (93.3)	102 (87.2)	421 (86.4)	0.09*	…
Coronary revascularization	370 (47.3)	50 (28.1)	54 (46.2)	266 (54.6)	0.22*	…
Diabetes mellitus	354 (45.3)	80 (44.9)	65 (55.6)	209 (42.9)	0.09*	…
Myocardial infarction	323 (41.3)	46 (25.8)	52 (44.4)	225 (46.2)	0.17*	…
Coronary artery disease	260 (33.2)	34 (19.1)	32 (27.4)	194 (39.8)	0.19*	…
Atrial fibrillation/flutter	264 (33.8)	41 (23.0)	26 (22.2)	197 (40.5)	0.18*	…
Ischemic cause for HF, N (%)	417 (53.3)	70 (39.3)	62 (53.0)	285 (58.5)	0.16*	…
Months since HF diagnosis, mean (±SD)	76.5 (±80.5)	68.3 (±69.4)	66.1 (±61.6)	81.9 (±87.5)	0.16	0.18
Guideline-directed therapy, N (%)						
Beta blocker	753 (96.3)	174 (97.8)	108 (92.3)	471 (96.7)	0.09*	…
ACE inhibitor/ARB	594 (76.0)	139 (78.1)	87 (74.4)	368 (75.6)	0.03*	…
MRA	325 (41.6)	90 (50.6)	27 (23.1)	208 (42.7)	0.17*	…
CRT/CRT-D	115 (14.7)	19 (10.7)	15 (12.8)	81 (16.6)	0.07*	…
ICD-alone	212 (27.1)	53 (29.8)	24 (20.5)	135 (27.7)	0.07*	…
Not taking ACE inhibitor/ARB, N (%)						
ACE inhibitor/ARB naive	47 (6.0)	7 (3.9)	10 (8.5)	30 (6.2)	0.04*	…
Previously taking	141 (18.0)	32 (18.0)	20 (17.1)	89 (18.3)		
Laboratory results, mean (±SD)						
eGFR, mL/(min·1.73m^2)	64.0 (±20.4)	71.5 (±21.7)	63.6 (±22.5)	61.3 (±18.6)	0.55	0.12
eGFR ≤60 mL/(min·1.73m^2), N (%)	347 (44.4)	57 (32.0)	53 (45.3)	237 (48.7)	0.14*	…
NT-proBNP, pg/Ml	772.8 (±574.4)	566.8 (±445.3)	727.8 (±541.0)	871.3 (±626.6)	0.34	0.14
Baseline vital signs, mean (±SD)						
Systolic BP, mm Hg	124.6 (±15.8)	126.2 (±16.4)	124.0 (±12.3)	124.2 (±16.3)	0.12	0.01
Diastolic BP, mm Hg	76.0 (±10.3)	79.1 (±10.0)	76.1 (±9.7)	74.8 (±10.3)	0.42	0.13
Heart rate, beats/min	72.2 (±11.3)	74.5 (±12.5)	72.9 (±9.7)	71.1 (±11.0)	0.31	0.17
Echocardiogram measurements, mean (±SD)						
LVEF, %	28.9 (±6.9)	27.8 (±6.7)	31.0 (±9.3)	28.8 (±6.1)	0.16	0.37
LVEDVi, mL/m^2	90.1 (±20.7)	89.5 (±19.8)	92.0 (±23.)	89.9 (±20.5)	0.02	0.10
LVESVi, mL/m^2	65.0 (±19.3)	65.5 (±18.8)	64.7 (±21.6)	64.8 (±18.9)	0.03	0.01
Baseline KCCQ summary scores, mean (±SD)						
Overall Summary	62.7 (±22.7)	61.4 (±23.4)	62.1 (±23.1)	63.3 (±22.4)	0.08	0.05
Clinical Summary	67.2 (±22.5)	66.3 (±24.1)	65.7 (±23.6)	67.8 (±21.6)	0.07	0.10
Total Symptom	69.5 (±23.2)	69.3 (±25.2)	69.6 (±25.1)	69.5 (±22.1)	0.01	0.01

ACE/ARB indicates angiotensin converting enzyme/angiotensin receptor blocker; BP, blood pressure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy–defibrillator; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, internal cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and PROVE-HF, Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure.

*Standardized mean difference for categorical variables is the Cramer phi (φ) coefficient.

Table 2. Adverse Events in Black, Hispanic, and White Patients Treated With Sacubitril/Valsartan

	All patients, N (%)	Black patients, N (%)	Hispanic patients, N (%)	White patients, N (%)	Standardized mean difference*
Hypotension (systolic blood pressure <90 mm mercury)	139 (17.5)	22 (12.4)	16 (13.7)	100 (20.5)	0.10
Dizziness	135 (17)	29 (16.3)	6 (5.1)	98 (20.1)	0.14
Hyperkalemia (potassium >5.3 milliequivalents/liter)	85 (10.7)	12 (6.7)	9 (7.7)	61 (12.5)	0.09
Worsening kidney function	39 (4.9)	7 (3.9)	4 (3.4)	25 (5.5)	0.03
Angioedema	3 (0.4)	2 (1.1)	0	1 (0.2)	0.06
No treatment or antihistamines only without hospitalization	0	0	0	0	
Use of catecholamines or glucocorticoids without hospitalization	0	0	0	0	
Hospitalization without airway compromise	0	0	0	0	
Airway compromise	0	0	0	0	

*Standardized mean difference for categorical variables is the Cramer phi (φ) coefficient.

Longitudinal Changes in NT-proBNP, LVEF, and KCCQ

Average change in NT-proBNP concentrations across study visits in the longitudinal cohort of the 3 groups is depicted in Figure 1. The 90-day linear rates of NT-proBNP change after S/V initiation were of similar magnitude in Black (slope, −0.4; Δ=7.7%) and in White (slope, −0.4; Δ=7.6%) patients when compared with Hispanic patients (slope, −0.3; Δ=6.3%; Table II in the Data Supplement). When adjusted for baseline covariates imbalanced at baseline between the 3 groups, these differences remained unchanged.

Change in reverse remodeling parameters following initiation and titration of S/V in the longitudinal cohort is depicted in Figure 2, which shows clinically similar magnitude of reverse remodeling in Black, Hispanic, and White patients, though with subtle difference in the timing of LVEF change. On average, patients improved LVEF by a median of 4.6 percentage points (25th–75th percentile: −2.58 to 6.74) every 180 days. Results showed that the rate of patients who achieved LVEF improvement above the median was higher in White patients (55.9%; χ^2=17.687; P<0.001) than in Black (40.4%) or Hispanic (40.2%) patients. Thus, average 90-day LVEF change was 2.5% (95% CI, 2.4–2.7) in White patients compared with 2.2% (95% CI, 1.9–2.5) in Black and 2.2% (95% CI, 1.7–2.6) Hispanic patients (Table II in the Data Supplement). Because of this, White patients achieved a higher magnitude of reverse remodeling within the first 6 months of the study followed by smaller magnitudes of change for each measure in the second half of the study period (Table III in the Data Supplement); in Black and Hispanic patients, change was more evenly distributed across the 12 months of follow-up (Table III in the Data Supplement). When adjusted for baseline covariates imbalanced at baseline between the 3 groups, patterns of improvement in LVEF remained unchanged.

Health Status

Ninety-day linear changes in KCCQ-23 TS scores were larger in Hispanic patients (Δ=6.4 points [95% CI, 2.5–10.4]) when compared with White (Δ=6.2 points [95% CI, 4.9–7.5]) and Black (Δ=4.3 points [95% CI, 1.6–7.0]) patients (Table II in the Data Supplement). Within-group paired mean differences showed that Hispanic patients achieved a higher magnitude of change by between baseline and month 3 when compared with Black and White patients (Table III in the Data Supplement).

Correlation Between NT-proBNP and Cardiac Reverse Remodeling

Across racial and ethnic groups, reduction in NT-proBNP is consistently associated with increases in LVEF. Such associations were comparable among Black patients (r=−0.26; P<0.001) and White patients (r=−0.14; P=0.003).

The overall shape of change in NT-proBNP was strongly associated with the magnitude of reverse remodeling; specifically, steeper early reduction was ultimately associated with larger improvements in LVEF across racial and ethnic groups.

DISCUSSION

In this subgroup analysis from PROVE-HF of patients with HFrEF initiated on S/V, 22.7% were Black, 14.9% were Hispanic, and 62.3% were White. At baseline, we found race-based differences in NT-proBNP and LV measurements. Following study procedures, more Black patients reached target S/V dose compared with Hispanic or White patients. Although Black and Hispanic patients had lower baseline NT-proBNP concentrations than White patients, all 3 patient groups had generally similar reduction in NT-proBNP concentrations by month 12. Hispanic patients had the largest magnitude

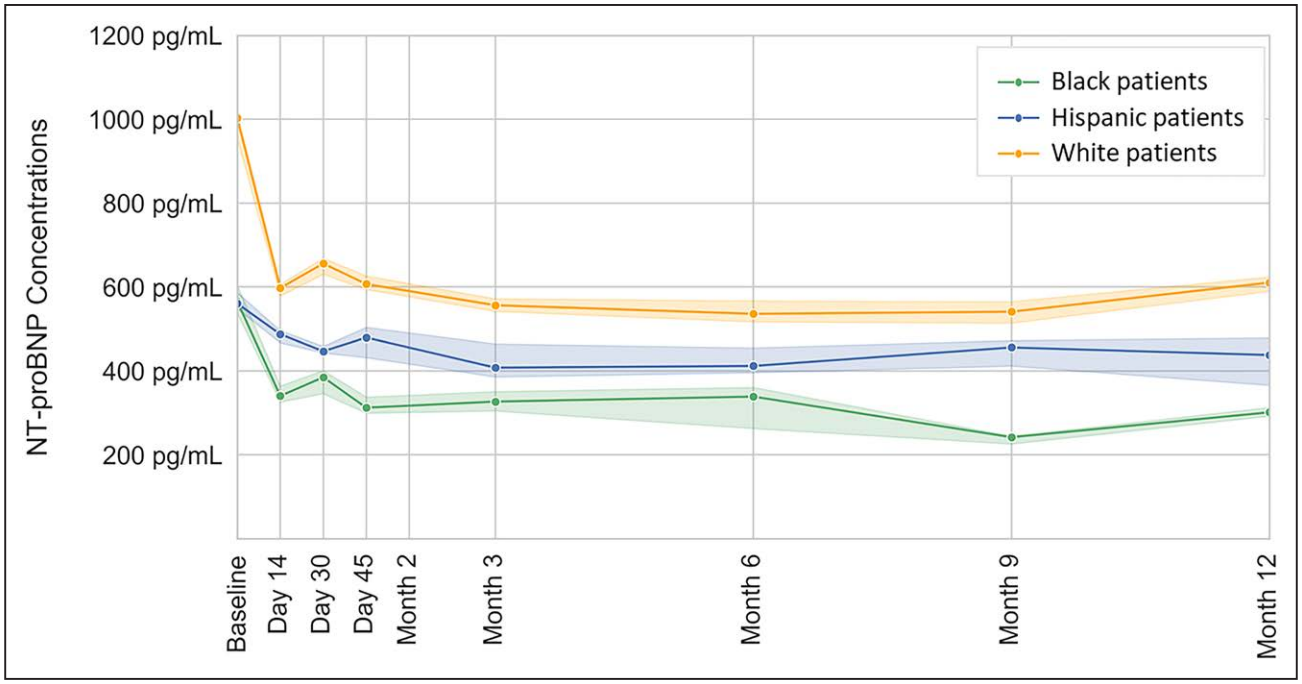

Figure 1. Racial/ethnic group longitudinal trajectories in average NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations by study visit.
All 3 groups showed reduction in NT-proBNP early after initiation of sacubitril/valsartan. 95% CI are indicated.

improvement in KCCQ-23 TS scores by study conclusion. Importantly, by month 12, Black, Hispanic, and White patients demonstrated comparable and substantial improvement in cardiac reverse remodeling parameters; however, we found subtle race-based differences in patterns of change in NT-proBNP, health status, and LV reverse remodeling. Lastly, S/V was well-tolerated in Black, Hispanic, and White patients.

In PROVE-HF Black and Hispanic patients had lower baseline NT-proBNP concentrations than White patients. Despite this, baseline correlation between NT-proBNP concentrations and LV measurements was strongest in

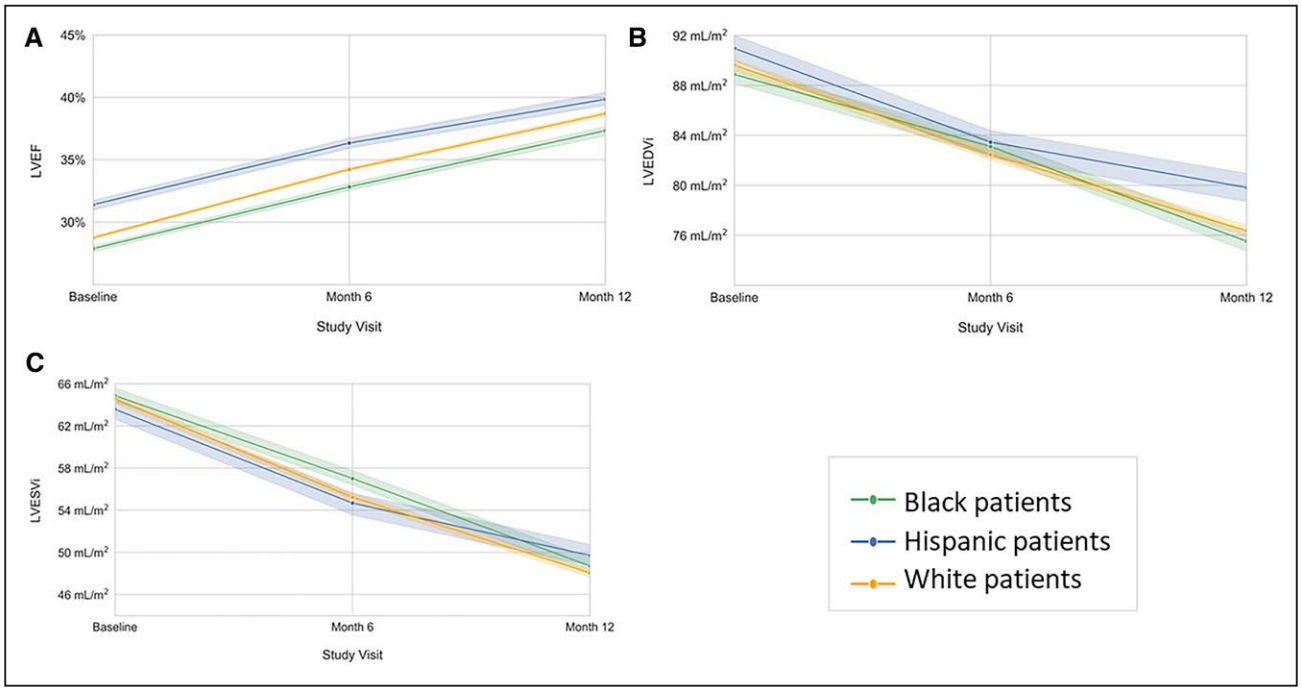

Figure 2. Change in cardiac remodeling parameters from baseline through 12 mo in Black, Hispanic, and White patients.
A, Change in left ventricular ejection fraction (LVEF). **B**, Change in left ventricular end-diastolic volume index (LVEDVi). **C**, Change in left ventricular end-systolic volume index (LVESVi). 95% CI are indicated.

Black patients. Following initiation of S/V, both Black and White patients had larger earlier change in NT-proBNP compared with Hispanic patients, who tended to have more constant reduction over the 12 months of follow-up. Despite these differences, correlation between NT-proBNP and LV reverse remodeling parameters was generally consistent across ethnic groups. Our results thus suggest that modest race-based differences exist with respect to the baseline concentrations of NT-proBNP and its changes after S/V therapy; however, the biomarker provides consistent clinical information across these important racial and ethnic groups, an important message for clinicians managing patients with NT-proBNP monitoring.

Our results provide important race-based comparisons of health status in HFrEF. In PROVE-HF, Black and Hispanic patients had worse KCCQ-23 scores compared with White patients but Hispanic patients had the largest magnitude of improvement in KCCQ-23 scores across all domains; these larger changes were associated with large changes in NT-proBNP. What remains unclear is whether the magnitude of such changes in Hispanic patients could be related to cultural or language barriers. In Hispanic patients with diabetes, for example, cultural expectations play an important role in framing their interactions and visit expectations including deference to physician expertise and authority.[18] Cultural differences like these may contribute to the larger magnitude improvement in KCCQ-23 scores based on the assumption that the clinician is expecting improvement in symptoms. Nonetheless, larger and more rapid improvement in health-related quality of life scores in Hispanic patients has been previously described in a randomized trial.[19] This interesting finding warrants further work in the health status arena with inclusion of significant numbers of Hispanic subjects.

Among patients with HFrEF, deleterious cardiac remodeling differs by race with Black and Hispanic patients typically showing worse cardiac structural changes over time when compared with White patients in other studies.[20,21] The natriuretic peptide system function is known to vary with genetics and race and the lower concentrations in Black patients compared with White patients in this study is consistent with previous observations.[3]

Although differences between races clearly exist at the genetic or phenotypic level, what remains unclear is whether race-based differences exist with respect to clinical response to S/V therapy. Given race/ethnicity differences in prevalence of HF risk factors, HF severity, and complications[1] an understanding of race/ethnicity differences in response to S/V is a relevant goal. In the present study, we found Black patients had the lowest average LVEF and Hispanic patients had the highest average LVEF throughout the trial. In longitudinal models, by months 6 and 12, Black, Hispanic, and White patients demonstrated comparable and substantial improvement in cardiac reverse remodeling parameters. The main difference detected between groups was variation in timing of reverse remodeling (with White patients showing earlier reversal of remodeling), but by 12 months, comparable improvement was seen in all 3 groups. Furthermore, in all patients, larger reductions in NT-proBNP were associated with generally greater LVEF gains, regardless of race. These findings were robust even when adjusting for baseline differences. Taken together, although we detected subtle race-based differences in timing of LV reverse remodeling parameters and correlation with NT-proBNP, in each race category therapy with S/V was associated with improved LV reverse remodeling parameters, which were reflected by reduced NT-proBNP.

Following report of higher rates of angioedema related to S/V among Black patients in the PARADIGM-HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial)[22] initial concern developed regarding angiotensin receptor blocker/neprilysin inhibitor use in Black patients. In PROVE-HF, admittedly a smaller and shorter study, only 3 patients had angioedema, of which only one patient was Black. Our results thus provide reassurance regarding this issue.

Several limitations exist for our analysis, including the single-group, open-label design of PROVE-HF. The reasons for this relate to the fact S/V was a class I guideline-recommended treatment and widely clinically available at the time of study execution, making it untenable to randomize patients. Besides this fact is the point that this was a comparison of how racial and ethnic groups responded to the initiation of S/V for the management of HFrEF, rather than a comparison of different therapies; the addition of a control group would not have altered the observation that initiation of S/V was significantly associated with reverse cardiac remodeling across these groups. Even if randomization would have mattered, >80% of the study participants were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at baseline, and yet our results are robust. In our study, LVEF improvement was larger than previously published registries examining effect of GDMT on LVEF improvement.[23] Although our analysis comprised of a higher percentage of Black patients compared with other recent HFrEF studies, it is nonetheless relatively small. The differences we found are modest but noteworthy. Additionally, the comparison of Hispanic patients to White patients may be confounded by race since Hispanic ethnicity includes both Black and White patients while White race includes only White patients. Despite these limitations, our results are novel, representing a first race and ethnicity-based analysis of effects of S/V relative to NT-proBNP, health status, and cardiac reverse remodeling.

In conclusion, in this post hoc analysis, although we found subtle race-based differences in association

between NT-proBNP concentrations, health status, and cardiac reverse remodeling, Black, Hispanic, and White patients exhibited similar overall changes in each of these measures after S/V treatment. The data from this study provide a unique look at race/ethnicity-based differences in numerous relevant domains in HF care, all indicating efficacy and safety of S/V treatment for management of HFrEF regardless of race or ethnicity.

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Supplemental Materials

Tables I–III

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