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)

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Underuse of hydralazine/nitrate (HYD/NIT) in black patients with heart failure and reduced ejection fraction (HFrEF) has been previously described, but whether this important treatment gap persists in contemporary practice is unknown. Sacubitril/valsartan has become a part of guideline-directed medical therapy for HFrEF but data on utilization of this therapy in black patients is lacking. This study addressed these issues by assessing the frequency of HYD/NIT and sacubitril/valsartan use in black patients with HFrEF in the Change the Management of Patients with Heart Failure Registry, a multicenter cohort study. The association of race with utilization rates of these agents was also evaluated. Clinical and medication data at baseline and during 12 months of follow-up from black and nonblack registry patients without documented contraindications or intolerance to the medications of interest were analyzed. Data were available from December 2015 to October 2017, in 4,848 HFrEF patients, of whom 853 were black (18%) and 3995 were nonblack. Black patients were younger, more likely to be female, and had lower ejection fractions compared with nonblacks. Only 11% of black patients were receiving HYD/NIT therapy at baseline and 13% at 1 year. The percentage of black patients treated at baseline with sacubitril/valsartan was also low at 18% and remained unchanged at 1 year. After adjustment for covariates, race was independently associated with HYD/NIT use (odds ratio 8.32; 95% confidence interval 6.12 to 11.3; $p < 0.0001$), but not for sacubitril/valsartan. In conclusion, study findings demonstrate a marked persistent treatment gap for HYD/NIT and similar poor utilization of sacubitril/valsartan in black patients with HFrEF despite current guideline recommendations. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:1900−1906)**

Use of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) including angiotensin-converting enzyme inhibitors (ACEI)/angiotensin-receptor blockers (ARB), β-blockers (BB), and mineralocorticoid receptor antagonists (MRA) is recommended for all patients, regardless of race. In addition, black patients with HFrEF also benefit from the use of the combination of hydralazine/isosorbide dinitrate (HYD/NIT).[1] Poor utilization of HYD/NIT in black patients with HFrEF has been previously described.[2,3] Furthermore, current use of new effective GDMT treatments in these patients, such as the angiotensin receptor neprilysin inhibitor, sacubitril/valsartan, is unknown.[4,5] To estimate contemporary use of HYD/NIT, as well as the adoption of sacubitril/valsartan in black patients with HFrEF, we analyzed data on utilization of GDMT in a large, contemporary, multicenter US cohort study of patients with HFrEF from the Change the Management of Patients with Heart Failure (CHAMP-HF) Registry. Utilization of these agents was also

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See page 1905 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2019.09.020

compared between black and nonblack patients to evaluate the influence of race on any treatment gaps observed.

Methods

Data for this analysis were extracted from the CHAMP-HF registry, an ongoing prospective, observational, nonrandomized study of adult outpatients with HFrEF at participating US sites. The study design for CHAMP-HF has been previously published.[6] All study participants provided written informed consent and there was site-specific institutional review board approval. Duke Clinical Research Institute (Durham, North Carolina) served as the data analytic center. Novartis Pharmaceuticals Corporation (East Hanover, New Jersey) sponsored CHAMP-HF and were involved in the study design; in the collection and interpretation of data; in writing the report; and in the decision to submit the article for publication.

Patients eligible for enrollment into CHAMP-HF met the following criteria: (1) Age ≥18 years old who provided informed consent, (2) primary diagnosis of HF, (3) reduced ejection fraction (left ventricular ejection fraction ≤40%) in the most recent report within 12 months before enrollment, (4) receiving an oral pharmacotherapy for management of HF before or at study enrollment, and (5) willing to complete protocol requirements for study visits, procedures, and questionnaires. Patients were excluded if they (1) were under current or planned participation in any interventional clinical research study, (2) were currently receiving comfort care measures only or enrolled in a hospice program, (3) had a life expectancy <1 year, or (4) had a planned or history of heart transplant, left ventricular assist device, or dialysis. In addition, this analysis only included data from patients without documented contraindications or intolerance to the medications of interest (i.e., HYD/NIT and sacubitril/valsartan). Data collected included patient-level demographics, clinical characteristics, medical history, laboratory results, HF medications used, procedure data, and patient-reported HF-related data. Race and ethnicity were based on patient self-report utilizing US census categorizations. With the exception of assessing frequency of use of HYD/NIT and/or sacubitril/valsartan at each data collection timepoint (baseline, 1 month, 3 months, 6 months, and 12 months), all data represented baseline information.

For the purpose of this study, NIT refers to all available oral forms of long-acting nitrates, including isosorbide dinitrate and isosorbide mononitrate. In addition, the appearance of an overlap in patients taking both an ACEI/ARB and sacubitril/valsartan as reported in this study can be explained by the data reporting process. Patients could be on the medication at any point during a specific data collection window, but were not necessarily on both medications at the same time (which is contraindicated). Although another important recent addition to GDMT, utilization of ivabradine was insufficient (1% in both black and nonblack study populations) to perform meaningful analysis.

The baseline characteristics of the study population were described by the use of HYD/NIT and sacubitril/valsartan, then stratified by race group. Proportions were used for categorical variables and means with standard deviations or medians with quartiles for continuous variables. Difference between groups was tested using chi-square tests for categorical variables and *t* tests (or Kruskal-Wallis tests if present median) for continuous variables. For continuous variables, means were calculated in patients without missing data.

Daily doses for HYD/NIT and sacubitril/valsartan were described by race group. The proportion of patients achieving 100% target dose were presented along with 95% confidence intervals (CI). The longitudinal status of HYD/NIT and sacubitril/valsartan use was described by race at baseline, 1 month, 3 months, 6 months, and 12 months. In black patients taking HYD/NIT, the distribution of type of NIT was also described to illustrate the various types of NIT used in this contemporary cohort.

A single data set with multiple imputations of missing values was used to identify race and other factors associated with use of HYD/NIT and sacubitril/valsartan. Hierarchical logistic regressions with a random site effect were used to account for the clustering of patients within sites. All continuous variables were standardized to a mean of 0 and a standard deviation of 1. For continuous variables, nonlinearity was tested using restricted cubic splines. If the nonlinearity was significant for a variable, linear splines were used in the model. Estimates and 95% CI are reported and $\alpha = 0.05$ was used to establish statistical significance of tests. All tests were 2-sided. All analyses were performed using SAS software (version 9.4 SAS Institute, Cary, North Carolina).

Results

Overall, 4,982 patients at 152 US sites were included in this analysis. Visit dates were conducted between December 14, 2015 and October 20, 2017. After applying exclusion criteria, 4,848 HFrEF patients were included in the final analysis; 853 were black (18%) and 3,995 (82%) were nonblack. The majority of sites included in the registry were teaching universities (78%) located in suburban areas (46%) in the South (49%). Fewer than half of the sites had a dedicated HF clinic (40%). Most sites had 1 to 5 physicians, with the majority practicing in cardiology, specifically interventional cardiology, followed by HF specialists.

Clinical characteristics and demographic features of the study cohort based on use of target medication are presented in Tables 1 and 2. Notably, black patients were younger than nonblack by about 10 years. Within each racial group, the median age of those treated with HYD/NIT versus not was similar. Conversely, the median age was slightly greater in patients not receiving sacubitril/valsartan compared with those receiving sacubitril/valsartan, regardless of race. The majority of the study cohort was male. Black patients treated with HYD/NIT tended to have higher rates of chronic kidney disease, diabetes, hypertension, and atrial fibrillation at baseline compared with those not treated. There was no statistical difference in New York Heart Association (NYHA) classification in those with or without HYD/NIT, regardless of race. As further illustrated in Table 2, patients on sacubitril/valsartan were more likely to be younger for both black and nonblack, and female if black than those not on sacubitril/valsartan.

Table 1
Demographic and clinical characteristics of the study population by use of hydralazine/nitrate at any time during the study

Hydralazine/Nitrate	Black (N = 853)			Nonblack (N = 3,995)		
	No (N = 729)	Yes (N = 124)	p Value	No (N = 3919)	Yes (N = 76)	p Value
Age (years), Median (Q1-Q3)	60.0 (52.0-69.0)	59.5 (51.0-67.5)	0.3186	69.0 (60.0-76.0)	69.5 (62.5-78.0)	0.3332
Women	289 (40%)	45 (36%)	0.4795	1,057 (27%)	15 (20%)	0.1445
Chronic obstructive lung disease	231 (32%)	39 (32%)	0.9584	1,198 (31%)	22 (29%)	0.7173
Chronic kidney disease	132 (18%)	42 (34%)	<0.0001	738 (19%)	43 (57%)	<0.0001
Depression	143 (20%)	19 (15%)	0.2598	1,026 (26%)	15 (20%)	0.1881
Diabetes mellitus	318 (44%)	67 (54%)	0.0313	1,596 (41%)	45 (59%)	0.0015
Atrial fibrillation	155 (21%)	35 (28%)	0.0849	1,505 (38%)	37 (49%)	0.0801
Coronary artery disease	315 (43%)	62 (50%)	0.1593	2,626 (67%)	52 (68%)	0.8938
Hyperlipidemia	485 (67%)	87 (70%)	0.4263	3,056 (78%)	60 (79%)	0.9723
Hypertension	651 (89%)	117 (94%)	0.0824	3,163 (81%)	65 (86%)	0.3744
Ventricular tachycardia/fibrillation	114 (16%)	20 (16%)	0.8895	796 (20%)	16 (21%)	0.9095
Left ventricular ejection fraction, Median (Q1-Q3)	28.0 (20.0-35.0)	25.0 (20.0-33.0)	0.0882	30.0 (25.0-36.0)	30.0 (23.0-35.0)	0.0857
New York Heart Association Classification			0.1237			0.0567
I	71 (10%)	15 (12%)		419 (11%)	5 (7%)	
II	421 (58%)	57 (46%)		2,205 (56%)	35 (46%)	
III	203 (28%)	44 (36%)		1,069 (27%)	33 (43%)	
IV	17 (2%)	5 (4%)		72 (2%)	1 (1%)	
Systolic blood pressure (mm Hg), mean (SD)	123.9 (19.88)	125.1 (21.17)	0.5921	120.4 (17.33)	126.7 (17.72)	0.0054
Diastolic blood pressure (mm Hg), mean (SD)	75.8 (12.06)	75.4 (13.8)	0.7744	71.8 (10.69)	72.6 (10.76)	0.6005
Blood urea nitrogen (mg/dl), Median (Q1-Q3)	18.0 (14.0-24.0)	22.5 (17.0-32.0)	<0.0001	20.0 (16.0-27.0)	33.0 (23.5-43.5)	<0.0001
Serum creatinine (mg/dl), Median (Q1-Q3)	1.1 (0.9-1.5)	1.3 (1.0-1.7)	0.0001	1.1 (0.9-1.4)	1.6 (1.2-2.0)	<0.0001
Serum potassium (mmol/L), Median (Q1-Q3)	4.2 (3.9-4.5)	4.2 (3.9-4.6)	0.8113	4.4 (4.1-4.7)	4.3 (3.9-4.5)	0.0281
Baseline medications						
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	467 (64%)	70 (57%)	0.1048	2,532 (65%)	33 (43%)	<0.0001
Beta blocker	654 (90%)	117 (94%)	0.1049	3,413 (87%)	67 (88%)	0.9637
Mineralocorticoid receptor antagonist	302 (41%)	73 (59%)	0.0003	1,314 (34%)	27 (36%)	0.7632
Sacubitril/valsartan	132 (18%)	29 (23%)	0.1648	596 (15%)	4 (5%)	0.0141
Loop Diuretic	534 (73%)	107 (86%)	0.0019	2,350 (60%)	62 (82%)	0.0002
Hydralazine/nitrate	-					
Digoxin	102 (14%)	14 (11%)	0.4172	560 (14%)	16 (21%)	0.1054
Ivabradine	7 (1%)	1 (1%)	1.0000	47 (1%)	1 (1%)	0.6082

Baseline medication use amongst black and nonblack patients, stratified by use of target medication, is also presented in Tables 1 and 2. Use of ACEI/ARB or sacubitril/valsartan was 82% in black compared to 79% in nonblack patients. More black than nonblack patients were receiving BB (90% vs 87%), MRA (41 vs 34%), and loop diuretics (73 vs 60%).

At baseline and at 1 year, only 11% and 13% of black patients, respectively, were receiving HYD/NIT therapy (Table 3). Most black patients treated with a NIT received isosorbide dinitrate (52%) rather than isosorbide mononitrate (21%) or the fixed dose combination of hydralazine 20 mg/ISDN 37.5 mg (27%). The use of sacubitril/valsartan was comparable between black and nonblack (26% vs 23%) patients receiving this medication at any point during the analysis period. The number of black patients receiving sacubitril/valsartan did not change from baseline (18%) to 1 year (18%; Table 3).

More black patients on MRA, but not other GDMT, were on HYD/NIT at baseline (59%, $p = 0.0003$) than black patients not on MRA. More black and nonblack patients were receiving sacubitril/valsartan at baseline if they were on a BB (98%, $p < 0.0001$ and 94%, $p < 0.0001$, respectively) and MRA (52%, $p = 0.0028$ and 46%, $p < 0.0001$, respectively) when compared with other GDMT. In black patients, only 2% of patients with HYD/NIT received target doses of the medications. The majority of patients on HYD/NIT or sacubitril/valsartan, irrespective of race, received <50% of the target dose of the medication (Table 4). Only 8% of black patients and 4% of nonblack patients treated with sacubitril/valsartan received therapy at the target dose.

Patients were more likely to be prescribed HYD/NIT if they were black (odds ratio [OR] 8.32; 95% CI 6.12 to 11.3; $p < 0.0001$) or had chronic kidney disease (OR 1.83; 95% CI 1.35 to 2.48; $p = 0.0001$) or diabetes (OR 1.45; 95% CI 1.11 to 1.88; $p = 0.0057$), as shown in Table 5. Furthermore, the greater the severity of renal impairment at baseline, the more likely both black and nonblack patients were treated with HYD/NIT. No differences were found in gender between those prescribed and not prescribed HYD/

Table 2
Demographic and clinical characteristics of the study population by use of sacubitril/valsartan at any time during the study

Sacubitril/Valsartan	Black (N = 853)			Nonblack (N = 3,995)		
	No (N = 628)	Yes (N = 225)	p Value	No (N = 3,066)	Yes (N = 929)	p Value
Age (years), Median (Q1-Q3)	61.0 (52.5-69.5)	59.0 (50.0-65.0)	0.0021	69.0 (61.0-77.0)	67.0 (58.0-74.0)	<0.0001
Women	229 (36%)	105 (47%)		836 (27%)	236 (25%)	
Chronic obstructive lung disease	205 (33%)	65 (29%)	0.2989	967 (32%)	253 (27%)	0.0064
Chronic kidney disease	135 (22%)	39 (17%)	0.1836	617 (20%)	164 (18%)	0.0668
Depression	120 (19%)	42 (19%)	0.8848	811 (27%)	230 (25%)	0.2161
Diabetes mellitus	288 (46%)	97 (43%)	0.4771	1,238 (40%)	403 (43%)	0.1818
Atrial fibrillation	137 (22%)	53 (24%)	0.5904	1,157 (38%)	385 (41%)	0.0796
Coronary artery disease	279 (44%)	98 (44%)	0.8214	2,064 (67%)	614 (66%)	0.2276
Hyperlipidemia	409 (65%)	163 (72%)	0.0451	2,400 (78%)	716 (77%)	0.1440
Hypertension	559 (89%)	209 (93%)	0.0958	2,498 (82%)	730 (79%)	0.0063
Ventricular tachycardia/fibrillation	97 (15%)	37 (16%)	0.7239	565 (18%)	247 (27%)	<0.0001
Left ventricular ejection fraction, Median (Q1-Q3)	28.0 (20.0-35.0)	25.0 (20.0-33.0)	0.0017	32.0 (25.0-37.0)	28.0 (22.0-33.0)	<0.0001
New York Heart Association Classification			0.0158			0.0015
I	74 (12%)	12 (5%)		345 (11%)	79 (9%)	
II	342 (55%)	136 (60%)		1,713 (56%)	527 (57%)	
III	179 (29%)	68 (30%)		810 (26%)	292 (31%)	
IV	20 (3%)	2 (1%)		58 (2%)	15 (2%)	
Systolic blood pressure (mm Hg), mean (SD)	124.0 (19.82)	124.0 (20.93)	0.9974	121.3 (17.24)	115.9 (17.39)	<0.0001
Diastolic blood pressure (mm Hg), mean (SD)	75.6 (12.51)	76.2 (11.24)	0.6133	72.1 (10.67)	70.1 (10.61)	<0.0001
Blood urea nitrogen (mg/dl), Median (Q1-Q3)	18.0 (14.0-25.7)	18.0 (14.0-24.0)	0.5466	20.0 (16.0-28.0)	21.0 (16.0-27.0)	0.9794
Serum creatinine (mg/dl), Median (Q1-Q3)	1.2 (0.9-1.5)	1.2 (0.9-1.4)	0.3768	1.1 (0.9-1.4)	1.1 (0.9-1.4)	0.1367
Serum potassium (mmol/L), Median (Q1-Q3)	4.2 (3.9-4.5)	4.2 (3.9-4.5)	0.6086	4.4 (4.0-4.7)	4.4 (4.1-4.7)	0.5993
Baseline medications						
Angiotensin-converting enzyme inhibitor/Angiotensin II receptor blocker	486 (77%)	51 (23%)	<0.0001	2,305 (75%)	260 (28%)	<0.0001
Beta blocker	551 (88%)	220 (98%)	<0.0001	2,603 (85%)	877 (94%)	<0.0001
Mineralocorticoid receptor antagonist	257 (41%)	118 (52%)	0.0028	911 (30%)	430 (46%)	<0.0001
Sacubitril/valsartan	N/A					
Loop Diuretic	464 (74%)	177 (79%)	0.1545	1,750 (57%)	662 (71%)	<0.0001
Hydralazine/nitrate	64 (10%)	33 (15%)	0.0696	54 (2%)	7 (1%)	0.0257
Digoxin	78 (12%)	38 (17%)	0.0934	403 (13%)	173 (19%)	<0.0001
Ivabradine	5 (1%)	3 (1%)	0.4732	31 (1%)	17 (2%)	0.0499

Table 3
Longitudinal use of hydralazine/nitrate and sacubitril/valsartan by race

Months	Black			Nonblack		
	On study	Hydralazine/Nitrate	Sacubitril/Valsartan	On study	Hydralazine/Nitrate	Sacubitril/Valsartan
0	853	11%	18%	3,955	1%	15%
1	822	11%	18%	3,861	1%	15%
3	791	12%	19%	3,731	1%	15%
6	655	12%	18%	3,228	1%	14%
12	411	13%	18%	2,186	2%	13%

NIT. Nonblack patients were no more likely to be treated with sacubitril/valsartan than black patients (OR 0.88; 95% CI 0.68 to 1.15; p = 0.3579). Patients on ACEI/ARB or sacubitril/valsartan were less likely to be on HYD/NIT at enrollment than those not treated with these medications, regardless of race. Those receiving a loop diuretic were more likely to receive HYD/NIT at enrollment, which contrasted with patients treated with sacubitril/valsartan. Patients receiving a BB were 3 times more likely to be on sacubitril/valsartan at baseline, but BB use did not statistically influence the use of HYD/NIT at baseline. Both black and nonblack patients receiving an MRA at baseline were more likely to receive sacubitril/valsartan. Family practice providers were significantly less likely to prescribe both

Table 4
Percent of participants reaching target dose of hydralazine/nitrate and sacubitril/valsartan by race

	Black				Nonblack			
	Target dose* achieved (patients on therapy)			Eligible patients on target dose	Target dose* achieved (patients on therapy)			Eligible patients on target dose
	Less than 50%	50% to <100%	100% or more	100% or More	Less than 50%	50% to <100%	100% or more	100% or More
Hydralazine/ Nitrate	56%	33%	10%	2%	65%	28%	7%	0.1%
Sacubitril/ Valsartan	33%	36%	29%	8%	49%	29%	19%	4%

* Target total daily doses were as follows: hydralazine 300 mg, nitrate (isosorbide dinitrate) 120 mg, and sacubitril/valsartan 400 mg.

Table 5
Adjusted* association between race, patient characteristics, and use of target analysis medications

	Hydralazine/Nitrate		Sacubitril/Valsartan	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Black	8.32 (6.12, 11.3)	<0.0001	0.88 (0.68, 1.15)	0.3579
Women	1.01 (0.76, 1.34)	0.9520	1.06 (0.87, 1.30)	0.5526
Chronic kidney disease	1.83 (1.35, 2.48)	0.0001	0.70 (0.54, 0.90)	0.0057
Diabetes mellitus	1.45 (1.11, 1.88)	0.0057	1.22 (1.02, 1.47)	0.0310
Physician specialty (ref: Other cardiologist)				
Family practice	0.21 (0.05, 0.88)	0.0332	0.26 (0.11, 0.64)	0.0035
Internal medicine	0.50 (0.19, 1.31)	0.1596	0.51 (0.25, 1.07)	0.0737
HF specialist	1.58 (0.88, 2.85)	0.1241	1.33 (0.82, 2.15)	0.2504
Medication at enrollment				
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	0.37 (0.27, 0.51)	<0.0001	0.08 (0.07, 0.10)	<.0001
Beta blocker	1.54 (0.96, 2.47)	0.0746	3.30 (2.34, 4.64)	<.0001
Mineralocorticoid receptor antagonist	1.61 (1.23, 2.11)	0.0005	1.48 (1.23, 1.78)	<.0001
Sacubitril/valsartan	0.36 (0.24, 0.55)	<0.0001	N/A	
Loop diuretic	1.61 (1.14, 2.28)	0.0073	0.58 (0.36, 0.94)	0.0274
Hydralazine/nitrate	N/A		1.74 (1.41, 2.14)	<0.0001
Digoxin	1.00 (0.70, 1.43)	0.9831	1.22 (0.96, 1.55)	0.1015
Left ventricular ejection fraction	0.97 (0.85, 1.11)	0.6592	0.77 (0.70, 0.84)	<0.0001
New York Heart Association Classification (ref: II)				
I	1.21 (0.79, 1.85)	0.3927	0.63 (0.46, 0.85)	0.0030
III	1.25 (0.94, 1.67)	0.1309	0.88 (0.72, 1.09)	0.2449
IV	1.55 (0.72, 3.36)	0.2656	1.01 (0.55, 1.86)	0.9767

* Adjusted based on demographics (race [black vs nonblack], age, sex, primary insurance, education, household income, employment), risk factors (COPD, renal insufficiency, depression, diabetes, and current smoker), cardiac history (history of atrial fibrillation, history of coronary artery disease, hyperlipidemia, ventricular tachycardia or fibrillation), devices and procedures (cardiac resynchronization therapy), HF history (HF hospitalization in the 12 months before enrollment), site variables (investigator specialty, region), baseline medications, vital signs, and health questionnaires (KCCQ-12 overall score, EQ-5D-5L index value, PHQ-2 depression score); Odds ratios and 95% confidence intervals correspond to the increased odds of receiving medication, per one unit increase in the covariates.

HYD/NIT and sacubitril/valsartan than other clinician group categories, regardless of racial group (OR 0.21; 95% CI 0.05 to 0.88; p = 0.0332 and OR 0.26; 95% CI 0.11 to 0.64; p = 0.0035, respectively).

Discussion

We found HYD/NIT continues to be used at a very low rate in black patients with HFrEF. However, use of sacubitril/valsartan was comparable in both black and nonblack patients with HFrEF. Our study is the first contemporary review of HYD/NIT and sacubitril/valsartan in black compared with nonblack patients. In both black and nonblack patients, there was significant undertreatment and suboptimal dosing based on well-accepted criteria for GDMT. Target dosing of GDMT for both HYD/NIT and sacubitril/valsartan was not achieved in the majority of treated patients, even over 1 year of observation, despite the fact that uptitration of these medications requires few steps. Similar to previous results with other combination therapies, very few black patients received both sacubitril/valsartan and HYD/NIT and <1% of these patients were on target doses of both medications.

Recent analyses have examined the use of HYD/NIT and sacubitril/valsartan in the overall HFrEF population using data from CHAMP-HF. Greene et al reviewed factors associated with the use and dosing of GDMT in contemporary practice.[7] Upwards of 67% of patients were found to not be

prescribed at least 1 medication considered to be GDMT. In addition, very few of these patients were receiving target doses.[8] In a similar subanalysis by Peri-Okonny et al, few patients were receiving target doses of ACEI, ARB, angiotensin receptor neprilysin inhibito, or BB.[9] Our findings support and extend this information and suggest use of sacubitril/valsartan is slightly greater in black than in nonblack patients, but still suboptimal, with very few patients receiving target doses. Conversely, use of sacubitril/valsartan in about one-quarter of the studied population is somewhat encouraging given relatively recent food and drug administration approval.

A critical feature of HFrEF in black patients is often overlooked. HF often develops a full decade earlier in black compared with nonblack patients, a finding that is again replicated in the CHAMP-HF registry data. Development of HFrEF at a significantly younger age means this syndrome represents a much greater midlife health burden for black Americans. This age gap magnifies the adverse effects of failure to optimize GDMT in black patients; leading to hospitalization and death in many youthful patients.[10,11]

Not surprisingly, family practice providers were less likely to treat patients, regardless of race/ethnicity, with HYD/NIT and sacubitril/valsartan than other clinicians. This gap is likely because nonspecialty clinicians are less familiar with the substantial clinical evidence that documents the significant morbidity and mortality reductions of these medications and may have less experience with initiation, up-titration, and continuation of therapies. More focus should be placed on encouraging treatment with GDMT by other, nonspeciality clinicians to better augment global use of GDMT.

We acknowledge there are limitations with the present study. First, although the registry does include a substantial number of black patients relative to previous registries and studies, this may not be representative of the general HF population. In addition, CHAMP-HF medication data capture was based on documentation within the medical record. Despite prespecified features designed to lessen any potential influence of documentation quality and completeness on registry data, inherent limitations remain. Contraindications to therapy may have been present in some patients but not documented. Some patients receiving lower doses may be individuals where dose increases were previously attempted but not tolerated. We cannot determine if patients are not achieving target dose due to intolerance, clinical inertia, or other reasons. Although study sites reflected a diverse set of cardiology and primary care outpatient practices, data reflect sites that elected to participate in the registry and thus may not be generalizable across all outpatient facilities. Moreover, this analysis may not represent treatment patterns in rural areas as the majority of the sites included were community-based practices in urban or suburban locations or major academic medical centers. Insurance information was not analyzed as part of this subanalysis, which limited the ability to compare barriers to medication accessibility in the 2 cohorts. Finally, several of the comparisons were based on small sample size owing to the low use of the targeted medications included in this analysis. Therefore, some potentially clinically significant differences were not statistically significant.

In conclusion, this analysis of the CHAMP-HF Registry highlights the persistent poor utilization of HYD/NIT in contemporary black patients with HFrEF, despite robust evidence and guideline recommendations. Likewise, utilization of sacubitril/valsartan is similarly low among black and nonblack patients with HFrEF; highlighting the broader challenge to achieving optimal use of GDMT in this syndrome.

Disclosures

KF Adams reports consulting and research support from Novartis; GC Fonarow reports consulting for Abbott, Amgen, Bayer, Janssen, Medtronic, and Novartis; NM Albert reports consulting for Novartis and Boston Scientific; J Butler has received research support from the NIH, PCORI and the European Union and serves as a consultant for Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Sanofi, and Vifor; JA Spertus reports consultative support from Novartis, AstraZeneca, Janssen, Bayer and ownership of the KCCQ copyright; JH Patterson reports consulting for Novartis. CI Duffy is an employee of Novartis Pharmaceuticals, Inc. PP Sharma and K McCague are former employees of Novartis Pharmaceuticals, Inc. All other authors have nothing to disclose.

1. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049–2057.
2. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the registry to improve the use of evidence-based heart failure therapies in the outpatient setting (IMPROVE HF). *Circulation* 2010;122:585–596.
3. Hong Y, LaBresh KA. Overview of the American Heart Association "Get with the Guidelines" programs: coronary heart disease, stroke, and heart failure. *Crit Pathw Cardiol* 2006;5:179–186.
4. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, Gong J, Rizkala AR, Brahimi A, Claggett B, Finn PV, Hartley LH, Liu J, Lefkowitz M, Shi V, Zile MR, Solomon SD. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J* 2015;36:1990–1997.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 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. *J Card Fail* 2017;23:628–651.
6. DeVore AD, Thomas L, Albert NM, Butler J, Hernandez AF, Patterson JH, Spertus JA, Williams FB, Turner SJ, Chan WW, Duffy CI, McCague K, Mi X, Fonarow GC. Change the management of patients with heart failure: rationale and design of the CHAMP-HF registry. *Am Heart J* 2017;189:177–183.
7. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol* 2018;72:351–366.
8. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, Duffy CI, Hill CL, McCague K, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Butler J. Titration of medical

therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;73:2365–2383.
9. Peri-Okonny PA, Mi X, Khariton Y, Patel KK, Thomas L, Fonarow GC, Sharma PP, Duffy CI, Albert NM, Butler J, Hernandez AF, McCague K, Williams FB, DeVore AD, Patterson JH, Spertus JA. Target doses of heart failure medical therapy and blood pressure: insights from the CHAMP-HF Registry. *JACC Heart Fail* 2019;7:350–358.
10. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol* 2008;101:1016–1022.
11. Sharma A, Colvin-Adams M, Yancy CW. Heart failure in African Americans: disparities can be overcome. *Cleve Clin J Med* 2014;81:301–311.