Clinical Effectiveness of Hydralazine–Isosorbide Dinitrate Therapy in Patients With Heart Failure and Reduced Ejection Fraction: Findings From the Get With The Guidelines-Heart Failure Registry

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Background—In clinical trials, hydralazine–isosorbide dinitrate (H-ISDN) for heart failure with reduced ejection fraction reduced morbidity and mortality among black patients and patients with intolerance to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. The effectiveness of H-ISDN in clinical practice is unknown.

Methods and Results—Using data from a clinical registry linked with Medicare claims, we examined the use and outcomes of H-ISDN between 2005 and 2011 among older patients hospitalized with heart failure and reduced ejection fraction. We adjusted for demographic and clinical characteristics using Cox proportional hazards models and inverse probability weighting. Among 4663 eligible patients, 22.7% of black patients and 18.2% of patients not on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker were newly prescribed H-ISDN therapy at discharge. By 3 years, the cumulative incidence rates of mortality and readmission were similar between treated and untreated patients. After multivariable adjustment, 3-year outcomes remained similar for mortality [black patients: hazard ratio (HR), 0.92; 95% confidence interval (CI), 0.75–1.13; other patients: HR, 0.93; 95% CI, 0.79–1.09], all-cause readmission (black patients: HR, 0.98; 95% CI, 0.84–1.13; other patients: HR, 1.02; 95% CI, 0.90–1.17), and cardiovascular readmission (black patients: HR, 0.99; 95% CI, 0.82–1.19; other patients: HR, 0.94; 95% CI, 0.81–1.09). A post hoc analysis of Medicare Part D data revealed low postdischarge adherence to therapy.

Conclusions—Guideline-recommended initiation of H-ISDN therapy at hospital discharge was uncommon, and adherence was low. For both black patients and patients of other races, there were no differences in outcomes between those treated and untreated at discharge. 

Key Words: cardiomyopathies □ heart failure □ mortality □ pharmacology □ registries □ survival

Clinical trials have established the efficacy of hydralazine–isosorbide dinitrate (H-ISDN) therapy in patients with heart failure and reduced ejection fraction in terms of mortality, morbidity, and quality of life.1–3 In particular, after the African-American Heart Failure Trial (A-HeFT) found that H-ISDN reduced mortality among black patients with heart failure and reduced ejection fraction,3 guidelines from both the American College of Cardiology/American Heart Association and the Heart Failure Society of America included H-ISDN as a class I recommendation for these patients if they were receiving optimal medical therapy.4–7 H-ISDN therapy is also a class IIa recommendation for patients of all races who experience intolerance to angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).

See Editorial by Taylor
See Clinical Perspective

Adoption of H-ISDN therapy in clinical practice has been slow and variable.6,8 Moreover, the overall effectiveness of H-ISDN therapy in clinical practice may differ from that seen in clinical trial populations, which are carefully selected and receive protocol-driven care and follow-up.1,3,10,11 In clinical practice, patients tend to be older, have a higher burden of comorbid illnesses, and have uncertain adherence to therapy,

Received May 12, 2015; accepted December 30, 2015.

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Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.115.002444
and the specific medication regimens prescribed may differ from those studied in clinical trials. In addition, the clinical effectiveness of H-ISDN therapy in populations other than black patients remains unclear.

We used data from the American Heart Association’s Get With The Guidelines-Heart Failure (GWTG-HF) registry linked with Medicare claims to examine incident use of H-ISDN therapy among patients with heart failure and reduced ejection fraction and its associations with outcomes among black patients and patients of other races.

Methods

Data Sources

Data for this analysis included clinical data from the GWTG-HF registry and Medicare claims from the US Centers for Medicare and Medicaid Services. The registry is an ongoing prospective Web-based registry and quality-improvement program to improve care for patients hospitalized with heart failure. It succeeded the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure registry. Details of the registry have been described previously.12 Quintiles (Cambridge, MA) is the data collection and coordination center for the registry, and the Duke Clinical Research Institute (Durham, NC) is the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes.

The Medicare data included the 100% Medicare inpatient claims files with corresponding denominator files for 2005 through 2011. We used Medicare Part D prescription drug data for 2006 (the year Part D was initiated) through 2011 in a post hoc analysis of medication adherence. The inpatient files contain institutional claims for facility costs covered by Medicare Part A and encrypted beneficiary identifiers; admission and discharge dates; dates of service; diagnosis-related groups; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes; reimbursement amounts; hospital providers; and beneficiary demographic information. The denominator files include encrypted beneficiary identifiers, dates of birth, sex, race/ethnicity, dates of death, and information about program eligibility and enrollment. Medicare Part D data include information from pharmacies about prescriptions covered by Part D insurance plans. Using indirect beneficiary identifiers consisting of hospital identifiers, admission dates, discharge dates, sex, and either birth date or month and year of birth, we linked the registry data to the claims data.13 Because combinations of these identifiers are almost always unique, we were able to identify registry hospital admissions in Medicare claims. For patients with multiple hospital admissions in the registry, we used the first admission for the analysis. After linking the data, we used Medicare beneficiary identifiers to obtain subsequent events for beneficiaries with eligible admissions.

Study Cohort

In the linked data set, we identified patients aged 265 years who were discharged alive between January 1, 2005, and December 31, 2011, and were enrolled in fee-for-service Medicare. We required that patients were discharged alive to home, did not leave against medical advice, were enrolled in fee-for-service Medicare. We required that patients were discharged alive between January 1, 2005, and December 31, 2011, or the date on which the patient’s inpatient claims data were no longer available because the patient enrolled in a Medicare managed care plan. We treated death as a competing risk for the readmission outcomes.

Subgroups

Subgroups of interest included black patients who received an ACE inhibitor or ARB at discharge (because use of an ACE inhibitor or ARB was an exclusion criterion for patients of other races) and patients with an estimated glomerular filtration rate <30 mL/min per 1.73 m². We identified both subgroups on the basis of registry data.

Covariates

Covariates from the registry data included demographic characteristics (ie, age and sex), medical history (ie, anemia, atrial fibrillation or flutter, cerebrovascular disease or transient ischemic attack, chronic obstructive pulmonary disease, depression, diabetes mellitus, heart failure with ischemic cause, hyperlipidemia, hypertension, implantable cardioverter-defibrillator, pacemaker, peripheral vascular disease, renal insufficiency, valvular heart disease, prior history of heart failure, smoking in the previous year, and number of prior admissions to the hospital in the previous year), vital signs at admission (ie, heart rate, respiratory rate, and systolic blood pressure), results of admission laboratory tests (ie, left ventricular ejection fraction, serum creatinine, sodium, and blood urea nitrogen); and discharge medications (ie, ACE inhibitor, aldosterone antagonist, anticoagulant, antiplatelet agent, ARB, β-blocker, digoxin, and diuretic). From the Medicare claims, we used Hierarchical Condition Category codes for the index admission to identify chronic liver disease (codes 25, 26, and 27), dementia (codes 49–50), disability (ie, 68 (paraplegia), 69 (spinal cord disorders or injuries), 100 (hemiplegia or hemiparesis), 101 (paralysis), 102 (speech, language, cognitive, and perceptual deficits), and 177 and 178 (amputation and complications)), protein-calorie malnutrition (code 21), and major psychiatric disorders (codes...
Statistical Analysis
We describe the baseline characteristics of the study population by treatment group, using proportions for categorical variables and means with SDs for continuous variables. We tested for differences between groups using $\chi^2$ tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. We also compared treatment groups using standardized differences, calculated as the difference in means or proportions divided by a pooled estimate of the SD.16,19

Compared with traditional significance tests, standardized differences are not as sensitive to sample size and are useful in identifying meaningful differences. A standardized difference $>$0.1 is considered meaningful.18

To describe observed outcomes for each treatment group, we compared the unadjusted cumulative incidence of each outcome at 3 years after discharge between treatment groups. For mortality, we calculated incidence at 3 years based on Kaplan–Meier estimates and used log-rank tests to test for differences. For the readmission outcomes, we calculated cumulative incidence estimates to account for the competing risk of mortality, and we used Gray tests to test for differences between groups.20

We estimate the association between treatment and outcomes using Cox proportional hazards models. We used robust SEs in all models to account for clustering of patients by hospital. We imputed missing values for variables with low rates of missingness (ie, <5%) by using the dominant value for categorical variables and the median value for continuous variables, and we treated missing data as a separate category for other variables. To address confounding by observed covariates, we used an inverse probability-weighted estimator. We calculated the inverse probability weights using the propensity score—the probability of a patient receiving the treatment he or she actually received conditional on observed covariates.21—by fitting a logistic regression model with H-ISDN therapy as the dependent variable, and the baseline characteristics of the study population after application of weights as the independent variables. To assess the adequacy of the treatment selection model, we again compared the baseline characteristics between the groups after weighting. We used weighted $\chi^2$ tests to test for differences in categorical variables and weighted ANOVA to test for differences in continuous variables. We calculated standardized differences between the groups to assess covariate balance.

In a post hoc analysis of adherence to H-ISDN therapy, we matched the mortality file to the patient identification in the registry file and the identification in the Medicare Part D file for all patients in the analysis between 2006 and 2011. We described prescriptions filled for hydralazine nitrate combinations (ie, fixed-dose combination of hydralazine and isosorbide dinitrate, hydralazine and isosorbide mononitrate, or hydralazine and isosorbide dinitrate), as well as mineralocorticoid antagonists as a positive control within 90 days after hospital discharge.

We report 95% confidence intervals and used $\alpha=0.05$ to establish the statistical significance of tests. All tests were 2-sided. We used SAS version 9.2 (SAS Institute Inc) for all analyses. The Institutional Review Board of the Duke University Health System approved the study.

Results
The Figure shows the derivation of the study cohort. The cohort consisted of 12,300 patients with heart failure and reduced ejection fraction from 243 hospitals, including 1392 black patients and 10,908 patients of other races. After further restriction of patients of other races to those with contraindication to ACE inhibitors or ARBs or those who were eligible for an ACE inhibitor or ARB but did not receive a prescription at discharge, the cohort included 3271 patients of other races.

Table 1 shows the baseline characteristics of the study population. Compared with the untreated groups, patients in the treated groups were of similar age and more frequently had diabetes mellitus, heart failure with ischemic cause, and renal insufficiency. The treated groups also had higher mean systolic blood pressure, greater use of $\beta$-blockers, and lower use of diuretics at discharge. Black patients in the treated group were more likely to have received an implantable cardioverter-defibrillator and to have a prior history of hospital admission, but they had lower use of ACE inhibitors or ARBs, compared with black patients in the untreated group. Patients of other races in the treated group less frequently had atrial fibrillation or flutter when compared with patients of other races in the untreated group.

Table I in the Data Supplement shows the baseline characteristics of the study population after application of weights.
Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Black Patients</th>
<th>Patients of Other Races</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H-ISDN at Discharge, n (%), P Value, Standardized Difference*</td>
<td>H-ISDN at Discharge, n (%), P Value, Standardized Difference*</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>Yes (n=316) 75.3 (7.6), No (n=1076) 75.9 (8.1), 0.26 0.07</td>
<td>Yes (n=595) 79.3 (7.7), No (n=2676) 80.2 (7.9), 0.01 0.11</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–79 y</td>
<td>230 (72.8), 737 (68.5), 0.15 0.09</td>
<td>293 (49.2), 1188 (44.4), &lt;0.001 0.20</td>
</tr>
<tr>
<td>≥80 y</td>
<td>86 (27.2), 339 (31.5)</td>
<td>302 (50.8), 1488 (55.6)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>138 (43.7), 527 (49.0), 0.10 0.11</td>
<td>214 (36.0), 975 (36.4), 0.83 0.01</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>56 (17.7), 150 (13.9), 0.10 0.10</td>
<td>113 (19.0), 491 (18.8), 0.71 0.02</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>74 (23.4), 238 (22.1), 0.63 0.03</td>
<td>206 (34.6), 1189 (44.4), &lt;0.001 0.20</td>
</tr>
<tr>
<td>Cerebrovascular accident or TIA</td>
<td>66 (20.9), 185 (17.2), 0.13 0.09</td>
<td>105 (17.6), 427 (16.6), 0.31 0.05</td>
</tr>
<tr>
<td>COPD</td>
<td>91 (28.8), 277 (25.7), 0.28 0.07</td>
<td>164 (27.6), 753 (28.1), 0.78 0.01</td>
</tr>
<tr>
<td>Depression</td>
<td>17 (5.4), 52 (4.8), 0.69 0.03</td>
<td>56 (9.4), 248 (9.3), 0.91 0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>159 (50.3), 421 (39.1), &lt;0.001 0.23</td>
<td>263 (44.2), 987 (36.9), 0.001 0.15</td>
</tr>
<tr>
<td>Heart failure with ischemic cause</td>
<td>179 (56.6), 510 (47.4), 0.004 0.19</td>
<td>455 (76.5), 1903 (71.1), 0.01 0.12</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>142 (44.9), 445 (41.4), 0.26 0.07</td>
<td>311 (52.3), 1376 (51.4), 0.71 0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>263 (83.2), 896 (83.3), 0.99 0.001</td>
<td>429 (72.1), 1802 (67.3), 0.02 0.10</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator</td>
<td>78 (24.7), 201 (18.7), 0.02 0.15</td>
<td>139 (23.4), 571 (21.3), 0.28 0.05</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>44 (13.9), 128 (11.9), 0.34 0.06</td>
<td>96 (16.1), 563 (21.0), 0.01 0.13</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>55 (17.4), 93 (8.6), &lt;0.001 0.26</td>
<td>110 (18.5), 419 (15.7), 0.09 0.08</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>82 (25.9), 178 (16.5), &lt;0.001 0.23</td>
<td>250 (42.0), 685 (25.6), &lt;0.001 0.35</td>
</tr>
<tr>
<td>Smoking in the previous year</td>
<td>54 (17.1), 191 (17.8), 0.79 0.02</td>
<td>54 (9.1), 265 (9.9), 0.54 0.03</td>
</tr>
<tr>
<td>No. of all-cause hospital admissions in the prior year, mean (SD)</td>
<td>1.8 (2.1), 1.3 (1.7), &lt;0.001 0.27</td>
<td>1.4 (1.6), 1.4 (1.6), 0.87 0.01</td>
</tr>
<tr>
<td>Chronic liver disease, n (%)</td>
<td>…† …† 0.15 0.10</td>
<td>…† …† 0.74 0.02</td>
</tr>
<tr>
<td>Dementia</td>
<td>19 (6.0), 83 (7.7), 0.31 0.07</td>
<td>30 (5.0), 178 (6.7), 0.15 0.07</td>
</tr>
<tr>
<td>Disability</td>
<td>14 (4.4), 28 (2.6), 0.09 0.10</td>
<td>…† …† 0.56 0.03</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>…† …† 0.08 0.12</td>
<td>25 (4.2), 133 (5.0), 0.43 0.04</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>…† …† 0.85 0.01</td>
<td>…† …† 0.14 0.08</td>
</tr>
<tr>
<td>Vital signs at admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, mean (SD), beats per minute</td>
<td>86.3 (20.1), 88.0 (19.9), 0.20 0.08</td>
<td>83.0 (19.3), 85.2 (20.2), 0.01 0.11</td>
</tr>
<tr>
<td>Heart rate, n (%)</td>
<td>0.79 0.04</td>
<td>0.06 0.11</td>
</tr>
<tr>
<td>&lt;80 beats per minute</td>
<td>115 (36.4), 369 (34.3)</td>
<td>284 (47.7), 1163 (43.5)</td>
</tr>
<tr>
<td>80–100 beats per minute</td>
<td>129 (40.8), 456 (42.4)</td>
<td>215 (36.1), 979 (36.6)</td>
</tr>
<tr>
<td>&gt;100 beats per minute</td>
<td>72 (22.8), 251 (23.3)</td>
<td>96 (16.1), 534 (20.0)</td>
</tr>
<tr>
<td>Respiratory rate, n (%)</td>
<td>0.66 0.03</td>
<td>0.01 0.11</td>
</tr>
<tr>
<td>&lt;30 breaths per minute</td>
<td>299 (94.6), 1011 (94.0)</td>
<td>546 (91.8), 2530 (94.5)</td>
</tr>
<tr>
<td>≥30 breaths per minute</td>
<td>17 (5.4), 65 (6.0)</td>
<td>49 (8.2), 146 (5.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>147 (31.9), 141 (29.4), 0.01 0.17</td>
<td>139 (28.4), 128 (25.4), &lt;0.001 0.42</td>
</tr>
<tr>
<td>Systolic blood pressure, n (%)</td>
<td>0.001 0.23</td>
<td>&lt;0.001 0.40</td>
</tr>
<tr>
<td>&lt;110 mmHg</td>
<td>39 (12.3), 138 (12.8)</td>
<td>82 (13.8), 650 (24.3)</td>
</tr>
<tr>
<td>110–150 mmHg</td>
<td>139 (44.0), 584 (54.3)</td>
<td>325 (54.6), 1576 (58.9)</td>
</tr>
<tr>
<td>&gt;150 mmHg</td>
<td>138 (43.7), 354 (32.9)</td>
<td>188 (31.6), 450 (16.8)</td>
</tr>
</tbody>
</table>

Tests at admission

| Left ventricular ejection fraction, mean (SD), % | 24.7 (7.6), 24.4 (7.8), 0.64 0.03 | 26.6 (6.9), 26.4 (7.3), 0.40 0.04 |

(Continued)
for the inverse probability of treatment. There were no significant differences between groups, except that treated black patients had lower use of ACE inhibitors or ARBs and higher use of aldosterone antagonists than untreated black patients, and treated patients of other races had higher use of β-blockers than those in the untreated group. Both treated groups had lower diuretic use than their respective untreated groups.

As shown in Table 2, rates of all-cause mortality, all-cause readmission, and cardiovascular readmission at 3 years were similar between the treatment groups for both black patients and patients of other races. Table 3 shows the estimated associations between H-ISDN therapy and the study outcomes. In the unadjusted analysis, there were no associations between treatment and the study outcomes. After inverse probability weighting, there were no significant differences in the hazards of all-cause mortality, all-cause readmission, or cardiovascular readmission.

In subgroup analyses, there were no significant associations between treatment and study outcomes among black patients by ACE inhibitor or ARB use at discharge or by having estimated glomerular filtration rate <30. Among patients of other races, H-ISDN therapy was associated with higher rates of all-cause and cardiovascular readmission in patients with estimated glomerular filtration rate <30.

In the analysis of adherence to H-ISDN therapy, 4935 eligible patients (44%) were enrolled in Medicare Part D during the first 90 days after the index hospitalization (Table II in the Data Supplement). Of these, 269 (3%) filled an outpatient prescription for hydralazine nitrates within 90 days after discharge. Of 353 patients who were prescribed a hydralazine nitrate at discharge, 161 (46%) filled an outpatient prescription within 90 days. Among 161 black patients, 69 (43%) filled a prescription within 90 days. Among patients of other races who were intolerant of ACE inhibitors of ARBs, the fill rate was 48% (92/191). For the positive control, of the 4935 patients who were eligible for H-ISDN therapy and were enrolled in Medicare Part D, 1162 (24%) were discharged with a mineralocorticoid receptor antagonist. Of these, 876 (75%) filled an outpatient prescription within 90 days after discharge (including 73% of black patients and 76% of patients of other races).

On further analysis of the formulation of H-ISDN used in the Medicare Part D subgroup, 87.3% of patients received individual hydralazine and individual nitrate agents, whereas 12.7% received the fixed-dose combination, as was used in A-HeFT. We were unable to separately evaluate the clinical effectiveness of the fixed-dose combination because only a small number of patients were receiving it.

### Discussion

Using a large registry of patients hospitalized with heart failure in the United States, we found that initiation of H-ISDN...
therapy at discharge was low among both black patients and patients of other races. Moreover, initiation of H-ISDN therapy at discharge was not associated with lower rates of mortality, all-cause readmission, or cardiovascular readmission within 3 years. We also observed poor adherence to H-ISDN therapy, with more than half of patients who were discharged on the therapy not filling an outpatient prescription for the therapy within the first 90 days after discharge. These findings illustrate the important difference between clinical efficacy and effectiveness; the need to implement guideline-directed medical therapies in a manner that replicates as closely as possible the treatments observed in clinical trial settings; and the need to ensure that clinical trial evidence is broadly generalizable.

The clinical trial A-HeFT showed significant efficacy of the fixed-dose combination of H-ISDN compared with usual care among black patients with heart failure and reduced ejection fraction, but adoption of the therapy was slow and varied across centers. Although a fixed combination of H-ISDN was used in A-HeFT, patients in clinical practice commonly receive individual generic formulations at different doses. The cost of a nongeneric fixed-dose combination of H-ISDN and interactions with other drugs such as erectile dysfunction medications may limit its use in practice. Some studies have suggested that generic formulations of H-ISDN are not bioequivalent to the fixed-dose combination. Thus, a potential explanation for our findings is that the specific agent and dosing found to be efficacious in A-HeFT is not being used in clinical practice.

Trial settings are often highly controlled and difficult to replicate in clinical practice, leading to questions of whether therapies such as H-ISDN can be truly effective in real-world settings. Most participants in A-HeFT were subject to titration to high doses of the therapy that are difficult to replicate in clinical practice. Although younger patients may be able to tolerate high doses, many older patients cannot because of side effects, potentially limiting the effectiveness of the regimen in real-world settings. Approximately 30% of participants in A-HeFT reported dizziness and other side effects of H-ISDN.

In the absence of the rigor of careful clinical trial management, adherence and persistence to such a regimen might be problematic. The rate of H-ISDN use is relatively low in clinical practice, and physicians may select patients for H-ISDN for whom other therapies have failed. A recent analysis of Medicare Part D participants found that only 3% of patients in our analysis and only 46% of patients who were discharged on H-ISDN actually filled a prescription within 90 days of discharge. This adherence rate is lower than what has been previously reported for ACE inhibitors or ARBs, β-blockers, and mineralocorticoid antagonists for patients with heart failure. For the positive control in this study, mineralocorticoid antagonist fill rates after discharge for patients who were discharged on the drug were 75%, consistent with previous studies. Thus, the lack of clinical differences seen in our analysis may largely be a result of low rates of persistence with H-ISDN therapy after discharge. In addition, the large majority of patients in this study were not receiving the fixed-dose combination that was studied in A-HeFT. One of the contributing possibilities for the lack of clinical effectiveness we observed may be the different formulations of H-ISDN along with poor adherence.

Another potential explanation for our findings is that H-ISDN therapy has limited effectiveness among older patients who begin H-ISDN therapy de novo during a heart failure hospitalization. Patients in our study were on average 20 to 25 years old and had more comorbid conditions than A-HeFT participants, but they had similar ejection fraction. It is unclear how well trial results extrapolate to patients who are not black, especially with changes in clinical care since the early trials of H-ISDN. Recent data from the A-HeFT genetic substudy suggest a strong correlation between guanine nucleotide-binding proteins, β-3 subunit genotype, and responsiveness to H-ISDN therapy. Previous reports identified other genotypes correlated with outcomes. A prospective trial is now testing whether these candidate genotypes obviate considerations of race in the effectiveness of H-ISDN therapy.

Observational studies from heart failure registries have repeatedly demonstrated a low use of H-ISDN in practice—4.5% among black patients and 2.6% among white patients in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure, and 7.3% among black patients in the Improving Evidence-Based Care for Heart Failure in Outpatient Cardiology Practices (IMPROVE-HF) registry. In a recent study of patients in the GWTG-HF registry examining current use, temporal trends, and clinical characteristics of H-ISDN in clinical practice, only 5115 of the 43,498 eligible patients overall (12.6%) and 2500 of 11,185 eligible black patients (22.4%) received H-ISDN at discharge, n (Rate)∗

### Table 2. Cumulative Incidence of Mortality and Readmission Within 3 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Black Patients</th>
<th>Patients of Other Races</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H-ISDN at Discharge, n (Rate)∗</td>
<td>H-ISDN at Discharge, n (Rate)∗</td>
</tr>
<tr>
<td></td>
<td>Yes (n=316)</td>
<td>Yes (n=595)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>149 (53.9)</td>
<td>357 (68.9)</td>
</tr>
<tr>
<td>All-cause readmission</td>
<td>241 (85.7)</td>
<td>459 (84.6)</td>
</tr>
<tr>
<td>Cardiovascular readmission†</td>
<td>192 (68.9)</td>
<td>325 (60.8)</td>
</tr>
</tbody>
</table>

H-ISDN indicates hydralazine–isosorbide dinitrate.

∗Values are expressed as number of events (cumulative incidence per 100 patients at risk) unless otherwise indicated.
†Subcategorization of cardiovascular readmission refers to the first readmission.
H-ISDN therapy at discharge.⁹ In all of these studies, patients who received the therapy often had more advanced disease and more comorbid conditions such as renal insufficiency. Chronic renal failure was one of the most important predictors of H-ISDN use among patients in this cohort (adjusted odds ratio, 2.56; 95% confidence interval, 2.33–2.82). H-ISDN use before admission was a critical factor in whether patients were discharged on the therapy, with 80.8% of patients receiving H-ISDN therapy at discharge if they were on it before admission, compared with 9.6% of patients without H-ISDN therapy before admission.

Although previous trials led to H-ISDN being a guideline-recommended therapy for patients with heart failure and reduced ejection fraction, particularly black patients, our analysis of clinical effectiveness analysis in the GWTG-HF registry suggests the need for either more rigorous use of the therapy at the doses studied in randomized clinical trials, with high adherence and persistence, or its true pharmaico-equivalent therapy given as the generic alternatives be applied in actual clinical practice. Moreover, it is important to understand the best methods for implementing trial evidence into clinical practice. We observed a modest association between H-ISDN use and both all-cause and cardiovascular readmission for groups other than black patients, although the results were limited by small sample size and wide confidence intervals. Overall, our findings highlight the importance of careful implementation and adherence in clinical practice, as well as the need for conducting future clinical trials that are more generalizable to real-world settings to truly test whether H-ISDN therapy is beneficial in racial subgroups and among older patients.

Our study has limitations. Because this was an observational study, we could not eliminate the possibility of unmeasured confounding and selection bias. Some clinical variables that may be associated with H-ISDN use and clinical outcomes were not available, including New York Heart Association functional class, symptom severity, renal function stability, and dosing of medications. We could not account for socioeconomic status, level of education, or the patient’s understanding of their health status. We did not have data on specific H-ISDN formulation, dosing, and postdischarge adherence, as well as persistence other than for patients enrolled in Medicare Part D, and some generic prescriptions filled but not billed for may have been missed. The observed prescription rate of H-ISDN may underestimate the true prescription rate because Part D participants can fill prescriptions at discount $4 formularies without creating a prescription drug event. However, in 2007, the vast majority of $4 prescriptions were adjudicated through Part D, and previous analyses noted minimal nonadjudicated use of discount drugs.²⁷ Because the population included older patients enrolled in fee-for-service Medicare, the findings may not be generalizable to all patients with heart failure and reduced ejection fraction. Finally, the GWTG-HF registry is a voluntary quality-improvement program that may not represent all hospitals.

**Conclusions**

In this observational study, initiation of H-ISDN therapy at hospital discharge was not independently associated with mortality, all-cause readmission, or cardiovascular readmission among eligible older patients with heart failure and reduced ejection fraction. Adherence to therapy after hospital discharge was low. Additional research is needed to evaluate the clinical effectiveness of H-ISDN in the larger population of patients with heart failure and to ensure that the efficacy observed in rigorous clinical trials is better translated into clinical practice.

**Acknowledgments**

Damon M. Seils, MA, Duke University, provided editorial assistance and prepared the article. Mr Seils did not receive compensation for his assistance apart from his employment at the institution where the study was conducted.

**Sources of Funding**

This project was supported, in part, by grant U19HS021092 from the Agency for Healthcare Research and Quality. Dr Khazanie was supported, in part, by grant T32HL069749 from the National Heart, Lung, and Blood Institute.

**Disclosures**

Dr Curtis received research funding from GlaxoSmithKline and Johnson & Johnson. Dr Butler reported serving as a consultant for Amgen, Bayer, Cardiocell, Celladon, Novartis, Ono Pharmaceutical, Relypsy, Takeda, Trevena, and Zensun. Dr Bhatt reported serving on advisory boards for Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; serving on
boards of directors for Boston VA Research Institute and Society of Cardiovascular Patient Care; serving as chair of the American Heart Association Get With The Guidelines Steering Committee; serving on data monitoring committees for Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; receiving honoraria from American College of Cardiology, Belvoir Publications, Duke Clinical Research Institute, Harvard Clinical Research Institute, HMP Communications, Population Health Research Institute, Slack Publications, and WebMD; serving as associate editor of Clinica Cardiologica and section editor of Journal of the American College of Cardiology; receiving research funding from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, Sanofi Aventis, and The Medicines Company; and conducting unfunded research for FlowCo, PLx Pharma, and Takeda. Dr Peterson reported receiving research funding from Eli Lilly & Company, Janssen Pharmaceuticals, Inc, and American Heart Association and serving as a consultant or advisory board member for Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Pharmaceuticals, Inc, Pfizer, and Genentech Inc. Dr Fonarow reported serving as a consultant for Amgen, Bayer, GSK, Novartis, and Janssen. Dr Fonarow holds the Eliot Corday Chair of Cardiovascular Medicine at UCLA and is also supported by the Ahmanson Foundation (Los Angeles, CA). Dr Hernandez reported serving as a consultant for AstraZeneca, Bristol-Myers Squibb, Corthera, Cytokinetics, and Johnson & Johnson and receiving research funding from Amylin, Bristol-Myers Squibb, Johnson & Johnson, and Portola. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

References


14. Cole RT, Kalogeropoulos AP, Georgiopoulou VV, Gheorghiade M, Quyyumi A, Yancy C, Butler J. Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and
Hydralazine–isosorbide dinitrates are an established group of medications that have been shown in clinical trials to reduce mortality and morbidity and to improve quality of life among patients with heart failure and reduced ejection fraction. They are recommended as class I therapies for black patients and class IIa therapies for patients of all races who experience intolerance to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. We sought out to test if the effectiveness of this medication combination in clinical trials translated to real-world effectiveness. We observed that initiation of therapy was not associated with lower rates of mortality or readmission. However, rates of initiation of hydralazine–isosorbide dinitrates were low among patients of all races. We also observed poor adherence to therapy after discharge. Thus, the lack of clinical differences seen may largely be a result of low rates of persistence of therapy after discharge. Our study highlights the importance of careful implementation and adherence to medical therapy in clinical practice.
Clinical Effectiveness of Hydralazine–Isosorbide Dinitrate Therapy in Patients With Heart Failure and Reduced Ejection Fraction: Findings From the Get With The Guidelines-Heart Failure Registry

Prateeti Khazanie, Li Liang, Lesley H. Curtis, Javed Butler, Zubin J. Eapen, Paul A. Heidenreich, Deepak L. Bhatt, Eric D. Peterson, Clyde W. Yancy, Gregg C. Fonarow and Adrian F. Hernandez

_Circ Heart Fail_. 2016;9:e002444
doi: 10.1161/CIRCHEARTFAILURE.115.002444
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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SUPPLEMENTAL MATERIAL

**Supplemental Table 1.** Baseline Characteristics of the Study Population After Application of Inverse Probability Weights

**Supplemental Table 2.** Medication Adherence Within 90 Days of Discharge Among Patients with Medicare Part D Coverage
## Supplemental Table 1. Baseline Characteristics of the Study Population After Application of Inverse Probability Weights

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Black Patients</th>
<th></th>
<th></th>
<th>Patients of Other Races</th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>H-ISDN at Discharge, No. (%)</td>
<td>P Value</td>
<td>Standardized Difference</td>
<td>H-ISDN at Discharge, No. (%)</td>
<td>P Value</td>
<td>Standardized Difference</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>Yes (n = 316)</td>
<td>75.9 (7.9)</td>
<td>.80</td>
<td>.02</td>
<td>Yes (n = 595)</td>
<td>80.2 (7.8)</td>
</tr>
<tr>
<td></td>
<td>No (n = 1076)</td>
<td>75.7 (8.1)</td>
<td></td>
<td></td>
<td>No (n = 2676)</td>
<td>80.1 (7.9)</td>
</tr>
<tr>
<td>Age group, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-79 y</td>
<td>225 (70.7)</td>
<td>745 (69.2)</td>
<td>.60</td>
<td>.03</td>
<td>270 (45.3)</td>
<td>1214 (45.3)</td>
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<tr>
<td>≥ 80 y</td>
<td>93 (29.3)</td>
<td>332 (30.8)</td>
<td></td>
<td></td>
<td>327 (54.7)</td>
<td>1463 (54.7)</td>
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<td>Women, No. (%)</td>
<td>158 (49.6)</td>
<td>517 (48.1)</td>
<td>.62</td>
<td>.03</td>
<td>221 (37.0)</td>
<td>971 (36.3)</td>
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<td>Medical history, No. (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anemia</td>
<td>48 (15.0)</td>
<td>160 (14.9)</td>
<td>.96</td>
<td>.004</td>
<td>114 (19.0)</td>
<td>493 (18.4)</td>
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<tr>
<td>Atrial fibrillation/ flutter</td>
<td>75 (2379)</td>
<td>245 (22.7)</td>
<td>.72</td>
<td>.02</td>
<td>256 (42.8)</td>
<td>1141 (42.6)</td>
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<td>Cerebrovascular accident or TIA</td>
<td>60 (18.8)</td>
<td>196 (18.2)</td>
<td>.79</td>
<td>.02</td>
<td>90 (15.1)</td>
<td>435 (16.3)</td>
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<tr>
<td>COPD</td>
<td>80 (25.3)</td>
<td>285 (26.5)</td>
<td>.66</td>
<td>.03</td>
<td>163 (27.2)</td>
<td>751 (28.1)</td>
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<tr>
<td>Depression</td>
<td>15 (4.6)</td>
<td>53 (5.0)</td>
<td>.79</td>
<td>.02</td>
<td>57 (9.5)</td>
<td>249 (9.3)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>130 (40.8)</td>
<td>448 (41.6)</td>
<td>.82</td>
<td>.02</td>
<td>243 (40.7)</td>
<td>1026 (38.3)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>131 (41.2)</td>
<td>455 (42.3)</td>
<td>.73</td>
<td>.02</td>
<td>304 (50.9)</td>
<td>1381 (51.6)</td>
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<tr>
<td>Hypertension</td>
<td>260 (81.9)</td>
<td>897 (83.3)</td>
<td>.56</td>
<td>.04</td>
<td>396 (66.3)</td>
<td>1826 (68.2)</td>
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<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>63 (19.8)</td>
<td>217 (20.1)</td>
<td>.91</td>
<td>.008</td>
<td>132 (22.1)</td>
<td>582 (21.8)</td>
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<tr>
<td>Heart failure with ischemic etiology</td>
<td>152 (47.8)</td>
<td>532 (49.4)</td>
<td>.61</td>
<td>.03</td>
<td>431 (72.1)</td>
<td>1932 (72.2)</td>
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<tr>
<td>Pacemaker</td>
<td>38 (11.8)</td>
<td>133 (12.3)</td>
<td>.81</td>
<td>.02</td>
<td>112 (18.8)</td>
<td>539 (20.2)</td>
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<td>Peripheral vascular disease</td>
<td>35 (11.0)</td>
<td>116 (10.7)</td>
<td>.90</td>
<td>.01</td>
<td>101 (16.9)</td>
<td>436 (16.3)</td>
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<td>Renal insufficiency</td>
<td>58 (18.3)</td>
<td>203 (18.8)</td>
<td>.83</td>
<td>.01</td>
<td>170 (28.5)</td>
<td>769 (28.7)</td>
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<td>Smoking in the previous year</td>
<td>55 (17.4)</td>
<td>191 (17.7)</td>
<td>.90</td>
<td>.01</td>
<td>59 (9.8)</td>
<td>262 (9.8)</td>
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<td>No. of all-cause hospital admissions in the prior year, mean (SD)</td>
<td>1.4 (1.8)</td>
<td>1.4 (1.9)</td>
<td>.85</td>
<td>.01</td>
<td>1.4 (1.8)</td>
<td>1.4 (1.6)</td>
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<td>Claims-based history at admission, No. (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Chronic liver disease</td>
<td>6 (1.8)</td>
<td>16 (1.5)</td>
<td>.71</td>
<td>.02</td>
<td>4 (0.6)</td>
<td>19 (0.7)</td>
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<tr>
<td>Dementia</td>
<td>20 (6.2)</td>
<td>80 (7.4)</td>
<td>.63</td>
<td>.03</td>
<td>35 (5.9)</td>
<td>170 (6.3)</td>
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<tr>
<td>Disability</td>
<td>11 (3.4)</td>
<td>34 (3.1)</td>
<td>.82</td>
<td>.01</td>
<td>8 (1.3)</td>
<td>43 (1.6)</td>
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<tr>
<td>Malnutrition</td>
<td>12 (3.9)</td>
<td>33 (3.1)</td>
<td>.48</td>
<td>.04</td>
<td>25 (4.1)</td>
<td>128 (4.8)</td>
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<tr>
<td>Psychiatric disorder</td>
<td>3 (0.8)</td>
<td>9 (0.9)</td>
<td>.93</td>
<td>.01</td>
<td>3 (0.6)</td>
<td>22 (0.8)</td>
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<td>Vital signs at admission</td>
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<tr>
<td>Heart rate, mean (SD), beats/min</td>
<td>87.9 (21.1)</td>
<td>88.0 (20.0)</td>
<td>.95</td>
<td>.004</td>
<td>84.1 (19.9)</td>
<td>84.9 (20.1)</td>
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<tr>
<td>Heart rate, No. (%)</td>
<td>.85</td>
<td>.04</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 80 beats/min</td>
<td>107 (33.7)</td>
<td>373 (34.6)</td>
<td></td>
<td></td>
<td>268 (44.9)</td>
<td>1184 (44.2)</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
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<tr>
<td>80-100 beats/min</td>
<td>131 (41.2)</td>
<td>450 (41.8)</td>
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<tr>
<td>&gt; 100 beats/min</td>
<td>80 (25.1)</td>
<td>254 (23.6)</td>
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<td>Respiratory rate, No. (%)</td>
<td>.81 .02</td>
<td>.75 .02</td>
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<tr>
<td>&lt; 30 breaths/min</td>
<td>298 (93.7)</td>
<td>1,013 (94.1)</td>
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<tr>
<td>≥ 30 breaths/min</td>
<td>20 (6.3)</td>
<td>64 (5.9)</td>
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<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>143 (29.5)</td>
<td>142 (29.9)</td>
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<tr>
<td>Systolic blood pressure, No. (%)</td>
<td>.63 .06</td>
<td>.97 .01</td>
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<tr>
<td>&lt; 110 mm Hg</td>
<td>35 (11.0)</td>
<td>136 (12.6)</td>
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<td></td>
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<tr>
<td>110-150 mm Hg</td>
<td>174 (54.8)</td>
<td>562 (52.2)</td>
<td></td>
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<tr>
<td>&gt; 150 mm Hg</td>
<td>109 (34.2)</td>
<td>379 (35.2)</td>
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<td>Tests at admission</td>
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<tr>
<td>Left ventricular ejection fraction, mean (SD), %</td>
<td>24.4 (7.4)</td>
<td>24.5 (7.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Serum creatinine, mean (SD), mg/dL</td>
<td>1.6 (0.9)</td>
<td>1.8 (7.3)</td>
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<td></td>
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<tr>
<td>Serum creatinine, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt; 1.5 mg/dL</td>
<td>184 (57.8)</td>
<td>623 (57.9)</td>
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<tr>
<td>1.5-2.0 mg/dL</td>
<td>85 (26.8)</td>
<td>287 (26.6)</td>
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<tr>
<td>&gt; 2.0 mg/dL</td>
<td>49 (15.4)</td>
<td>167 (15.5)</td>
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<td></td>
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<tr>
<td>Serum urea nitrogen, mg/dL</td>
<td>27.3 (15.8)</td>
<td>26.9 (16.4)</td>
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<td></td>
<td></td>
<td></td>
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<td>Serum urea nitrogen, No. (%)</td>
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<tr>
<td>&lt; 20 mg/dL</td>
<td>111 (35.0)</td>
<td>384 (35.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>20-50 mg/dL</td>
<td>182 (57.4)</td>
<td>608 (56.4)</td>
<td></td>
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<tr>
<td>&gt; 50 mg/dL</td>
<td>24 (7.6)</td>
<td>85 (7.9)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Medications at discharge, No. (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitor</td>
<td>179 (56.3)</td>
<td>686 (63.7)</td>
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<td>ARB</td>
<td>48 (15.3)</td>
<td>158 (14.7)</td>
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<td>ACE inhibitor and/or ARB</td>
<td>222 (69.9)</td>
<td>830 (77.1)</td>
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<td>Aldosterone antagonist</td>
<td>85 (26.8)</td>
<td>240 (22.3)</td>
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<td>β-Blocker</td>
<td>280 (88.3)</td>
<td>933 (86.6)</td>
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<td>Digoxin</td>
<td>69 (21.7)</td>
<td>199 (18.5)</td>
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<tr>
<td>Diuretic</td>
<td>169 (53.1)</td>
<td>664 (61.7)</td>
<td></td>
<td></td>
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</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; H-ISDN, hydralazine-isosorbide dinitrate; TIA, transient ischemic attack.

SI conversion factors: To convert creatinine from mg/dL to µmol/L, multiply by 88.4; and to convert urea nitrogen from mg/dL to mmol/L, multiply by 0.357.

a Calculated as the difference in means or proportions divided by a pooled estimate of the SD. A standardized difference greater than 0.1 is typically considered meaningful.

b In accordance with the privacy policy of the Centers for Medicare & Medicaid Services, data for cells containing 10 or fewer observations and data for cells that would allow for calculation of cells containing 10 or fewer observations are not reported.
**Supplemental Table 2. Medication Adherence Within 90 Days of Discharge Among Patients with Medicare Part D Coverage**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Hydralazine-Nitrate</th>
<th>Mineralocorticoid Receptor Antagonist (Positive Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part D patients who filled an outpatient prescription within 90 days (irrespective of whether discharged on the drug), No. (%)</td>
<td>161/4935 (3)</td>
<td>876/4935 (18)</td>
</tr>
<tr>
<td>Part D patients who filled an outpatient prescription among those who were discharged from the hospital on the drug, No. (%)</td>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>161/353 (46)</td>
<td>876/1162 (75)</td>
</tr>
<tr>
<td>Black patients</td>
<td>69/161 (43)</td>
<td>107/146 (73)</td>
</tr>
<tr>
<td>Patients of other races</td>
<td>92/192 (48)</td>
<td>769/1016 (76)</td>
</tr>
</tbody>
</table>