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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