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Clinical Effectiveness of Hydralazine-Isosorbide Dinitrate Therapy in Patients With Heart Failure and Reduced Ejection Fraction: Findings From the GWTG-HF Registry

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Abstract

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 (ACE) inhibitors or angiotensin II receptor blockers (ARBs). 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 ACE inhibitor or ARB 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% 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.

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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.

Keywords

cardiomyopathy; drug; 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 (ACC/AHA) and the Heart Failure Society of America (HFSA) 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).

Adoption of H-ISDN therapy in clinical practice has been slow and variable.[8,9] 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, 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 AHA'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 & 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 (OPTIMIZE-HF) registry. Details of the registry have been described previously.[12] Quintiles (Cambridge, Massachusetts) is the data collection and coordination center for the registry, and the Duke Clinical Research Institute (Durham, North Carolina) 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 (DRGs), *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 65 years or older 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 not transferred to another short-term hospital or hospice, had a principal cardiac or heart failure diagnosis, and were eligible for H-ISDN therapy according to registry documentation of left ventricular ejection fraction of 40% or less or a qualitative description of moderate or severe left ventricular systolic dysfunction. We required that patients had not received H-ISDN therapy before the index hospitalization in order to avoid prevalent user bias.[14] The date of cohort entry was the date of discharge from the index hospitalization. Race and ethnicity were recorded by admissions or medical staff during registration on the basis of patient self-report. Race was recorded as part of a multiple-choice data entry tool as American Indian or Alaska native, Asian, black, native Hawaiian or Pacific Islander, or white. The tool included a separate data element for Hispanic ethnicity. For patients who did not identify as black, we further restricted the definition of eligibility for H-ISDN therapy to patients with a contraindication to ACE inhibitors or ARBs, because patients who receive ACE inhibitor or ARB therapy concomitant with H-ISDN may represent a population with worse hypertension necessitating use of H-ISDN.

Treatment

The treatment of interest was H-ISDN therapy prescribed at discharge as recorded in the registry. The treated group included all patients who received the prescription at discharge from the index hospitalization; the untreated group included all other patients in the study population. We stratified the cohort based on black race and other race as recorded in the registry, comparing treated black patients with untreated black patients and comparing treated patients of other races with untreated patients of other races.

Outcomes

The outcomes of interest were all-cause mortality, all-cause readmission, and cardiovascular readmission within 3 years. We determined all-cause mortality on the basis of death dates in the Medicare denominator files, and we identified readmissions on the basis of Medicare inpatient claims. We defined all-cause readmission as any new nonelective inpatient claim, excluding the index hospitalization claim, transfers to or from another hospital, and admissions for rehabilitation. We defined cardiovascular readmission using DRGs 104–112, 115–118, 121–145, 479, 514–518, 525–527, 535, 536, and 547–558 before October 1, 2007, and DRGs 215–238, 242–254, 258–262, and 280–316 on or after October 1, 2007.[15]

The follow-up period for all events was 3 years after discharge from the index hospitalization. We calculated days to events from the date of discharge. For patients who did not experience an event, we defined a censoring date as the earliest of 3 years after discharge, the end of the period for which data were available (ie, 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 (eGFR) less than 30 mL/min/1.73 m^2. 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 etiology, 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 (HCC) 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 54, 55, and 56).[16] These variables have independent prognostic value for modeling all-cause readmission and mortality after a hospitalization for heart failure.[16,17]

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 χ^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.[18,19] Compared with traditional significance tests, standardized differences are not as sensitive to sample size and are useful in identifying meaningful differences. A standardized difference greater than 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 estimated the association between treatment and outcomes using Cox proportional hazards models. We used robust standard errors in all models to account for clustering of patients by hospital. We imputed missing values for variables with low rates of missingness (ie, less than 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 (ie, age, sex, medical history, claims-based history at admission, vital signs at admission, laboratory test results at admission, and left ventricular ejection fraction) 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 χ^2 tests to test for differences in categorical variables and weighted analysis of variance 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 (MRAs) as a positive control within 90 days after hospital discharge.

We report 95% CIs 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 contraindications 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 etiology, and renal insufficiency. The treated groups also had higher mean systolic blood pressure, greater use of β-blockers, and lower use of diuretics at discharge. Black patients in the treated group were more likely to have received an ICD 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, compared with patients of other races in the untreated group.

Supplemental Table 1 shows the baseline characteristics of the study population after application of weights 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 eGFR less than 30. Among patients of other races, H-ISDN therapy was associated with higher rates of all-cause and cardiovascular readmission in patients with eGFR less than 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 (Supplemental Table 2). 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,[3] but adoption of the therapy was slow and varied across centers. Whereas a fixed combination of H-ISDN was used in A-HeFT, patients in clinical practice commonly receive individual generic formulations at different doses.[22] 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.[23] 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 enrollees with heart failure found that only 2% of patients with an indication or potential indication for H-ISDN actually filled their prescriptions.[24] Our 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 MRAs for patients with heart failure.[8] For the positive control in the present study, MRA 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 older 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, beta-3 subunit genotype, and responsiveness to H-ISDN therapy.[25] 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 OPTIMIZE-HF,[26] and 7.3% among black patients in the Improving Evidence-Based Care for Heart Failure in Outpatient Cardiology Practices (IMPROVE-HF) registry.[8] 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 therapy at discharge.[9] In all of these studies, patients who received the therapy often had more advanced disease and more comorbid conditions like 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% CI, 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 pharmaco-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, though the results were limited by small sample size and wide CIs. 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 in order 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] Since 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. Lastly, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspective

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 very 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.

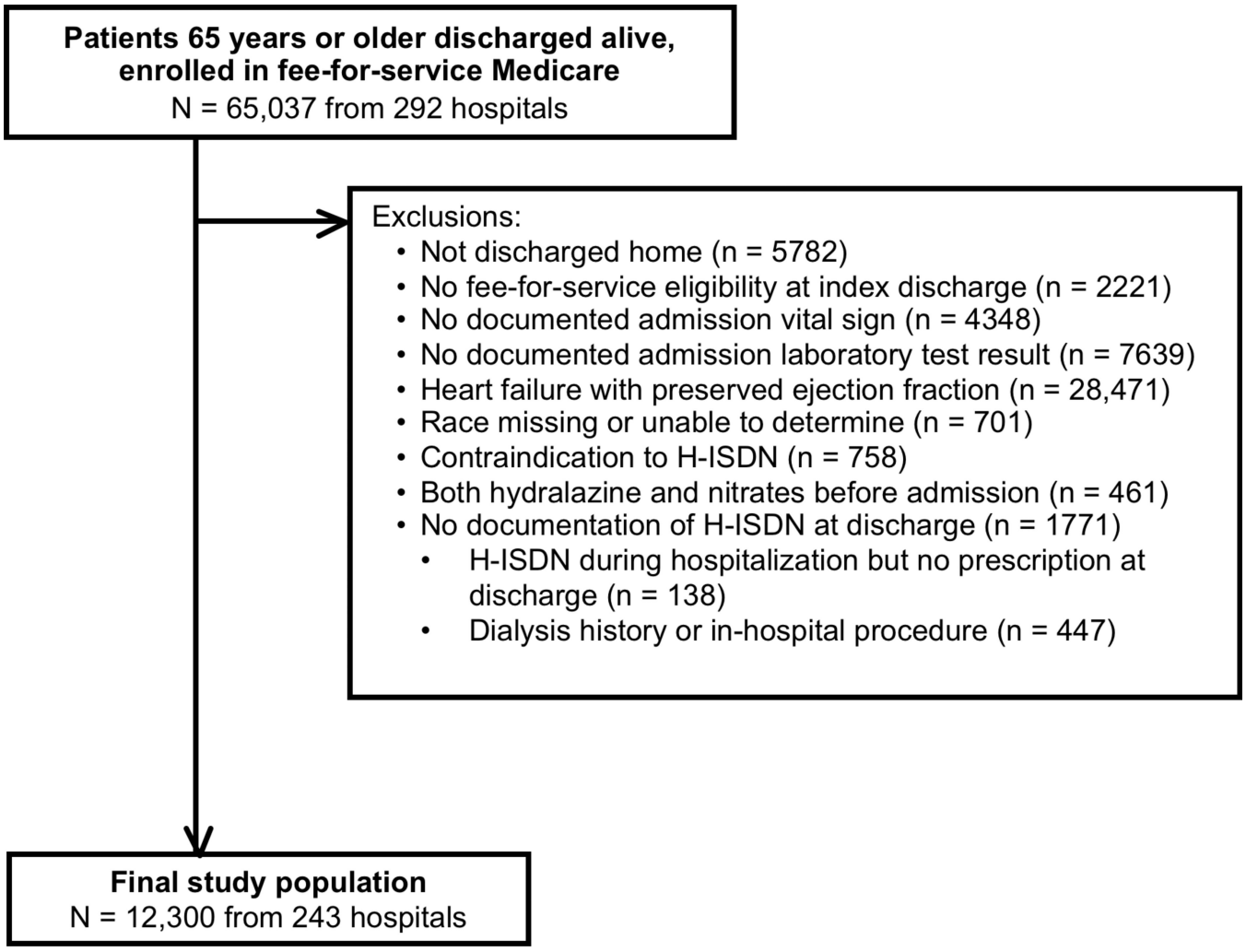

Figure.
Derivation of the Study Population

Table 1

Baseline Characteristics of the Study Population

Characteristic	Black Patients				Patients of Other Races			
	H-ISDN at Discharge, No. (%)		*P* Value	Standardized Difference[a]	H-ISDN at Discharge, No. (%)		*P* Value	Standardized Difference[a]
	Yes (n = 316)	No (n = 1076)			Yes (n = 595)	No (n = 2676)		
Age, mean (SD), y	75.3 (7.6)	75.9 (8.1)	.26	.07	79.3 (7.7)	80.2 (7.9)	.01	.11
Age group, No. (%)							.03	.10
65–79 y	230 (72.8)	737 (68.5)	.15	.09	293 (49.2)	1188 (44.4)		
≥ 80 y	86 (27.2)	339 (31.5)			302 (50.8)	1488 (55.6)		
Women, No. (%)	138 (43.7)	527 (49.0)	.10	.11	214 (36.0)	975 (36.4)	.83	.01
Medical history, No. (%)								
Anemia	56 (17.7)	150 (13.9)	.10	.10	113 (19.0)	491 (18.3)	.71	.02
Atrial fibrillation or flutter	74 (23.4)	238 (22.1)	.63	.03	206 (34.6)	1189 (44.4)	< .001	.20
Cerebrovascular accident or TIA	66 (20.9)	185 (17.2)	.13	.09	105 (17.6)	427 (16.0)	.31	.05
COPD	91 (28.8)	277 (25.7)	.28	.07	164 (27.6)	753 (28.1)	.78	.01
Depression	17 (5.4)	52 (4.8)	.69	.03	56 (9.4)	248 (9.3)	.91	.01
Diabetes mellitus	159 (50.3)	421 (39.1)	< .001	.23	263 (44.2)	987 (36.9)	.001	.15
Heart failure with ischemic etiology	179 (56.6)	510 (47.4)	.004	.19	455 (76.5)	1903 (71.1)	.01	.12
Hyperlipidemia	142 (44.9)	445 (41.4)	.26	.07	311 (52.3)	1376 (51.4)	.71	.02
Hypertension	263 (83.2)	896 (83.3)	.99	.001	429 (72.1)	1802 (67.3)	.02	.10
Implantable cardioverter-defibrillator	78 (24.7)	201 (18.7)	.02	.15	139 (23.4)	571 (21.3)	.28	.05
Pacemaker	44 (13.9)	128 (11.9)	.34	.06	96 (16.1)	563 (21.0)	.01	.13
Peripheral vascular disease	55 (17.4)	93 (8.6)	< .001	.26	110 (18.5)	419 (15.7)	.09	.08
Renal insufficiency	82 (25.9)	178 (16.5)	< .001	.23	250 (42.0)	685 (25.6)	< .001	.35
Smoking in the previous year	54 (17.1)	191 (17.8)	.79	.02	54 (9.1)	265 (9.9)	.54	.03
No. of all-cause hospital admissions in the prior year, mean (SD)	1.8 (2.1)	1.3 (1.7)	< .001	.27	1.4 (1.6)	1.4 (1.6)	0.87	.01
Claims-based history at admission, No. (%)								
Chronic liver disease	__[b]	__[b]	.15	.10	__[b]	__[b]	.74	.02

Characteristic	Black Patients				Patients of Other Races			
	H-ISDN at Discharge, No. (%)		*P* Value	Standardized Difference[a]	H-ISDN at Discharge, No. (%)		*P* Value	Standardized Difference[a]
	Yes (n = 316)	No (n = 1076)			Yes (n = 595)	No (n = 2676)		
Dementia	19 (6.0)	83 (7.7)	.31	.07	30 (5.0)	178 (6.7)	.15	.07
Disability	14 (4.4)	28 (2.6)	.09	.10	__[b]	__[b]	.56	.03
Malnutrition	__[b]	__[b]	.08	.12	25 (4.2)	133 (5.0)	.43	.04
Psychiatric disorder	__[b]	__[b]	.85	.01	__[b]	__[b]	.14	.08
Vital signs at admission								
Heart rate, mean (SD), beats/min	86.3 (20.1)	88.0 (19.9)	.20	.08	83.0 (19.3)	85.2 (20.2)	.01	.11
Heart rate, No. (%)			.79	.04			.06	.11
< 80 beats/min	115 (36.4)	369 (34.3)			284 (47.7)	1163 (43.5)		
80–100 beats/min	129 (40.8)	456 (42.4)			215 (36.1)	979 (36.6)		
> 100 beats/min	72 (22.8)	251 (23.3)			96 (16.1)	534 (20.0)		
Respiratory rate, No. (%)			.66	.03			.01	.11
< 30 breaths/min	299 (94.6)	1011 (94.0)			546 (91.8)	2530 (94.5)		
≥ 30 breaths/min	17 (5.4)	65 (6.0)			49 (8.2)	146 (5.5)		
Systolic blood pressure, mean (SD), mm Hg	147 (31.9)	141 (29.4)	.01	.17	139 (28.4)	128 (25.4)	< .001	.42
Systolic blood pressure, No. (%)			.001	.23			< .001	.40
< 110 mm Hg	39 (12.3)	138 (12.8)			82 (13.8)	650 (24.3)		
110–150, mm Hg	139 (44.0)	584 (54.3)			325 (54.6)	1576 (58.9)		
> 150, mm Hg	138 (43.7)	354 (32.9)			188 (31.6)	450 (16.8)		
Tests at admission								
Left ventricular ejection fraction, mean (SD), %	24.7 (7.6)	24.4 (7.8)	.64	.03	26.6 (6.9)	26.4 (7.3)	.40	.04
Serum creatinine, mean (SD), mg/dL	1.8 (1.0)	1.7 (6.0)	.73	.03	2.1 (1.3)	1.7 (1.1)	< .001	.29
Serum creatinine, No. (%)								
< 1.5 mg/dL	137 (43.4)	670 (62.3)	< .001	.39	144 (24.2)	1252 (46.8)	< .001	.51
1.5–2.0 mg/dL	110 (34.8)	260 (24.2)			210 (35.3)	792 (29.6)		
> 2.0 mg/dL	69 (21.8)	146 (13.6)			241 (40.5)	632 (23.6)		
Serum urea nitrogen, No. (%)			< .001	.29			< .001	.31

Characteristic	Black Patients				Patients of Other Races			
	H-ISDN at Discharge, No. (%)		*P* Value	Standardized Difference[a]	H-ISDN at Discharge, No. (%)		*P* Value	Standardized Difference[a]
	Yes (n = 316)	No (n = 1076)			Yes (n = 595)	No (n = 2676)		
< 20 mg/dL	86 (27.2)	412 (38.3)			49 (8.2)	458 (17.1)		
20–50 mg/dL	191 (60.4)	595 (55.3)			391 (65.7)	1747 (65.3)		
> 50 mg/dL	39 (12.3)	69 (6.4)			155 (26.1)	471 (17.6)		
Medications at discharge, No. (%)								
ACE inhibitor	165 (52.2)	695 (64.6)	< .001	.25	---	---	---	---
ARB	40 (12.7)	156 (14.5)	.41	.05	---	---	---	---
ACE inhibitor and/or ARB	202 (63.9)	838 (77.9)	< .001	.31	---	---	---	---
Aldosterone antagonist	83 (26.3)	245 (22.8)	.20	.08	107 (18.0)	551 (20.6)	.15	.07
â-Blocker	285 (90.2)	934 (86.8)	.11	.11	514 (86.4)	2087 (78.0)	< .001	.22
Digoxin	69 (21.8)	198 (18.4)	.17	.09	136 (22.9)	662 (24.7)	.33	.04
Diuretic	164 (51.9)	661 (61.4)	.002	.19	324 (54.5)	1689 (63.1)	< .001	.18

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.

Table 2

Cumulative Incidence of Mortality and Readmission Within 3 Years

Outcome	Black Patients			Patients of Other Races		
	H-ISDN at Discharge, No. (Rate)[a]		*P* Value	H-ISDN at Discharge, No. (Rate)[a]		*P* Value
	Yes (n = 316)	No (n = 1076)		Yes (n = 595)	No (n = 2676)	
All-cause mortality	149 (53.9)	453 (51.9)	.39	357 (68.9)	1585 (70.7)	.13
All-cause readmission	241 (85.7)	779 (83.9)	.53	459 (84.6)	1944 (81.2)	.15
Cardiovascular readmission	192 (68.9)	593 (65.2)	.33	325 (60.8)	1401 (59.7)	.26

[a] Values are expressed as number of events (cumulative incidence per 100 patients at risk) unless otherwise indicated.

[b] Subcategorization of cardiovascular readmission refers to the first readmission.

Table 3

Associations Between Hydralazine-Isosorbide Dinitrate Therapy and Study Outcomes Within 3 Years

Outcome	Unadjusted		Inverse-Weighted		Inverse-Weighted and Adjusted	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Black Patients						
All-cause mortality	1.06 (0.88–1.28)	.53	0.97 (0.79, 1.20)	.78	0.92 (0.75, 1.13)	.45
All-cause readmission	1.09 (0.96–1.24)	.17	1.00 (0.86, 1.16)	> .99	0.98 (0.84, 1.13)	.76
Cardiovascular readmission	1.13 (0.96–1.31)	.13	1.01 (0.84, 1.20)	.95	0.99 (0.82, 1.19)	.91
Patients of Other Races						
All-cause mortality	0.92 (0.82–1.04)	.18	0.92 (0.79, 1.09)	.34	0.93 (0.79, 1.09)	.35
All-cause readmission	1.07 (0.97–1.18)	.18	1.03 (0.91, 1.17)	.68	1.02 (0.90, 1.17)	.71
Cardiovascular readmission	1.02 (0.90–1.15)	.81	0.95 (0.81, 1.10)	.48	0.94 (0.81, 1.09)	.38