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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

| Citation | Golwala, Harsh B., Udho Thadani, Li Liang, Stavros Stavrakis, Javed Butler, Clyde W. Yancy, Deepak L. Bhatt, Adrian F. Hernandez, and Gregg C. Fonarow. 2013. “Use of Hydralazine#Isosorbide Dinitrate Combination in African American and Other Race/Ethnic Group Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction.” Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease 2 (4): e000214. doi:10.1161/JAHA.113.000214. http://dx.doi.org/10.1161/JAHA.113.000214. |
| Published Version | doi:10.1161/JAHA.113.000214 |
| Citable link | http://nrs.harvard.edu/urn-3:HUL.InstRepos:11879104 |
| Terms of Use | This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA |
Use of Hydralazine-Isosorbide Dinitrate Combination in African American and Other Race/Ethnic Group Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction

Harsh B. Golwala, MD; Udho Thadani, MD; Li Liang, PhD; Stavros Stavrakis, MD, PhD; Javed Butler, MD, MPH; Clyde W. Yancy, MD; Deepak L. Bhatt, MD, MPH; Adrian F. Hernandez, MD, MHS; Gregg C. Fonarow, MD

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
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.\textsuperscript{19,20} 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.\textsuperscript{19,20} 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-Haenzel 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 (%) |       | No, n=38 383 | P Value |
|-------------------------------------------------|--------------------------------------------|-------|--------------|---------|
|                                                 | Total, n=43 898                             |       |              |         |
| 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 (%)                               |                                           |       |              |         |
| White                                           | 26 922 (61.3)                               | 2409 (43.7) | 24 513 (63.9) | <0.0001 |
| 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) | <0.0001 |
| Body mass index (kg/m²), 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 (%)                              |                                           |       |              | <0.0001 |
| 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
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). 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. 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...
outpatient cardiology practices, demonstrated that the mean prescription rate for H-ISDN was only 7.3% in African American patients with HFrEF. 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 American 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. Mullen et al 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. 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

| Characteristics | Total, n=43 898 | Yes, n=5515 | No, n=38 383 | P Value |
|-----------------|----------------|-------------|--------------|---------|
| Hospital        |                |             |              |         |
| 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 |
| Region (%)      |                |             |              |         |
| 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 |
| Intervenational status (%) |            |             |              |         |
| 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 |
| Performance status and quality measures |             |             |              |         |
| 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.

DOI: 10.1161/JAHA.113.000214
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 1. Hydralazine-isosorbide dinitrate (H-ISDN) use overall in hospitals with ≥10 patients.

Figure 2. Hydralazine-isosorbide dinitrate (H-ISDN) use in African American patients in hospitals with ≥10 self-identified African American patients.
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 3. Patterns of Hydralazine-Isosorbide Dinitrate Use (H-ISDN)

| Use in overall cohort | n (%) |
|-----------------------|-------|
| 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.

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

| Use in overall cohort | n (%) |
|-----------------------|-------|
| 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 Patients Meeting Guideline Criteria.
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 measure, 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.\(^{24}\) 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.

Sources of Funding
The Get With The Guidelines–Heart Failure (GWTG-HF) program is provided by the American Heart Association. GWTG-HF has been funded in the past through support from Medtronic, GlaxoSmithKline, Ortho-McNeil, and the American Heart Association Pharmaceutical Roundtable.

Disclosures
Drs Golwala and Stavrakis report no conflicts of interest. Dr Bhatt discloses the following relationships—advisory board: Medscape Cardiology; Board of Directors: Boston VA Research Institute, Society of Chest Pain Centers; Chair: American Heart Association Get With The Guidelines Science Subcommittee; honoraria (all significant): American College of Cardiology (Editor, Clinical Trials, Cardiosource), Duke Clinical Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, Cardiology Today Intervention), WebMD (CME steering committees); Other: Senior Associate Editor, *Journal of Invasive Cardiology*; research grants (all significant): Aminar, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company; unfunded research: FlowCo, PLx Pharma, Takeda. Dr Butler reports support from the NIH and clinical trials event committee participation with Corthera (both significant), and consultant to Alere, Bayer, CardioMEMS, Gambro, Takeda, Trevena, Ono Pharma, and AMGEN (all modest). Dr Hernandez reports research support from the NHLBI, AHRQ, Amylin, Johnson & Johnson, Portola Pharmaceuticals (significant); consulting for Astra Zeneca (modest), Corthera (significant), Sanofi (modest), and Bristol Myers Squib (modest). Dr Thadani discloses the following relationships—the University of Oklahoma and VA Medical Center receive study grant money from NIH, VA Cooperative Studies, Gilead Science, Eli Lilly, Novartis, Bristol Myers Squib, Pfizer, Astra Zeneca, Bi, and Merck, for which Dr Thadani is the local PI. Consultant to Servier, Arbor Pharmaceuticals, Speaker’s Bureau Gilead sciences, Eli Lilly, and Diachi-Sankyo. Dr Yancy reports no disclosures. Dr Fonarow reports research support from the NHLBI and AHRQ (both significant), consulting for Novartis (significant), Gambro (significant), and Medtronic (modest).

References
1. Fonarow GC. Epidemiology and risk stratification in acute heart failure. *Am Heart J*. 2008;155:200–207.
2. Gottlieb SS, Khatta M, Friedemann E, Einbinder L, Katzen S, Baker B, Marshall J, Minshall S, Robinson S, Fisher ML, Potenza M, Sigler B, Baldwin C, Thomas SA. The influence of age, gender, and race on the prevalence of depression in heart failure patients. J Am Coll Cardiol. 2004;43:1542–1549.

3. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Flegal KM, Ford ES, Hu S,功选择, Hsia R, Hong Y, Howard VJ, Johnson CL, Kmer L, Lichtenstein PD, Liu Y, Makuc DM, Nasir K, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123:e18–e209.

4. Adams KS Jr, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, Jensen LR, Tomasko L, Koch G. Relation between gender, etiology and survival in patients with symptomatic heart failure. J Am Coll Cardiol. 1996;28:1781–1788.

5. Adams KS Jr, Sueta CA, Gheorghie M, O’Connor CM, Schwartz TA, Koch GG, Uretsky B, Swedberg K, McKenna W, Soler-Soler J, Califf RM. Gender differences in survival in advanced heart failure. Insights from the FIRST study. Circulation. 1999;99:1816–1821.

6. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316:1429–1435.

7. SOLVD Investigators. Effect of enalapril on survival in patients with reduced ejection fraction. N Engl J Med. 1994;325:293–302.

8. CIBIS-II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.

9. MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:201–207.

10. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal trial in myocardial infarction with angiotensin II antagonist losartan. Lancet. 2002;360:752–760.

11. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334:1349–1355.

12. Packer M, Fowler MB, Roeccker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendler M, Staiger C, Holclaw TL, Amann-Zalan I, DeMets DL. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106:2194–2199.

13. Pitt B, Zannad F, Remme WJ, C:reda J, Castaigne A, Perez A, Palensky J, Writtes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709–717.

14. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman F, Cobb F, Shah P, Saunders R, Fletcher S, Loeb H, Hughes V, Baker B. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314:1547–1552.

15. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, Bhat G, Goldman S, Fletcher R, Doherty J, Hughes C, Carson P, Cintron G, Shabetai R, Haakenson C. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325:303–310.

16. Taylor AL, Ziesche S, Yancy C, Carson P, D’Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Wocel M, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–2057.

17. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michi K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53:e1–e90.

18. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klaholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16:e1–e194.

19. LaBresh KA, Gliklich R, Lijestrand J, Peto R, Elliott AG. Using “Get With The Guidelines” to improve cardiovascular secondary prevention. J Am Coll Cardiol. 2003;9:539–550.

20. Smaha LA. The American Heart Association Get With The Guidelines program. Am J Heart. 2004;148:548–548.

21. Yancy CW, Abraham WT, Albert NM, Clare R, Stough WG, Gheorghie M, Greenberg BH, O’Connor CM, She L, Sun JL, Young JB, Fonarow GC. Quality of care of and outcomes for African Americans hospitalized with heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. J Am Coll Cardiol. 2008;51:1675–1684.

22. Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghie M, Heywood JT, McBride ML, Mehra MR, O’Connor CM, Reynolds D, Walsh MN. Adherence to guideline-recommended adjunctive heart failure therapies among outpatient cardiology practices (findings from IMPROVE HF). Am J Cardiol. 2010;105:255–260.

23. Mullens W, Abrahams Z, Francis GS, Sokos G, Starling RC, Young JB, Taylor DO, Tang WH. Usefulness of isosorbide dinitrate and hydralazine as add-on therapy in patients discharged for advanced decompensated heart failure. Am J Cardiol. 2009;103:1113–1119.

24. Butler J, Arboagast PG, Daugherty J, Jain MK, Ray WA, Griffin MR. Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. J Am Coll Cardiol. 2004;43:2036–2043.