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Clinical Effectiveness of Hydralazine–Isosorbide Dinitrate in African-American Patients With Heart Failure

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ABSTRACT

OBJECTIVES This study sought to evaluate the effectiveness of hydralazine-isosorbide dinitrate (H-ISDN) in African Americans with heart failure (HF) with reduced ejection fraction (HFrEF).

BACKGROUND Among African-American patients with HFrEF, H-ISDN was found to improve quality of life and lower HF-related hospitalization and mortality rates in the A-HEFT (African-American Heart Failure Trial). Few studies have evaluated the effectiveness of this therapy in clinical practice.

METHODS Veterans Affairs patients with a hospital admission for HF between 2007 and 2013 were screened. Inclusion criteria included African-American race, left ventricular ejection fraction <40%, and receipt of Veterans Affairs medications. Exclusions were documented contraindications to H-ISDN, creatinine >2.0 mg/dl, or intolerance to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Adjusted hazard ratios were calculated for patients who received H-ISDN 6-months before admission compared with patients who did not receive H-ISDN, by using inverse probability weighting of propensity scores and a time to death analysis for 18 months of follow-up. Propensity scores were generated using patients' characteristics, left ventricular ejection fraction, laboratory values, and hospital characteristics.

RESULTS The final cohort included 5,168 African-American patients with HF (mean age 65.2 years), with 15.2% treated with H-ISDN before index admission. After 18 months, there were 1,275 reported deaths (24.7%). The adjusted mortality rate at 18 months was 22.1% for patients receiving H-ISDN treatment and 25.2% for untreated patients ($p = 0.009$); adjusted hazard ratio: 0.85 (95% confidence interval: 0.73 to 1.00; $p = 0.057$).

CONCLUSIONS H-ISDN remains underused in African-American patients with HFrEF. In this cohort, the study found that H-ISDN use was associated with lower mortality rates in African-American patients with HFrEF when controlling for patient selection by using an inverse probability weighting of propensity scores. (J Am Coll Cardiol HF 2017;■:■–■) Published by Elsevier on behalf of the American College of Cardiology Foundation.

The efficacy of hydralazine-isosorbide dinitrate (H-ISDN) therapy for heart failure (HF) was established in the first V-HeFT I (Vasodilator-Heart Failure Trial), regarded as the first major randomized controlled in cardiovascular medicine (1,2). Subsequent trials established angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs) as preferred agents in patients with HF with reduced

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin II receptor blocker

CI = confidence interval

H-ISDN = hydralazine–isosorbide dinitrate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

IPWT = inverse probability of treatment weighting

LVEF = left ventricular ejection fraction

VA = Veterans Affairs

VHA = Veterans Health Administration

ejection fraction (HFrEF), although post hoc analyses suggested that African-American patients may particularly benefit from H-ISDN (3–6). In the A-HeFT (African-American Heart Failure Trial), the addition of a combination pill of H-ISDN to optimal medical therapy was found to improve quality of life and to reduce HF-related hospitalizations and mortality rates (7). This finding earned H-ISDN a Class I guideline recommendation in 2009 and the only Food and Drug Administration race-specific therapy approved for African Americans with HFrEF (8,9). H-ISDN has a Class IIa recommendation for all other ethnicities with HFrEF if they do not tolerate an ACE inhibitor, ARB, or angiotensin receptor-neprilysin inhibitors.

Clinical usage rates of H-ISDN have been low among outpatients and inpatients eligible for treatment (10,11). Furthermore, real-world clinical effectiveness of H-ISDN prescription remained to be demonstrated (12). The Veterans Health Administration (VHA) is the largest integrated health system in the United States, and it serves 8.76 million veterans (13). We used national data from the VHA to determine whether an observable mortality benefit could be identified in a large cohort of African Americans with HFrEF who were eligible for treatment with H-ISDN.

METHODS

DATA SOURCES. Data for this analysis were extracted from the VHA standard electronic health record system through the External Peer Review Program linked to patient-level data from the electronic health record that included demographics, medical history, laboratory values, and prescription drug use (14). The External Peer Review Program generates a national chart abstraction database containing performance data for all Veterans Affairs (VA) hospitals on more than 90 metrics including quality of care. These data were used to determine the left ventricular ejection fraction (LVEF) and physicians' documentation of contraindications or intolerance to medications. Charts are abstracted by the West Virginia Medical Institute using explicit rules and auditing. Health records were linked to the VHA death files. The study was approved by the Institutional Review Board at Stanford University in Stanford, California.

STUDY COHORT. VA patients with a primary admission for HF between January 1, 2007, and December 31, 2013 were screened for inclusion in the observational cohort. Inclusion criteria included age >18 years, African-American race, LVEF less than or equal to 40%, and regular VA pharmacy benefit use. A primary HF hospitalization was defined by International Classification of Diseases-9th Revision (ICD-9) codes (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428), as previously described (15). Patients were excluded from the cohort if they had contraindications to receiving H-ISDN, renal insufficiency (creatinine >2.0), or documented intolerance to ACE inhibitors or ARBs or if they received hospice services.

TREATMENT. Exposure was defined as a filled prescription for hydralazine nitrate combinations (i.e., fixed-dose combinations of H-ISDN, H-ISDN, or hydralazine and isosorbide mononitrate) in the 6 months before index admission. The lack of an H-ISDN filled prescription was defined as nonexposure.

OUTCOME. The primary outcome measure was all-cause mortality in a time-to-event analysis. Health records were linked to VHA death files to identify the primary outcome. Patients were followed up for 18 months after index admission to assess mortality. The period of observation mirrors that from the A-HeFT (7).

COVARIATES. Clinical data included the following: the dates of admission and discharge; age; race; sex; comorbidities; LVEF; prescription drug use; laboratory values (white blood cell count, hemoglobin, sodium, blood urea nitrogen, serum creatinine, and B-type natriuretic peptide); and date of death. Hospital characteristics (from the American Hospital Association) included the following: region (Northeast, Midwest, South, West); teaching status; academic affiliation; and Accreditation Council for Graduate Medical Education approved training status.

STATISTICAL ANALYSIS. Patients' characteristics are described with averages and prevalence rates for relevant factors among exposed and nonexposed patients with HF. The medication possession ratios for H-ISDN and other medications were estimated before hospitalization. The risk of mortality was modeled as a time-to-event analysis after the index admission. Missing covariate data (rare) were imputed using the mean for continuous variables and the most common category for categorical variables. An inverse probability of treatment weighting (IPTW) propensity score model adjusted for the patients' and hospital characteristics in a Cox proportional hazards model to control for potential selection bias or confounding related to H-ISDN prescription use (16,17). Patients' factors used to risk adjust were determined on the basis of available known predictors of mortality for VHA patients with HF (18). The propensity score

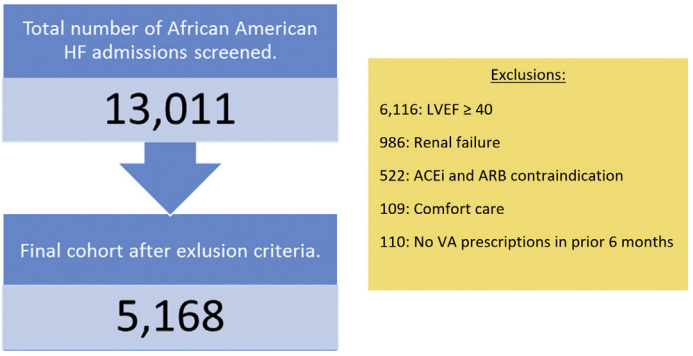
model used patients' and hospital characteristics to generate individual patient weights. Comparisons of propensity scoring methods report negligible bias with correctly specified IPTW models (19). The model used general estimating equations to account for clustering of patients within hospitals. Cumulative incidence plots were made to display survival curves. An additional analysis of the factors associated with receipt of H-ISDN at baseline was performed. We report 95% confidence intervals (CIs) and used $\alpha = 0.05$ to establish the statistical significance of tests. Analyses were performed in SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina) and STATA software version 11.1 (StataCorp, College Station, Texas).

RESULTS

The final observational cohort included a sample of 5,168 African Americans with HFrEF from 105 VHA medical centers (Figure 1). The mean number of patients per hospital was 49 (range 1 to 257 subjects). In 2011, an estimated 48% of VHA medical centers had clinics devoted to HF. The exposure cohort consisting of those treated with H-ISDN before the index admission represented 15.2% of the total cohort (Table 1). Patients treated with H-ISDN before admission were slightly younger, at 63.6 ± 11.8 years, compared with 65.5 ± 12.2 years for the nontreated cohort. Female representation was <3% in both cohorts. The distribution of LVEF was similar between treated and nontreated cohorts. Rates of ACE inhibitor or ARB use was greater than 90% in both cohorts. Beta-blocker use was higher in the treated H-ISDN cohort in comparison with the nontreated cohort. Medication possession ratios for hydralazine and nitrates were 54.3% and 59.3%, respectively, before the index admission. Good adherence is typically categorized as >80% (20,21). With respect to comorbidities, the prevalence of chronic kidney disease, diabetes mellitus, ischemic heart disease, hypertension, cerebrovascular disease, and acute myocardial infarction was higher among the treated cohort. The nonexposed cohort had slightly more chronic obstructive pulmonary disease and previous histories of malignant disease. Laboratory values were generally similar between cohorts. There was evidence of slightly worse renal function on average, with higher serum blood urea nitrogen and creatinine, in the treated cohort. C-reactive protein levels were also slightly higher in the treated cohort.

Treatment with H-ISDN was more common in the Midwest and South compared with other regions. More exposed patients were treated at hospitals with

FIGURE 1 Observational Cohort Selection Between 2007 and 2013 to VHA



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HF = heart failure; LVEF = left ventricular ejection fraction; VA = Veterans Affairs; VHA = Veterans Health Administration.

TABLE 1 Baseline Characteristics Determined on the Basis of Treatment Exposure With H-ISDN

	Taking H-ISDN	No H-ISDN	p Value
n (%)	786 (15.2)	4,382 (84.8)	
Age, yrs	63.6 ± 11.8	65.5 ± 12.2	<0.0001
Female	2.54	2.21	0.5657
Admission year			<0.0001
2007	23.0	19.2	
2008	13.4	13.1	
2009	14.6	14.9	
2010	16.5	15.4	
2011	13.2	14.3	
2012	7.3	14.6	
2013	12.0	8.6	
LVEF			0.7918
Mean	23.6 ± 11.8	23.3 ± 8.1	
<20	24.2	24.8	
20–29	44.9	45.4	
30–35	30.9	29.7	
Medications			
ACE or ARB	96.1	93.8	0.01
ACE inhibitor	83.0	83.8	0.5767
ARB	19.0	13.7	<0.0001
BB	96.3	88.5	<0.0001
Medication possession ratio			
Hydralazine	54.3 ± 31.4	–	–
Nitrates	59.3 ± 32.0	–	–
ACE inhibitor	73.4 ± 29.6	74.7 ± 29.1	0.31
ARB	66.1 ± 33.4	68.9 ± 32.2	0.30
BB	78.2 ± 26.0	78.4 ± 26.7	0.81
NYHA functional class			0.0057
1	3.82	3.86	
2	20.74	23.19	
3	29.77	24.26	
4	5.98	4.77	
Missing	39.69	43.93	

Continued on the next page

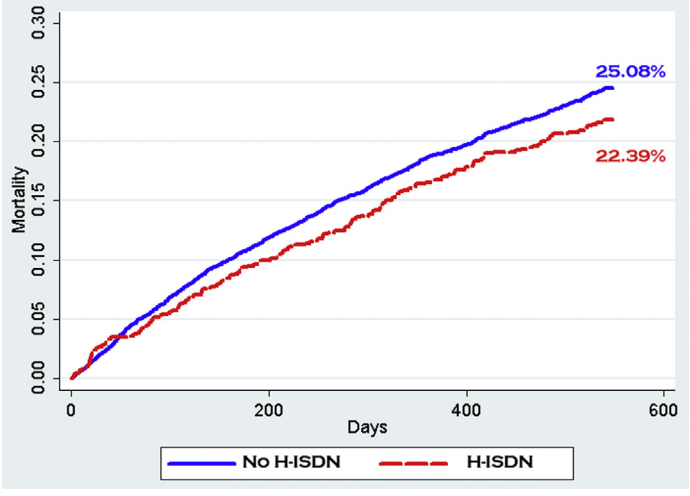
TABLE 1 Continued

	Taking H-ISDN	No H-ISDN	p Value
Comorbidities			
Chronic kidney disease	39.19	25.38	<0.0001
Diabetes mellitus	53.69	45.98	<0.0001
Ischemic heart disease	66.54	57.05	<0.0001
Hypertension	95.17	90.71	<0.0001
COPD	33.08	34.66	0.3889
Cerebrovascular disease	19.72	15.15	0.0012
Acute myocardial infarction	22.52	17.32	0.0005
Malignant disease (past 2 yrs)	11.70	13.81	0.1122
Laboratory values			
Hemoglobin (mg/dl)	12.37 ± 1.92	12.73 ± 1.86	0.27
White blood cells (/μl)	6.83 ± 3.14	6.82 ± 6.22	0.97
Sodium (mmol/l)	138.62 ± 3.20	138.48 ± 3.28	0.27
BUN (mg/dl)	23.67 ± 10.52	21.65 ± 10.16	<0.0001
Serum creatinine (mg/dl)	1.35 ± 0.31	1.25 ± 0.29	<0.0001
CRP (mg/l)	14.71 ± 27.65	12.46 ± 26.20	0.63
Region			<0.0001
Midwest	22.77	19.86	
Northeast	8.27	11.96	
South	61.45	56.77	
West	7.51	11.41	
Hospital characteristics			
Member of Council on Teaching Hospitals	59.61	59.03	0.7628
Accreditation Council for Graduate Medical Education	97.16	94.14	0.0006
Academic affiliation	97.81	96.30	0.0347

Values are n (%), %, or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BB = beta-blocker; COPD = chronic obstructive pulmonary disease; BUN = blood urea nitrogen; CRP = C-reactive protein; H-ISDN = hydralazine-isosorbide dinitrate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

FIGURE 2 Unadjusted Cumulative Incidence Survival Plots



Cumulative mortality rates over days since discharge for patients treated and not treated with hydralazine–isosorbide dinitrate (H-ISDN).

training programs approved by the Accreditation Council for Graduate Medical Education compared with patients in the nontreated cohort. After 18 months of follow-up from index admission, there were 1,275 (24.67%) reported deaths. The unadjusted mortality rate was lower in the treated cohort (22.39%) compared with the nontreated cohort (25.08%).

Unadjusted cumulative incidence survival plots show the separation and lower mortality rates among those patients treated with H-ISDN compared with the nontreated cohort (Figure 2). The unadjusted hazard ratio (HR) for mortality at 18 months with H-ISDN treatment is 0.878 (95% CI: 0.75 to 1.03; p = 0.110). The partially adjusted model using IPTW without cluster adjustment estimates an HR of 0.853 (95% CI: 0.76 to 0.96; p = 0.006). After risk adjustment, the mortality rate at 18 months was 22.1% for patients receiving H-ISDN treatment and 25.2% for untreated patients (p = 0.009). The fully adjusted model using IPTW and general estimating equations to account for clustering estimates an HR of 0.85 (95% CI: 0.73 to 1.00; p = 0.057) for H-ISDN exposure (Table 2).

A few patient-related and hospital factors were associated with an increased odds of receiving H-ISDN at baseline (Table 3). Patients who were younger; who were taking an ARB or beta-blocker; who had a history of ischemic heart disease, hypertension, or cerebrovascular disease; who had lower hemoglobin levels; and who were treated in the South and Midwest were more likely to receive H-ISDN at baseline.

DISCUSSION

This observational study of real-world clinical practice suggests a benefit of H-ISDN use for African Americans with HFrEF. The use of H-ISDN was associated with a 15% lower mortality hazard during 18 months of observation post-hospitalization. In the fully adjusted model, the statistical significance was marginal but still suggestive of benefit. A larger cohort or less clustering may have strengthened the observed statistical significance in the fully adjusted model.

A-HeFT reported a 43% reduction in mortality rate and was terminated early for benefit. The lower benefit observed in this study may reflect differences in medication adherence between clinical practice and randomized controlled trials. The medication possession ratio for H-ISDN in our study (54.9%) was lower than research standards for good adherence. In A-HeFT, adherence was high at 84.6% (22).

TABLE 2 Proportional Cox Model Comparison for H-ISDN Benefit on Mortality*

	HR	95% CI	p Value
Unadjusted model	0.88	0.75–1.03	0.110
Adjusting for patient characteristics only	0.83	0.70–0.98	0.024
IPTW without cluster adjustment	0.85	0.76–0.96	0.006
Fully adjusted (IPTW and GEE)	0.85	0.73–1.00	0.057

Values are unadjusted and adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and associated p values. *Patients' characteristics controlled for include the following: age, sex, year of admission, LVEF category, medications (ACE or ARB, beta-blocker), NYHA functional class, comorbidities (chronic kidney disease, diabetes mellitus, ischemic heart disease, hypertension, COPD, cerebrovascular disease, acute myocardial infarction, malignant disease), laboratory values (hemoglobin, sodium, BUN, creatinine, B-type natriuretic protein), region, hospital characteristics (teaching status, Accreditation Council for Graduate Medical Education, academic affiliation).

GEE = generalized estimating equations (cluster adjustment); IPTW = inverse propensity of treatment weighting (patient selection adjustment); other abbreviations as in Table 1.

TABLE 3 Factors Associated With H-ISDN Receipt

	OR	95% CI	p Value
Age, yrs	0.98	0.97–0.98	<0.001
Female	1.12	0.67–1.88	0.674
Admission year			<0.0001
2007	ref.		
2008	0.82	0.63–1.08	
2009	0.83	0.63–1.08	
2010	0.90	0.69–1.16	
2011	0.80	0.60–1.05	
2012	0.44	0.32–0.62	
2013	1.17	0.88–1.57	
LVEF			0.92
30%–35%	ref.		
<20%	0.96	0.77–1.19	
20%–29%	0.99	0.82–1.19	
Medications			
ACE inhibitor	1.02	0.76–1.37	0.896
ARB	1.34	1.00–1.78	0.047
BB	2.41	1.62–3.58	<0.001
Comorbidities			
Diabetes mellitus	1.16	0.98–1.36	0.081
Ischemic heart disease	1.34	1.12–1.61	0.002
Hypertension	1.66	1.16–2.37	0.005
COPD	0.91	0.77–1.08	0.269
Cerebrovascular disease	1.24	1.01–1.53	0.040
Acute myocardial infarction	1.08	0.88–1.33	0.476
Malignant disease (past 2 yrs)	0.84	0.66–1.08	0.175
Laboratory values			
Hemoglobin (mg/dl)	0.91	0.87–0.95	<0.001
Sodium (mmol/l)	1.02	1.00–1.05	0.081
Creatinine (mg/dl)			<0.0001
<1.0	ref.		
1.0–1.5	1.13	0.86–1.49	
1.5–2.0	2.09	1.54–2.85	
Missing	1.52	1.05–2.19	
BUN (mg/dl)			0.27
<15	ref.		
15–25	1.17	0.92–1.48	
25–35	1.01	0.76–1.35	
35–45	1.21	0.83–1.76	
>45	1.58	1.00–1.68	
Missing	1.10	0.72–1.68	

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Medications that require administration 3 times a day are expected to have lower adherence in comparison with medication taken once a day (23). In this VHA study, more than 95% of the H-ISDN prescribed was a generic formulation. Given the evidence for H-ISDN use, the pharmaceutical industry should prioritize the development of a once-daily, long-acting formulation of H-ISDN to improve real-world adherence by patients. Concerns have been described regarding the differences in bioavailability of H-ISDN formulations used in the previous randomized trials. All 3 previous randomized controlled trials of H-ISDN used different formulations of H-ISDN with varied bioavailabilities, and this factor may explain the differential results among the trials (2). The branded combination pill of H-ISDN used in A-HeFT has the greatest measured serum concentration when compared with other H-ISDN formulations (2). Whether the lower bioavailability of the generic formulations of H-ISDN influences patients' outcomes is unknown.

A previous study from the Get With The Guidelines-HF Registry linked to Medicare data did not find an observed benefit on all-cause mortality or readmissions for African Americans treated with H-ISDN (12). The sample size in that study was limited to 1,392 African-American patients with HF with a mean age of 75 years. The current VHA study observed a larger population and featured a younger cohort of patients with HFrEF, features that may explain the beneficial response to treatment. Older patients with more comorbid conditions may not derive the same degree of benefit as observed in the A-HeFT trial, where the average age of enrolled patients was 57 years. Generally, patients treated with H-ISDN had more comorbidities and mildly worse renal function. Despite the greater burden of comorbid conditions, unadjusted mortality rates were observed to be lower for patients treated with H-ISDN.

Despite the guideline recommendations to prescribe H-ISDN for African-American patients with HFrEF, the observed prescription rates in this cohort are low (6,8). In our study, only 15% of African Americans with HFrEF who were determined as eligible received H-ISDN. Because regions with larger African-American populations had higher observed rates of H-ISDN use, providers' familiarity with the management of African-American patients with

TABLE 3 Continued

	OR	95% CI	p Value
BNP (pg/ml)			
<100	ref.		0.65
100–500	1.37	0.74–2.54	
500–750	1.15	0.61–2.18	
750–1,000	1.40	0.73–2.66	
1,000–5,000	1.36	0.75–2.47	
>5,000	1.46	0.67–3.19	
Missing	1.50	0.83–2.72	
Region			0.003
West	ref.		
Northeast	0.89	0.6–1.32	
South	1.43	1.05–1.93	
Midwest	1.43	1.01–1.98	
Hospital characteristics			
Member of Council on Teaching Hospitals	1.02	0.86–1.21	0.811
Accreditation Council for Graduate Medical Education	1.59	0.94–2.68	0.081
Academic affiliation	1.26	0.70–2.27	0.447

Values are adjusted odds ratios (ORs), 95% confidence intervals (CIs), and associated p values.
BNP = B-type natriuretic peptide; ref. = reference; other abbreviations as in Tables 1 and 2.

HFrEF is likely a factor in better guideline adherence. Given the high risk of mortality and readmission for hospitalized patients, efforts to improve the receipt of guideline-directed medical therapy are desperately needed, especially for African-American patients (24). Although ivabradine and valsartan-sacubitril are newer evidence-based therapies for all patients with HFrEF, representation of African-American patients in these trials was low (5,25). Strong consideration for the prescription of H-ISDN is encouraged, given the level of evidence.

Outpatient networks providing care for patients with HFrEF require greater implementation efforts to assess the prescription of evidence-based therapies for all patients, especially African Americans who benefit from the additional therapeutic class. The development of performance metrics and provider feedback would be beneficial in improving the prescription rates of H-ISDN for indicated patients, as was seen with quality improvement efforts for beta-blocker and ACE inhibitor or ARB use. African Americans with newly diagnosed HFrEF should be educated on all their therapeutic options. Partnering with community stakeholders in areas with high HF prevalence to improve education and adherence through multifaceted interventions is recommended (26). The known efficacy and effectiveness of H-ISDN should be communicated to patients regarding improved life expectancy, decreased hospitalization burden, and higher quality of life. Careful attention should be paid by providers in dosing H-ISDN and monitoring for adherence to therapy.

STUDY LIMITATIONS. For this study, a hospital cohort was identified and followed for events retrospectively. Of further interest would be the clinical effectiveness among outpatient African Americans with HFrEF. Unfortunately, the LVEF data were available only for inpatients. Approximately 15% of VA patients may be readmitted to non-VA hospitals; therefore we did not attempt to identify additional outcomes beyond death that were not reliably captured.

Given the nature of observational data, confounding related to patient selection and exposure status is a concern. We did not have vital measurements for systolic blood pressure or heart rate reliably captured and are unable to comment on differences in hemodynamic parameters during hospitalization. H-ISDN is frequently prescribed to patients with HF and renal insufficiency, hyperkalemia, or intolerance to ACE inhibitors or ARBs. Patients taking H-ISDN may be more likely to have greater comorbidities and be at risk for more adverse events and death. This cohort excluded patients with renal insufficiency and documented ACE inhibitor and ARB intolerance, to minimize treatment selection biases. We found that after adjustment for patients' characteristics the benefit of H-ISDN increased. Although most risk factors predicative of HF-related mortality were included in the IPTW model, if complete risk adjustment were possible, the benefit of H-ISDN may have been greater (27). If H-ISDN use correlates with other guideline-directed medical therapies not included in the model, such as implantable cardioverter-defibrillator placement, then H-ISDN exposure may be positively biased (11).

The IPTW model attempts to adjust for possible confounding related to patient selection. The IPTW model may not perform well if factors that increase the risk of death are not included in the model and are differentially distributed on the basis of H-ISDN exposure. Blood pressure and heart rate at admission were not available. However, the VHA dataset includes detailed comorbidities in patients and laboratory values that permit appropriate risk adjustment of patients with HF (18). If hospitals with higher or lower prescription rates of H-ISDN for HFrEF exhibit characteristics not controlled for in the model and that influence mortality rates, then the model without clustering adjustments may be biased. Our study included primarily men, and our findings may not be generalizable to women; however, H-ISDN had similar benefit for men and women in A-HEFT (5).

CONCLUSIONS

The goal of this analysis was to evaluate the clinical effectiveness of H-ISDN on mortality rates among African-American patients with HFrEF. These findings suggest a modest benefit associated with the use of H-ISDN among African Americans with HFrEF. The mortality benefits observed were not as robust as those observed in the A-HeFT trial. This difference may be related to the observational nature of the VHA study, the lower rates of medication adherence, or differences in bioavailability of H-ISDN formulations. H-ISDN remains an underused medication for HF despite guideline endorsement. Efforts to improve medication adherence to H-ISDN therapy may further improve outcomes. African Americans with HF have a high mortality risk, especially after hospitalization for acute HF. Efforts to improve the receipt of guideline-directed medical therapy are likely to reduce morbidity and mortality. On the basis of previous research and the current findings, H-ISDN therapy should be considered for all African-American patients with HFrEF who do not have contraindications to this therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The combination of H-ISDN in African-American patients with HFrEF is observed to lower the risk of mortality in clinical practice.

TRANSLATIONAL OUTLOOK: Further research is needed to encourage improved guideline adherence to H-ISDN therapy. Identifying strategies to improve patients' adherence to medication are also needed.

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