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## Use of Hydralazine Isosorbide Dinitrate Combination in African American and Other Race/Ethnic Group Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction

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# Use of Hydralazine-Isosorbide Dinitrate Combination in African American and Other Race/Ethnic Group Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction

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**Background**—Hydralazine-isosorbide dinitrate (H-ISDN) therapy is recommended for African American patients with moderate to severe heart failure with reduced ejection fraction (<40%) (HFrEF), but use, temporal trends, and clinical characteristics associated with H-ISDN therapy in clinical practice are unknown.

**Methods and Results**—An observational analysis of 54 622 patients admitted with HFrEF and discharged home from 207 hospitals participating in the Get With The Guidelines–Heart Failure registry from April 2008 to March 2012 was conducted to assess prescription, trends, and predictors of use of H-ISDN among eligible patients. Among 11 185 African American patients eligible for H-ISDN therapy, only 2500 (22.4%) received H-ISDN therapy at discharge. In the overall eligible population, 5115 of 43 498 (12.6%) received H-ISDN at discharge. Treatment rates increased over the study period from 16% to 24% among African Americans and from 10% to 13% among the entire HFrEF population. In a multivariable model, factors associated with H-ISDN use among the entire cohort included younger age; male sex; African American/Hispanic ethnicity; and history of diabetes, hypertension, anemia, renal insufficiency, higher systolic blood pressure, and lower heart rate. In African American patients, these factors were similar; in addition, being uninsured was associated with lower use.

**Conclusions**—Overall, few potentially eligible patients with HFrEF are treated with H-ISDN, and among African-Americans fewer than one-fourth of eligible patients received guideline-recommended H-ISDN therapy. Improved ways to facilitate use of H-ISDN therapy in African American patients with HFrEF are needed. (*J Am Heart Assoc.* 2013;2:e000214 doi: 10.1161/JAHA.113.000214)

**Key Words:** guideline adherence • heart failure • quality • race/ethnicity • registry

**H**eat failure (HF) results in substantial morbidity, mortality, and healthcare expenditures.<sup>1–3</sup> African Americans are at increased risk for developing HF and experience worse outcomes post-HF development.<sup>4,5</sup> Beyond angioten-

sin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, and aldosterone antagonists use in patients with heart failure with reduced ejection fraction (HFrEF),<sup>6–13</sup> clinical trials have established incremental benefit with hydralazine-isosorbide dinitrate (H-ISDN) therapy in African American HFrEF patients in terms of mortality, morbidity, and quality of life. In addition, data in non-African American HF patients with H-ISDN are encouraging, with proven benefits in terms of remodeling and exercise tolerance, but not on hard outcomes such as mortality and morbidity.<sup>14–16</sup> Both the American College of Cardiology/American Heart Association and Heart Failure Society of America guidelines recommend H-ISDN as a part of standard therapy for self-identified African American patients with HFrEF. In addition, these guidelines also recommend H-ISDN therapy to be considered in non-African American patients with HFrEF who remain symptomatic despite optimized standard therapy.<sup>17,18</sup>

Despite these guideline recommendations, there are very few contemporary studies regarding the utilization of H-ISDN

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in real-world practice. The Get With The Guidelines–Heart Failure (GWTG-HF) program is a national quality improvement program designed to promote adherence to guideline-based medical therapies.<sup>19,20</sup> Using data from GWTG-HF, we conducted an analysis to examine contemporary use of H-ISDN in the overall cohort of HFrEF patients and then specifically in self-identified African American patients hospitalized with HFrEF, temporal trends in H-ISDN use over time, and patient and hospital factors associated with H-ISDN prescription.

## Methods

### Data Collection

GWTG-HF is an ongoing prospective registry and quality improvement program initiated in January 2005 by the American Heart Association.<sup>19,20</sup> Participating hospitals include institutions from all regions of the United States and represent community hospitals as well as tertiary-care referral centers. The registry enrolls adults hospitalized with new or worsening HF as the primary diagnosis or with significant HF symptoms that develop during the hospitalization for which HF is the primary discharge diagnosis. Data collected include demographic and clinical characteristics, comorbidities, previous therapies and interventions, laboratory values, pharmacological and nonpharmacological interventions, contraindications to evidence-based therapies, and in-hospital outcomes. Patient's self-identified race (American Indian or Alaska Native, Asian, African American or black, Native Hawaiian or Pacific Islander, white, or unable to be determined) and ethnicity (Hispanic, yes, no, or unable to be determined) is registered. Hospital personnel are trained to use standardized definitions. All participating institutions are required to comply with local regulatory and privacy guidelines and to obtain approval from their institutional review boards before participation. As data are primarily collected for quality improvement purposes, all sites are granted a waiver for informed consent under the Common Rule. Internet-based system checks of data quality are performed to ensure their completeness and accuracy. Outcome Sciences, Inc (Cambridge, MA), serves as the data collection and coordination center, and the Duke Clinical Research Institute (Durham, NC) serves as the data analysis center under an agreement to analyze the aggregate deidentified data for research purposes.

### Study Population

From April 1, 2008, through March 24, 2012, 122 395 patients admitted with HF were discharged from 207 hospitals participating in the GWTG-HF program. The use of

H-ISDN prior to 2008 was collected differently and could not be directly compared, and hence the study period was 2008 onward. The use of H-ISDN was defined as patients prescribed either (1) the fixed dose combination of H-ISDN or (2) hydralazine+any formulation of nitrates (ie, mononitrate or dinitrate). The following groups of patients were excluded from the study analysis: patients with missing data on ejection fraction (n=3868) or ejection fraction >40% (n=63 905); patients with unknown race or ethnicity (n=2288); those with documented contraindication to H-ISDN therapy (n=2508); those who were comfort care only (n=2974); and those who died, left against medical advice, transferred to another hospital, discharged to hospice, or had missing information on discharge destination (n=2954). The final study population thus included 43 898 patients with HFrEF from 195 hospitals who were discharged home without medical contraindications to H-ISDN therapy.

### Outcome and Definitions

The primary outcome was prescription rate of H-ISDN in HFrEF patients at discharge in (1) African Americans patients and (2) the entire study population irrespective of race/ethnicity. We also studied the temporal trends in the use of H-ISDN over the study period (2008–2012), variation in use of H-ISDN across hospitals, patterns of use at various times (eg, newly started, discontinued or continued during hospitalization, or at discharge), and factors associated with its use.

### Statistical Analysis

Data were compared between patients prescribed and not prescribed H-ISDN using chi-square tests for categorical data and Wilcoxon rank sum tests for continuous variables. Percentages and means with standard deviations (SDs) were reported for categorical and normally distributed continuous variables, and medians with 25th and 75th percentiles were reported for nonnormally distributed continuous variables. Chi-square tests were used to test associations between prescription and patient groups. Time was divided into yearly intervals. Cochran-Mantel-Haenszel row mean scores statistics were used to test the trend of prescription over the study period. A multivariable logistic regression model was used to examine factors associated with H-ISDN use among eligible patients (in overall population as well as among African American patients). The generalized estimating equations approach was employed to account for within-hospital clustering. The candidate variables in the initial models included demographics, medical history, vital signs, insurance status, hospital teaching status, region, and number of beds. Also performed was a similar model including the variables mentioned above and use of H-ISDN before admission or

during hospitalization as well. Some patient variables, including body mass index, weight, and laboratory values and hospital-level variables including capability of percutaneous coronary intervention, surgery, and heart transplant had >10% to 20% missing data and thus were not included in the multivariate model. The patient characteristic variables included in the model had <5% missing data, and their missing data were imputed to median value for continuous variables and dominant level for categorical variables. Hospital region data were complete, and there was 2% missing data on teaching status and number of beds, and these missing data were excluded from the multivariable analysis. All tests were 2-sided, and because of the large cohort studied,  $P < 0.01$  was considered statistically significant. Analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

## Results

Irrespective of race/ethnicity, overall 43 898 patients from 195 hospitals treated with HFrEF were potentially eligible for H-ISDN therapy at discharge. Of these patients, 5515 (12.6%) were prescribed H-ISDN. Baseline demographic and clinical characteristics of patients stratified by prescription of H-ISDN at the time of discharge are shown in Table 1. Patients who received H-ISDN at discharge were younger, more likely to be male and African American, appeared to have more advanced disease, and were more likely to have comorbidities including history of chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, hypertension, peripheral vascular disease, stroke, anemia, renal insufficiency, chronic dialysis, lower heart rate, and higher systolic blood pressure. Even more importantly, patients who received H-ISDN were more likely to be treated with beta-blockers, aldosterone antagonists, calcium channel blockers, and diuretics and less likely to be treated with ACEIs before admission.

H-ISDN use at the time of discharge differed by race/ethnic group, being more frequent in African American patients (2500 of 11 185 [22.4%] among African American patients; 2409 of 26 922 [9.0%] among white patients, 414 of 3824 [10.8%] among Hispanic patients, and 192 of 1967 [9.8%] among other race/ethnic group patients). In the entire cohort, the discharge prescription of H-ISDN was more common among those patients with H-ISDN from before admission (1469 of 1818, 80.8%). This is in comparison with discharge prescription of H-ISDN in patients without H-ISDN before admission (4046 of 42 080, 9.6%). In the African American subgroup, the discharge prescription of H-ISDN was 84.6% versus 17.3% in those with versus without H-ISDN before admission.

Table 2 shows hospital characteristics, American College of Cardiology/American Heart Association performance measures, and GWTG-HF quality measures stratified by H-ISDN

use. Patients discharged with H-ISDN were more likely to be treated at academic medical centers, hospitals with surgical capabilities, and those with a greater number of beds.

At the time of discharge, the use of H-ISDN in eligible patients varied widely by hospital. The mean rate of H-ISDN use in 167 hospitals with  $\geq 10$  eligible patients was 12.1%, with a median (25th, 75th percentiles) of 9.6% (4.4%, 15.1%) (Figure 1). Among 90 hospitals with  $\geq 10$  African American eligible patients, mean H-ISDN rate among all patients was 13.6%, with a median (25th, 75th percentiles) of 11.6% (7.7%, 17.2%) (Figure 2) and mean rate of 21.0% with a median (25th, 75th percentiles) of 19.2% (12.1%, 26.3%) among African American patients.

Table 3 shows the patterns of use at the time of admission, hospitalization, and discharge. Of the patients already on H-ISDN before hospital admission, 61.3% had H-ISDN continued through the entire hospitalization, 19.5% had it stopped during hospitalization but restarted at discharge, whereas 11.6% had H-ISDN stopped at discharge. Among African American patients on H-ISDN before hospitalization, 63.7% had it continued through discharge, whereas 8.9% had it discontinued at discharge. Among patients not on H-ISDN at the time of admission, only 3.6% had H-ISDN initiated at the time of discharge in the entire cohort; among African American patients, this figure was 6.5%. Table 4 shows the patterns of H-ISDN use among HF patients with documented contraindication/intolerance to ACEIs/ARBs. The percentage of African American HFrEF patients with documented contraindication/intolerance to ACEIs/ARBs who were not receiving H-ISDN before hospital admission was 85.5%. In this patient group, H-ISDN therapy was initiated in 25.3% during hospitalization and started in another 11.8% of patients at the time of hospital discharge.

Table 5 demonstrates independent patient and hospital characteristics associated with H-ISDN prescription. In the overall population, factors associated with H-ISDN use were younger age, male sex, African American/Hispanic race, and history of diabetes mellitus, hypertension, implantable cardioverter defibrillator implantation, heart failure, anemia, renal insufficiency, higher systolic blood pressure, and lower heart rate. On the other hand, patients with a history of smoking and on chronic dialysis had lower use of H-ISDN at discharge. In African American patients, factors associated with H-ISDN use were similar except that being uninsured was associated with lower use, and history of chronic obstructive pulmonary disease was associated with higher use (Table 6). Furthermore, when prior use of H-ISDN before discharge (either before admission or during hospitalization) was included in the model for overall population, age, history of hypertension, and chronic dialysis were no longer significantly associated factors, and the strength of association decreased for those other significant characteristics for the overall population.

**Table 1.** Patient Characteristics by Hydralazine-Isosorbide Dinitrate Use at Hospital Discharge

Patient Characteristics	Hydralazine-Isosorbide Dinitrate Use, n (%)			P Value
	Total, n=43 898	Yes, n=5515	No, n=38 383	
Age (y), mean (SD)	68.3 (15.1)	65.4 (15.2)	68.7 (15.0)	<0.0001
Male (%)	27 381 (62.4)	3628 (65.8)	23 753 (61.9)	<0.0001
Race/ethnicity (%)				<0.0001
White	26 922 (61.3)	2409 (43.7)	24 513 (63.9)	
African American	11 185 (25.5)	2500 (45.3)	8685 (22.6)	
Hispanic	3824 (8.7)	414 (7.5)	3410 (8.9)	
Other	1967 (4.5)	192 (3.5)	1775 (4.6)	
Body mass index (kg/m <sup>2</sup> ), mean (SD)	28.8 (8.1)	30.0 (8.4)	28.65 (8.0)	<0.0001
Insurance (%)				<0.0001
Uninsured	26 222 (5.97)	352 (6.38)	2270 (5.91)	
Medicare	23 338 (53.1)	2752 (49.9)	20 586 (53.6)	
Medicaid	4687 (10.7)	840 (15.2)	3847 (10.0)	
Other	11 383 (25.9)	1285 (23.3)	10 098 (26.3)	
Medical history (%)				
Hypertension	31 702 (74.2)	4471 (82.1)	27 231 (73.1)	<0.0001
Diabetes	17 627 (41.2)	2754 (50.5)	14 873 (39.9)	<0.0001
Hyperlipidemia	20 585 (48.2)	2728 (50.1)	17 857 (47.9)	0.003
Atrial fibrillation	12 770 (29.9)	1434 (26.3)	11 336 (30.4)	<0.0001
Atrial flutter	1065 (2.5)	150 (2.7)	015 (2.5)	0.19
COPD/asthma	11 813 (27.7)	1580 (29.0)	10 233 (27.5)	0.018
Peripheral vascular disease	4952 (11.6)	744 (13.7)	4208 (11.3)	<0.0001
Coronary artery disease	21 732 (50.9)	2839 (52.1)	18 893 (50.7)	0.05
Prior myocardial infarction	10 899 (25.5)	1335 (24.5)	9564 (25.7)	0.07
Cerebrovascular disease	5760 (13.5)	871 (16.0)	4889 (13.1)	<0.0001
ICD	8380 (19.6)	1380 (25.3)	7000 (18.8)	<0.0001
Prior heart failure	31 266 (73.2)	4331 (79.5)	26 935 (72.2)	<0.0001
Anemia	6504 (15.2)	1164 (21.3)	5340 (14.3)	<0.0001
Pacemaker	6116 (14.3)	738 (13.5)	5378 (14.4)	0.08
CRT-P	360 (0.84)	43 (0.79)	317 (0.85)	0.64
CRT-D	3781 (8.9)	659 (12.1)	3122 (8.4)	<0.0001
Chronic dialysis	1278 (2.9)	214 (3.9)	1064 (2.9)	<0.0001
Renal insufficiency	8764 (20.5)	2085 (38.2)	6679 (17.9)	<0.0001
Depression	3725 (8.7)	2085 (38.2)	6679 (17.9)	<0.0001
Prior PCI	7239 (16.9)	910 (16.7)	6239 (16.9)	<0.0001
Prior CABG	9842 (23.0)	1221 (22.4)	6621 (23.1)	0.24
Valvular heart disease	6870 (16.0)	832 (15.3)	6038 (16.2)	0.08
Smoking	9584 (21.8)	1214 (22.0)	8370 (21.8)	0.78
Vital signs on admission, mean (SD)				
Heart rate, bpm	88 (20)	86 (19)	88 (20)	<0.0001
Systolic blood pressure	136 (29)	145 (32)	134 (28)	<0.0001

Continued



**Table 1.** Continued

Patient Characteristics	Hydralazine-Isosorbide Dinitrate Use, n (%)			
	Total, n=43 898	Yes, n=5515	No, n=38 383	P Value
Diastolic blood pressure	80 (19)	84 (21)	79 (19)	<0.0001
Respiratory rate, bpm	21 (5)	21 (5)	21 (5)	0.054
Serum lab values at admission, median (25th, 75th percentiles)				
Sodium	138 (135, 140)	138 (135, 140)	138 (135, 140)	<0.0001
Creatinine	1.3 (1.0, 1.8)	1.8 (1.3, 2.4)	1.3 (1.0, 1.7)	<0.0001
BUN	24 (17, 36)	32 (21, 48)	23 (17, 35)	<0.0001
BNP	1154 (538, 2238)	1262 (577, 2507)	1140 (534, 2160)	<0.0001
Medications prior to admission (%)				
Aspirin	17 904 (40.8)	2417 (43.8)	15 487 (40.3)	0.02
Beta-blockers	24 805 (56.5)	3551 (64.4)	21 254 (55.4)	<0.0001
ACE inhibitors	15 280 (34.8)	1605 (29.1)	13 675 (35.6)	<0.0001
ARBs	4880 (11.1)	631 (11.4)	4249 (11.1)	0.70
Aldosterone antagonists	5868 (13.4)	881 (16.0)	4987 (13.0)	<0.0001
CCBs	3966 (9.0)	752 (13.6)	3214 (8.4)	<0.0001
Digoxin	6994 (15.8)	924 (16.7)	6020 (15.7)	0.58
Statins	17 086 (38.9)	2388 (43.3)	14 698 (38.3)	<0.0001
In-hospital procedures (%)				
PCI	616 (1.6)	76 (1.6)	540 (1.7)	0.59
ICD placed	1823 (4.9)	172 (3.5)	1651 (5.1)	<0.0001
Cardiac valve or CABG	321 (0.86)	18 (0.37)	303 (0.94)	<0.0001
Ejection fraction (SD)	24.7 (7.8)	24.8 (7.8)	24.7 (7.8)	0.31
Days of hospital stay (median)	4.0 (2.0 to 7.0)	5.0 (3.0 to 8.0)	4.0 (2.0 to 6.0)	<0.0001

SI conversion factors: to convert BUN values to millimoles per liter, multiply by 0.357; to convert creatinine values to micromoles per liter, multiply by 88.4. SD indicates standard deviation; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; CRT-D/P, cardiac synchronization therapy-defibrillator/pacemaker; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BUN, blood urea nitrogen; BNP, brain-type natriuretic peptide; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

Figure 3 shows the temporal trends in the use of H-ISDN over time. H-ISDN prescription increased over 4 years in the overall population from 10.1% in 2008 to 13.3% in 2011–2012 ( $P<0.0001$ ). This trend was significant in both African American (16.6% to 25.0%,  $P<0.0001$ ) and white (7.2% to 9.3%,  $P=0.0004$ ) patients, whereas statistically nonsignificant trends were noted between Hispanic and other race/ethnic groups.

## Discussion

Both the American College of Cardiology/American Heart Association and the Heart Failure Society of America HF management guidelines recommend the use of a fixed-dose combination of H-ISDN added to a standard medical regimen for HF, including ACEIs and beta-blockers, in self-identified African American patients with symptomatic HFrEF (class I, level of evidence B). In addition, H-ISDN use is also

recommended in non-African American patients who remain symptomatic on optimized medical therapy (class IIb, level of evidence C).<sup>7,18</sup> In this cohort of >40 000 patients with HFrEF, we demonstrate that <15% of the overall cohort and <25% of the eligible African American patients were prescribed H-ISDN therapy at the time of discharge. Prescription of H-ISDN varied at discharge widely across hospitals and according to patient characteristics.

When compared with reports from prior registries, the findings of this study suggest higher rates of treatment with H-ISDN. Reports from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure registry from 2003 to 2004 showed that only 4.5% of African American patients and 2.6% of white patients hospitalized with HF were discharged with prescriptions for H-ISDN.<sup>21</sup> In addition, Improving Evidence-Based Care for Heart Failure in Outpatient Cardiology Practices registry data, which studied the use of evidence-based medical therapy in

**Table 2.** Hospital Characteristics and Adherence to Performance and Quality Measures by Hydralazine-Isosorbide Dinitrate Use at Hospital Discharge

Characteristics	Total, n=43 898	Yes, n=5515	No, n=38 383	P Value
<b>Hospital</b>				
Bed size, median	462 (328, 620)	527 (346, 656)	438 (311, 616)	<0.0001
Academic or residents status (%)	34 095 (77.7)	4399 (79.8)	29 696 (77.4)	<0.0001
<b>Region (%)</b>				
Northeast	16 170 (36.8)	2077 (37.7)	14 093 (36.7)	<0.0001
South	11 524 (26.3)	1634 (29.6)	9890 (25.8)	<0.0001
Midwest	10 702 (24.4)	1285 (23.3)	9417 (24.5)	<0.0001
West	5502 (12.5)	519 (9.4)	4983 (13.0)	<0.0001
<b>Interventional status (%)</b>				
PTCA	33 718 (76.8)	4374 (79.3)	29 344 (76.5)	<0.0001
Surgery	30 956 (70.5)	4137 (75.0)	26 819 (69.9)	<0.0001
Heart transplant capable (%)	5768 (12.9)	1188 (21.5)	4490 (11.7)	<0.0001
<b>Performance status and quality measures</b>				
Discharge instructions documented for all 6 criteria*	35 833 (93.3)	4656 (95.3)	31 177 (93)	<0.0001
ACE inhibitors at discharge	31 607 (93.8)	2662 (89.0)	28 945 (94.2)	<0.0001
Evidence-based beta-blockers at discharge	32 502 (79.7)	4279 (83.4)	28 223 (79.1)	<0.0001
Aldosterone antagonists at discharge	12 037 (30.5)	1556 (32.8)	10 481 (29.9)	<0.0001
Counseling for smoking cessation	9464 (98.8)	1199 (98.8)	8265 (98.8)	0.96
Anticoagulation for atrial fibrillation	8986 (72.7)	1019 (74.6)	7967 (72.5)	0.10
Lipid-lowering medication at discharge	20 167 (67.6)	2869 (71.2)	17 298 (67.0)	<0.0001
BP control at discharge (SBP <140 and DBP <90 mm Hg)	33 800 (83.2)	3935 (74.0)	29 865 (84.6)	<0.0001
ICD counseling or ICD placed or prescribed at discharge for EF <30%	12 544 (47.1)	1797 (54.1)	10 747 (46.1)	<0.0001

PTCA indicates percutaneous transluminal coronary angioplasty; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICD, implantable cardioverter-defibrillator; EF, ejection fraction.

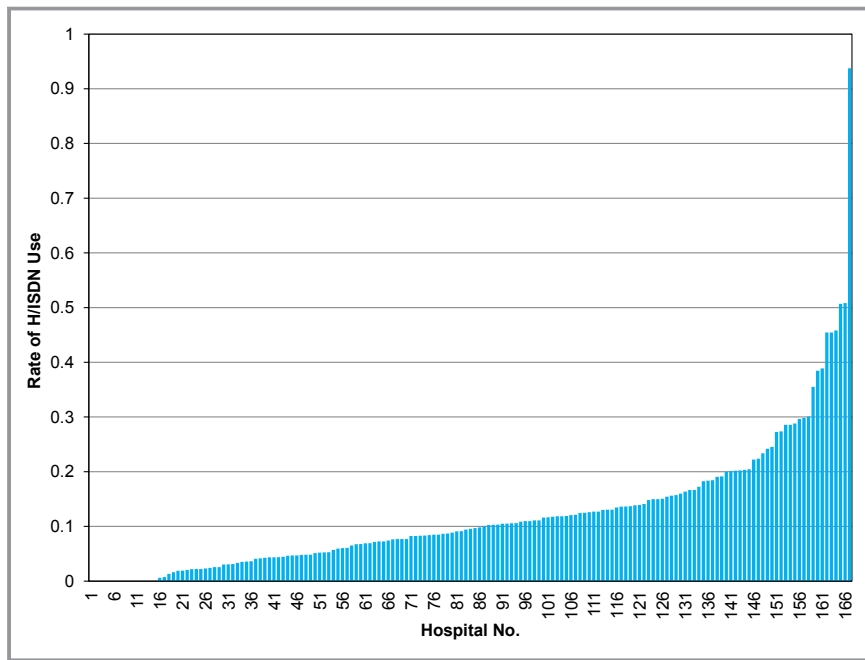
\*Diet, medications, activity level, follow up appointment, weight monitoring, what to do if symptoms worsen.

outpatient cardiology practices, demonstrated that the mean prescription rate for H-ISDN was only 7.3% in African American patients with HFrEF.<sup>22</sup> Together, these findings suggest that the use of H-ISDN in eligible patients with HFrEF has improved over time but still is low during hospitalization, low in the transition from the hospital to the outpatient setting, and low during longitudinal follow-up in outpatient practices. The small but statistically significant increase in the use of H-ISDN over the study period among African Americans could potentially be explained by participation in the GWTG-HF quality improvement registry among other factors.

Although the African American Heart Failure Trial proved the effectiveness of H-ISDN in self-identified African American patients, there has been greater uncertainty regarding the efficacy of H-ISDN in other race/ethnic groups.<sup>16</sup> Mullen et al<sup>23</sup> demonstrated that H-ISDN when added to ACEIs/ARBs was associated with a favorable hemodynamic profile and long-term clinical outcomes in HFrEF patients with acute decompensated

HF, regardless of race or ethnicity. However, prospective randomized, double-blind, placebo-controlled outcome studies with H-ISDN added to other contemporary HF therapies are lacking in non-African American patients with HFrEF. Thus, the usefulness of routine use of H-ISDN in non-African patients with HFrEF is far from certain. In our study, when H-ISDN use was stratified among different racial/ethnic groups, the prescription of H-ISDN at the time of discharge as expected was lower for Hispanic patients, white patients, and other race/ethnic groups compared with African American patients.<sup>17,18</sup> Chronic renal failure was identified as 1 of the most important predictors of H-ISDN use among African American patients with HFrEF (2.33, adjusted OR, 2.02 to 2.69;  $P<0.0001$ ) as well as the overall cohort. This suggests that H-ISDN is being applied in patients who were or are perceived to be intolerant to ACEIs. It is also notable that patients who were prescribed H-ISDN were less likely to receive ACEIs at discharge.

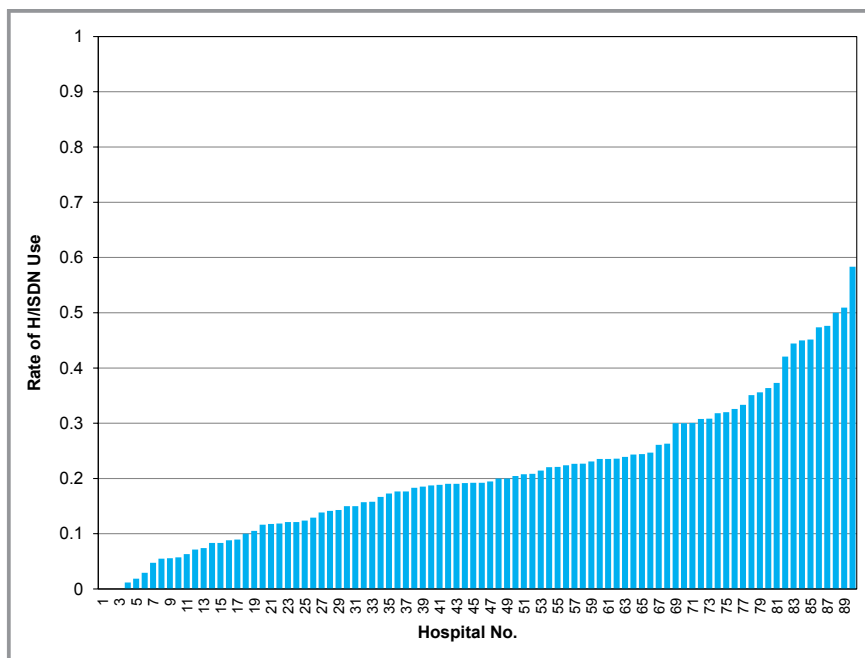
Although the prescription of H-ISDN increased over time in GWTG-HF, its use among African American HFrEF patients



**Figure 1.** Hydralazine-isosorbide dinitrate (H-ISDN) use overall in hospitals with  $\geq 10$  patients.

was unacceptably low considering the conclusive clinical trial evidence demonstrating substantial reductions in all-cause mortality and hospitalizations with H-ISDN use. More importantly, our results indicate that the prescription of H-ISDN at discharge was significantly higher in patients already on H-ISDN before the time of admission, whereas in patients without prior H-ISDN, only 8.5% had this therapy initiated during the hospitalization, and 3.6% had this therapy initiated

at the time of discharge. These data demonstrate the reluctance to initiate H-ISDN therapy in eligible patients as opposed to continuing the therapy in patients already on H-ISDN. However, data with multiple drugs in both patients with HF and patients with acute myocardial infarction demonstrate that by far the best predictor of long-term adherence with therapy is prescription at the time of hospital discharge. Although there have been no specific clinical



**Figure 2.** Hydralazine-isosorbide dinitrate (H-ISDN) use in African American patients in hospitals with  $\geq 10$  self-identified African American patients.



**Table 3.** Patterns of Hydralazine-Isosorbide Dinitrate Use (H-ISDN)

	n (%)
Use in overall cohort	
Patterns for patients already receiving H-ISDN before hospital admission	1818 (4.1)
Medication persisted from admission through discharge	1115 (61.3)
Medication held during hospitalization but restarted at discharge	354 (19.5)
Medication discontinued during hospitalization	211 (11.6)
Patterns for patients who did not have H-ISDN before hospital admission	42 080 (95.9)
Medication initiated during hospitalization	3578 (8.5)
Medication initiated at hospital discharge	1507 (3.6)
Use in African Americans	
Patterns for patients already receiving H-ISDN before hospital admission	844 (7.6)
Medication persisted from admission through discharge	538 (63.7)
Medication held during hospitalization but restarted at discharge	176 (20.9)
Medication discontinued during hospitalization	75 (8.9)
Patterns for patients who did not have H-ISDN before hospital admission	10 341 (92.4)
Medication initiated during hospitalization	1524 (14.7)
Medication initiated at hospital discharge	675 (6.5)

H-ISDN indicates hydralazine-isosorbide dinitrate.

trials performed with H-ISDN therapy among HF patients hospitalized with HF, the cumulative clinical trials and observational data suggest that hospitalization provides a potential opportunity to improve adherence with this therapy.

If this cannot be achieved during the hospitalization, a mandatory follow-up visit with instructions to consider adding H-ISDN therapy in African American patients with HFrEF may be warranted.

**Table 4.** Patterns of Hydralazine-Isosorbide Dinitrate Use in Patients With Documented Contraindication/Intolerance to ACEIs/ARBs

	n (%)
Use in overall cohort	
Patterns for patients already receiving H-ISDN before hospital admission	898 (8.8)
Medication persisted from admission through discharge	588 (65.5)
Medication held during hospitalization but restarted at discharge	168 (18.7)
Medication discontinued during hospitalization	84 (9.4)
Patterns for patients who did not have H-ISDN before hospital admission	9297 (91.2)
Medication initiated during hospitalization	1418 (15.3)
Medication initiated at hospital discharge	608 (6.5)
Use in African Americans	
Patterns for patients already receiving H-ISDN before hospital admission	309 (14.5)
Medication persisted from admission through discharge	200 (64.7)
Medication held during hospitalization but restarted at discharge	70 (22.7)
Medication discontinued during hospitalization	17 (5.5)
Patterns for patients who did not have H-ISDN before hospital admission	1821 (85.5)
Medication initiated during hospitalization	460 (25.3)
Medication initiated at hospital discharge	215 (11.8)

ACEIs indicates angiotension-converting enzyme inhibitors; ARBs, angiotension receptor blockers; H-ISDN, hydralazine-isosorbide dinitrate.

**Table 5.** Patient and Hospital Factors Associated With Hydralazine-Isosorbide Dinitrate Use in Overall Cohort

Variable	Adjusted OR (95% CI)	P Value
Age, per 10 years	0.92 (0.89 to 0.96)	<0.0001
Female	0.82 (0.77 to 0.87)	<0.0001
Race, African American vs white	2.24 (2.00 to 2.84)	<0.0001
Race, Hispanic vs white	1.24 (1.05 to 1.46)	0.009
Medical history		
Diabetes	1.27 (1.17 to 1.37)	<0.0001
Hypertension	1.27 (1.13 to 1.44)	0.0001
ICD implantation	1.26 (1.15 to 1.39)	<0.0001
Prior heart failure	1.27 (1.16 to 1.38)	<0.0001
Anemia	1.35 (1.23 to 1.49)	<0.0001
Renal insufficiency	2.56 (2.33 to 2.82)	<0.0001
Chronic dialysis	0.66 (0.49 to 0.90)	0.008
Smoking	0.84 (0.78 to 0.92)	<0.0001
Systolic BP, per 10 mm Hg	1.14 (1.12 to 1.16)	<0.0001
Heart rate, per 10 beats/minute	0.92 (0.90 to 0.94)	<0.0001

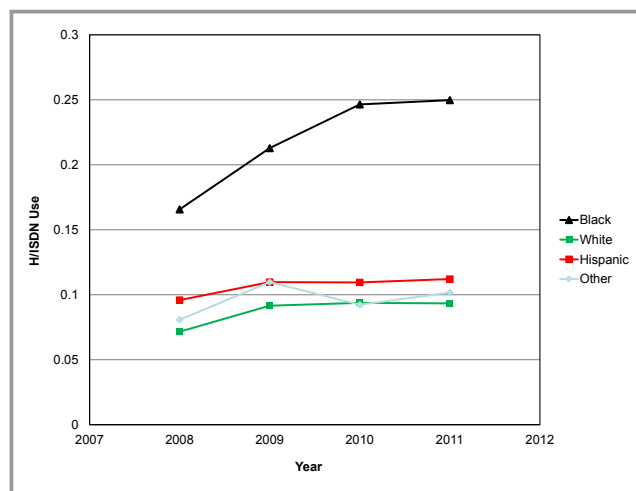
Candidate variables in the model included demographics (age, sex, race), insurance status, medical history (atrial fibrillation or flutter, chronic obstructive pulmonary disease, diabetes, dyslipidemia, hypertension, peripheral vascular disease, stroke, implantable cardioverter defibrillator implantation, previous history of heart failure, anemia, pacemaker, dialysis, renal insufficiency, depression, ischemic etiology of heart failure, smoker), vital signs (systolic BP and heart rate), hospital characteristics (region, teaching status and number of beds). Only statistically significant factors are reported in the table. CI indicates confidence interval; ICD, implantable cardioverter-defibrillator; BP, blood pressure.

Slow adoption of H-ISDN use by hospitals and clinicians is likely multifactorial. Lack of monitoring of H-ISDN use, because it is not an HF performance measure selected by The Joint Commission/Centers for Medicare and Medicaid Services or the American College of Cardiology/American Heart Association, could partially explain its limited uptake in clinical practice. Despite a mean systolic blood pressure of >120 mm Hg in the treatment arm of the African American Heart Failure Trial, about 30% of the patients taking H-ISDN reported dizziness. This along with other side effects, which may be more prominent in the real-world population, which tends to be older, has multiple comorbidities, and is on polypharmacy, could also contribute to diminished use of H-ISDN in practices. In addition, many HFREF patients, especially those with severely depressed ejection fraction, tend to have low baseline blood pressure, especially when receiving other guidelines-recommended therapy, which may deter providers from prescribing H-ISDN because of concern for hypotension. Three-times-a-day dosing may also affect both prescription and adherence. Many HF patients have erectile dysfunction and desire to use medications like sildenafil, which limits the concomitant use of nitrate therapy.

**Table 6.** Patient and Hospital Factors Associated With Hydralazine-Isosorbide Dinitrate Use in Self-Identified African American Patients Meeting Guideline Criteria

Variable	Adjusted OR (95% CI)	P Value
Age, per 10 years	0.89 (0.85 to 0.94)	<0.0001
Female vs male	0.77 (0.69 to 0.87)	<0.0001
Insurance, uninsured vs Medicare	0.80 (0.68 to 0.94)	0.0072
Medical history		
COPD	1.18 (1.06 to 1.31)	0.0021
Diabetes	1.21 (1.07 to 1.37)	0.0021
Hypertension	1.31 (1.07 to 1.61)	0.0091
ICD implantation	1.36 (1.19 to 1.55)	<0.0001
Prior heart failure	1.40 (1.23 to 1.59)	<0.0001
Anemia	1.28 (1.07 to 1.52)	0.006
Chronic dialysis	0.60 (0.42 to 0.86)	0.0055
Renal insufficiency	2.31 (1.99 to 2.69)	<0.0001
Smoking	0.82 (0.72 to 0.94)	0.0036
Systolic BP, per 10 mm Hg	1.15 (1.12 to 1.18)	<0.0001
Heart rate, per 10 beats/minute	0.93 (0.91 to 0.95)	<0.0001

Candidate variables in the model included demographics (age, sex), insurance status, medical history (atrial fibrillation or flutter, chronic obstructive pulmonary disease, diabetes, dyslipidemia, hypertension, peripheral vascular disease, stroke, implantable cardioverter-defibrillator implantation, history of heart failure, anemia, pacemaker, dialysis, renal insufficiency, depression, ischemic etiology of heart failure, smoker), vital signs (systolic BP and heart rate), hospital characteristics (region, teaching status, and number of beds). Only statistically significant factors are reported in the table. CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; BP, blood pressure.



**Figure 3.** Trends in the use of hydralazine-isosorbide dinitrate (H-ISDN) at discharge in eligible patients from 2008 to 2012.

In the case of branded fixed-dose combination of H-ISDN (BiDil), cost may be an important consideration and may explain the low use of H-ISDN in the uninsured African

American population. Finally, the use of H-ISDN was significantly higher in patients also receiving other evidence-based therapies, raising the possibility of increased compliance in general with all therapies if further education were imparted to providers about HF care in general. Incorporation of some of these interventions in clinical practice, including, for example, H-ISDN as a core performance measures, appropriate documentation of contraindication of its use, further educating primary care physicians and cardiologists, and other interventions, might help to improve prescription patterns with H-ISDN in clinical practice. Regardless of these issues, there remains a substantial gap between guideline recommendations and implementation of clinical use of H-ISDN in African American patients with HFrEF.

### Limitations

Our study has several limitations. The data collection was dependent on the accuracy and completeness of data abstraction from medical chart review, particularly because eligibility for care metrics is based on documentation. In addition, measured and unmeasured confounding factors may have affected results. The doses of hydralazine and nitrates that patients were discharged home on were not recorded. We did not have information about why H-ISDN was discontinued or not started in the absence of documented contraindications or intolerance. This should be evaluated in future studies. Because our data set also did not include longitudinal follow-up, a portion of eligible patients may have been started on H-ISDN as outpatients, underestimating its real use. However, previous data suggest that if a medication is not started at the time of discharge, the subsequent new prescription rate in the outpatient setting for ACEIs and beta-blockers is very low.<sup>24</sup> With the large number of patients studied, some statistically significant differences may be of questionable clinical relevance and should be interpreted with caution. Finally, GWTG-HF hospitals were self-selected and may not be representative of all hospitals in the United States.

### Conclusions

Hydralazine-isosorbide dinitrate use in eligible African American patients with HFrEF remains very low in real-world practice despite clinical trial evidence and incorporation of these data into recommendations by multiple professional guidelines for many years. Moreover, H-ISDN use varies widely by hospital. Although its use has increased over time from 2008 through 2011, it has nevertheless remained <25%, even in African American patients with HFrEF. Given the substantial morbidity and mortality faced by patients with

HFrEF and the established efficacy of H-ISDN among African American patients, aggressive measures to facilitate adherence to H-ISDN should be sought.

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