Adv Ther (2017) 34:1976–1988
DOI 10.1007/s12325-017-0584-x

ORIGINAL RESEARCH

Fixed-Dose Versus Off-Label Combination of Isosorbide Dinitrate Plus Hydralazine Hydrochloride: Retrospective Propensity-Matched Analysis in Black Medicare Patients with Heart Failure

Elizabeth Ofili · Inder Anand · Richard Allen Williams · Ola Akinboboye · Liou Xu · Gary Puckrein

Received: May 19, 2017 / Published online: July 13, 2017

ABSTRACT

Introduction: Based upon the findings of the African-American Heart Failure Trial, the US Food and Drug Administration approved the fixed-dose combination of isosorbide dinitrate (ISDN) and hydralazine hydrochloride (HYD) (FDC-ISDN/HYD) as a new drug for treatment of heart failure (HF) in self-identified African Americans. According to the FDA, FDC-ISDN/HYD has no therapeutic equivalent. However, off-label combinations of the separate generic drugs ISDN and HYD (OLC-ISDN+HYD) or isosorbide mononitrate (ISMN) and HYD (OLC-ISMN+HYD) are routinely substituted without any supporting outcome data. We conducted an exploratory retrospective propensity-matched cohort study using Medicare data to determine whether a survival difference exists between these treatments in medication-adherent patients.

Methods: Black Medicare beneficiaries with HF were matched with Medicare Part D data to identify patients with prescriptions to FDC-ISDN/HYD or the off-label combinations. Only patients with 1-year adherence levels ≥80% were included in the analysis. Propensity-matched scoring created two sets of matched cohort pairs on a 1:1 basis, each set comparing FDC-ISDN/HYD with one of the off-label combinations. Kaplan-Meier (KM) survival curves with the log-rank test were then calculated for each pair for the year of medication adherence.

Results: The analysis population was relatively older (77 years) and mainly female (66.7%), with a high burden of comorbid disease. The KM estimates of 1-year survival were 87.9% (95% CI 85.6–89.9%) and 83.0% (95% CI 80.3–85.3%) (log rank $p = 0.0024$), respectively, for the matched cohorts FDC-ISDN/HYD and OLC-ISDN+HYD ($n = 886$ in each group) and 88.2% (95% CI 85.9–90.2%) and 84.8% (95% CI 82.2–87.0%) (log rank $p = 0.0320$), respectively, for the matched cohorts FDC-ISDN/HYD and OLC-ISMN+HYD ($n = 868$ in each group).

Conclusion: The 1-year survival advantage for FDC-ISDN/HYD compared with off-label

Enhanced content To view enhanced content for this article go to http://www.medengine.com/Redeem/2DD8F0602EB45EFE.

E. Ofili (✉)
Morehouse School of Medicine, Atlanta, GA, USA
e-mail: eofili@msm.edu

I. Anand
University of Minnesota Medical School, VA Medical Centers, Minneapolis, MN, USA

R. A. Williams
UCLA School of Medicine, Los Angeles, CA, USA

O. Akinboboye
Mount Sinai Medical Center, New York, NY, USA

L. Xu · G. Puckrein
National Minority Quality Forum, Washington, DC, USA

combinations in adherent black Medicare beneficiaries with HF suggests a genuine difference between these medications and warrants prospective investigation.

Keywords: African American; BiDil; Black; Heart failure; Hydralazine hydrochloride; Isosorbide dinitrate; Isosorbide mononitrate; Medicare; Mortality; Race

INTRODUCTION

In 2004, Taylor et al. reported results from the African-American Heart Failure Trial (A-HeFT), which compared a fixed-dose combination (FDC) of isosorbide dinitrate (ISDN) and hydralazine hydrochloride (HYD) (FDC-ISDN/HYD) versus placebo in self-identified African Americans with heart failure (HF) [1]. The trial was terminated early, after a mean follow-up of 10 months, primarily because in the FDC-ISDN/HYD-treated group there was a 43% reduction in all-cause mortality, a 39% reduction in the risk of a first hospitalization for HF, and a statistically significant improvement in response to the Minnesota Living with Heart Failure questionnaire (a self-report of the patient's functional status). Based upon these findings, the US Food and Drug Administration (FDA) approved FDC-ISDN/HYD in June 2005 as a new drug (brand name BiDil) for the treatment of HF in self-identified African Americans.

As used in A-HeFT, FDC-ISDN/HYD was a new combination drug based upon two older generic drugs—ISDN and HYD—neither of which had been approved by the FDA for use in HF. ISDN had been approved by the FDA as a treatment for angina pectoris due to coronary artery disease, while HYD had been approved by the FDA for the treatment of hypertension. In the Orange Book, the FDA resource in which FDA-approved drug products are listed with therapeutic equivalence evaluations, there is no therapeutic equivalent documented for FDC-ISDN/HYD [2]. A pharmacokinetics study has also suggested that generic combinations of ISDN and HYD are not bioequivalent to the fixed-dose combination [3].

Nonetheless, the off-label combination (OLC) of the generic drugs ISDN and HYD (OLC-ISDN+HYD) as a substitute for FDC-ISDN/HYD in treatment of HF in self-identified African Americans is regularly prescribed in clinical practice. Moreover, use of this off-label combination has been acknowledged in some professional clinical guidelines, although it has not been separately studied. For example, in their 2013 HF guideline, the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) endorsed the combination of ISDN and HYD "to reduce morbidity and mortality for patients self-described as African Americans with New York Heart Association class III–IV HF with reduced ejection fraction receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated"—a recommendation that the ACCF/AHA ranked as class I, with evidence graded level A. The 2013 guideline then provided advice for initiating and maintaining treatment not only with FDC-ISDN/HYD but also with OLC-ISDN+HYD [4].

In addition to OLC-ISDN+HYD, another off-label combination, which substitutes isosorbide mononitrate (ISMN) for ISDN in combination with HYD (OLC-ISMN+HYD), is also used in clinical practice as an alternative to FDC-ISDN/HYD for treatment of HF in self-identified African Americans [5]. As with OLC-ISDN+HYD, this off-label combination of drugs has also not been clinically studied.

Because these off-label generic combinations have never been compared to FDC-ISDN/HYD for treatment of HF in black subjects with HF, we conducted a retrospective propensity-matched cohort study using Medicare data to explore whether there might be an overall survival difference between the treatments for medication-adherent patients. Demonstration of such a difference might support the FDA position that FDC-ISDN/HYD is without a generic equivalent and might lead to further research into the use of FDC-ISDN/HYD for treatment of HF.

METHODS

Study Population and Databases

The study population consisted of black Medicare beneficiaries with HF whose primary payer was Medicare and who received their prescription drugs through Medicare Part D. From the Centers for Medicare and Medicaid Services (CMS) enrollment files, administrative data were extracted for the years 2006–2013 [6]. Medicare beneficiary annual summary files were then used to identify beneficiaries whose health-care costs were insured by Medicare, the year in which Medicare first noted that the beneficiaries had HF, and the date of death of the beneficiaries.

Medicare files contain demographic information and data about 21 chronic conditions for all beneficiaries enrolled in Medicare for any part of a year [7]. The files provide two variables for each of these 21 chronic conditions: (1) a yearly indicator, which specifies whether the beneficiary has met the criteria for the chronic condition during the year, and (2) a first-indication date, which is the year in which the beneficiary was first identified as having met the criteria for the chronic condition. HF is one of the 21 chronic conditions tracked by Medicare; the type of HF (whether with reduced or preserved ejection fraction) is not specified. For the analysis database used in this study, all black Medicare beneficiaries who were alive and identified within Medicare as having HF in 2006 were included. Then, for each year after 2006 through 2012, based on the first-indication date for HF, black beneficiaries newly identified within Medicare as having HF were included.

Because health-maintenance organizations do not report all reimbursements to CMS, the study excluded Medicare beneficiaries who were covered for more than 2 months by an HMO. The study also excluded beneficiaries who did not receive their prescription drugs through Medicare Part D. Medicare Part D data include information from pharmacies about prescriptions covered by Part D insurance plans. Using the Medicare Part D Event (PDE) file, which is linked to Medicare by patient identification numbers, it was possible to determine medications prescribed to black beneficiaries with HF. Each row in the PDE file corresponded to a single prescription drug refill for a beneficiary, listing the national drug code, the date of refill, and days of supply. The PDE file, however, does not specify the indication for which any drug is prescribed. Prescription refills of FDC-ISDN/HYD, ISDN, ISMN, and HYD were identified by the national drug codes for the medications. For one of the generic combinations to qualify as a substitute for FDC-ISDN/HYD, we required that prescription refills of the two separate drugs (ISDN and HYD, or ISMN and HYD) be made within 30 days of each other.

We also required adherence to the medications as measured by the proportion-of-days-covered (PDC) method [8]. The PDC score was calculated based on fill dates and days of supply for each prescription appearing in the PDE file. In the PDC score, the numerator was the total number of days covered by the medication refills during the measurement period, defined as extending from the index prescription date to the end of the calendar year. The PDC-score denominator was the total number of days between the first prescription fill and the end of the study period or disenrollment or death. Any black beneficiary with HF and a PDC score $\geq$80% was considered adherent to FDC-ISDN/HYD, OLC-ISDN+HYD, or OLC-ISMN+HYD. Any beneficiary with a PDC score <80% was excluded from the analysis.

The outcome of interest for comparison between the treatment groups was all-cause mortality on the basis of death dates registered in the Medicare file. Using the PDC method, it was possible to identify a sufficient number of adherent patients for survival analysis after the first year of inclusion in the study database. But it was not possible to do that for any subsequent years, because the number of PDC-defined adherent patients was too low after the first year. Consequently, survival rates were determined for only the single year of demonstrated medication adherence. For the black beneficiaries identified as having HF in 2006 or before and who were included in the study database, the year of adherence used for survival analysis

was 2007. For black beneficiaries newly identified as meeting the Medicare criteria for HF in the years 2007–2012, the year of adherence used for the survival analysis was the immediately following year, 2008–2013, respectively.

Compliance with Ethics Guidelines

This article was based on an analysis of publically available US Medicare data and did not involve any studies in humans and animals performed by the authors.

Statistical Methods and Study Endpoint

Two sets of matched cohort pairs were produced on a 1:1 ratio basis using propensity-score probabilities [9–11]. The first set of matched cohort pairs included beneficiaries adherent to FDC-ISDN/HYD and beneficiaries adherent to OLC-ISDN+HYD. The second set of matched cohort pairs included beneficiaries adherent to FDC-ISDN/HYD and beneficiaries adherent to OLC-ISMN+HYD. Demographic factors (age, sex) and medical conditions at baseline (presence of acute myocardial infarction, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, stroke or transient ischemic attack, and cancer) were treated as covariates for propensity matching. A generalized SAS macro for propensity-score matching was used [12]. Standardized mean differences quantified the bias in the means or proportions of the matched cohorts. Differences between the cohorts were evaluated using the *t* test for continuous variables and the chi-square test for categorical variables. For the analysis of death from any cause, standard Kaplan-Meier survival curves with the log-rank test were separately calculated for the FDC-ISDN/HYD and OLC-ISDN+HYD matched cohorts and for the FDC-ISDN/HYD and OLC-ISMN+HYD matched cohorts. Additional descriptive statistics were reported as mean ± SD or the total number (percentage). Statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Relatively few black Medicare beneficiaries identified as having HF received FDC-ISDN/HYD or the off-label combinations. For example, in 2007, 59,758 black beneficiaries were newly identified within Medicare as having HF. Of these, 34,804 (58%) received prescriptions for treatment of HF under Medicare Part D in 2008. Of these prescriptions, 352 (1.0%) were for FDC-ISDN/HYD, 344 (0.99%) were for OLC-ISDN+HYD, and 347 (1.0%) were for OLC-ISMN+HYD (Table 1).

The overall rate of adherence to the medications, as defined by a PDC score ≥80%, was approximately 33%. In the study database, 28.2% of the black patients prescribed FDC-ISDN/HYD were adherent, 31.3% of patients prescribed OLC-ISDN+HYD were adherent, and 36.2% of patients prescribed OLC-ISMN+HYD were adherent (Table 1).

Table 2 presents the demographic and clinical characteristics of the black Medicare beneficiaries with HF who were adherent to FDC-ISDN/HYD or to the off-label combinations. The beneficiaries were relatively older (mean age 77.3 ± 7.8 years) and predominantly female (66.7%). The beneficiaries had a high prevalence of ischemic heart disease (85.9%), chronic kidney disease (74.9%), diabetes (70.9%), and chronic obstructive pulmonary disease (28.6%). The prevalence of atrial fibrillation was also high for a black population (17.3%) [13].

After propensity-score matching, there were 886 matched pairs in the FDC-ISDN/HYD and OLC-ISDN+HYD matched cohorts (Table 3), and there were 868 matched pairs in the FDC-ISDN/HYD and OLC-ISMN+HYD matched cohorts (Table 4). The standardized mean differences for the patient variables in the two matched-pair composite cohorts were consistently <0.1.

During the single years of medication adherence for the black Medicare beneficiaries in the FDC-ISDN/HYD and OLC-ISDN+HYD matched cohorts, there were 107 deaths (12.1%) from all causes in the FDC-ISDN/HYD cohort and 151 deaths (17.0%) from all causes in the

Table 1 Black Medicare beneficiaries identified as having heart failure who received Part D prescriptions to FDC-ISDN/HYD or off-label combinations and were adherent

Year identified as having HF within Medicare	Total no.	No. who received Part D prescriptions in following year	FDC-ISDN/HYD prescriptions, *n* (%)	FDC-ISDN/HYD adherent, *n* (%)	OLC-ISDN+HYD prescriptions, *n* (%)	OLC-ISDN+HYD adherent, *n* (%)	OLC-ISMN+HYD prescriptions, *n* (%)	OLC-ISMN+HYD adherent, *n* (%)
2006 or before	309,613	191,068	2322 (1.2%)	782 (33.7%)	2723 (1.4%)	889 (32.6%)	4963 (2.6%)	1690 (34.1%)
2007	59,758	34,804	352 (1.0%)	88 (25.0%)	344 (0.99%)	110 (32.0%)	347 (1.0%)	198 (57.0%)
2008	58,615	28,208	278 (1.0%)	50 (18.0%)	286 (1.0%)	83 (29.0%)	282 (1.0%)	127 (45.0%)
2009	57,332	27,538	277 (1.0%)	47 (17.0%)	272 (1.0%)	82 (30.2%)	274 (1.0%)	167 (61.0%)
2010	59,649	27,280	269 (1.0%)	43 (16.0%)	271 (1.0%)	76 (28.0%)	271 (1.0%)	122 (45.0%)
2011	57,683	28,994	296 (1.0%)	68 (23.0%)	292 (1.0%)	73 (25.0%)	290 (1.0%)	122 (42.1%)
2012	54,133	31,522	320 (1.0%)	80 (25.0%)	310 (1.0%)	93 (30.0%)	317 (1.0%)	57 (18.0%)
Total		369,414	4114 (1.1%)	1158 (28.2%)	4498 (1.2%)	1406 (31.3%)	6744 (1.8%)	2483 (36.2%)

Adherence was defined as a proportion of days covered (PDC) score ≥80%

FDC-ISDN/HYD fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride, *HF* heart failure, *OLC-ISDN+HYD* off-label combination use of isosorbide dinitrate and hydralazine hydrochloride, *OLC-ISMN+HYD* off-label combination use of isosorbide mononitrate and hydralazine hydrochloride

Table 2 Before propensity-score matching: demographic and clinical characteristics of black Medicare beneficiaries prescribed and adherent to FDC-ISDN/HYD or to off-label combinations

Variables	FDC-ISDN/HYD adherent ($n = 1158$)	OLC-ISDN+HYD adherent ($n = 1406$)	OLC-ISMN+HYD adherent ($n = 2483$)	Total adherent to medication ($n = 5047$)
Age, years (mean ± SD)	77.2 ± 7.8	77.2 ± 7.9	77.3 ± 7.7	77.3 ± 7.8
Sex, *n* (%)				
Male	402 (34.7%)	512 (36.4%)	769 (31.0%)	1683 (33.3%)
Female	756 (65.3%)	894 (63.6%)	1714 (69.0%)	3364 (66.7%)
Medical conditions, *n* (%)				
Acute myocardial infarction	70 (6.0%)	114 (8.1%)	191 (7.7%)	375 (7.4%)
Atrial fibrillation	228 (19.7%)	251 (17.9%)	392 (15.8%)	871 (17.3%)
Chronic kidney disease	786 (67.9%)	1075 (76.5%)	1920 (77.3%)	3781 (74.9%)
Chronic obstructive pulmonary disease	324 (28.0%)	405 (28.8%)	714 (28.8%)	1443 (28.6%)
Diabetes	825 (71.2%)	962 (68.4%)	1792 (72.2%)	3579 (70.9%)
Ischemic heart disease	982 (84.8%)	1179 (83.9%)	2173 (87.5%)	4334 (85.9%)
Stroke or transient ischemic attack	144 (12.4%)	236 (16.8%)	389 (15.7%)	769 (15.2%)
Any cancer	98 (8.5%)	124 (8.8%)	177 (7.1%)	339 (6.7%)

Adherence was defined as a proportion-of-days covered (PDC) score ≥80%
FDC-ISDN/HYD fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride, *OLC-ISDN+HYD* off-label combination use of isosorbide dinitrate and hydralazine hydrochloride, *OLC-ISMN+HYD* off-label combination use of isosorbide mononitrate and hydralazine hydrochloride

OLC-ISDN+HYD cohort, a percentage difference of 41%. Similarly, during the single years of medication adherence in the FDC-ISDN/HYD and OLC-ISMN+HYD matched cohorts, there were 102 deaths (11.8%) from all causes in the FDC-ISDN/HYD cohort and 132 deaths (15.9%) from all causes in the OLC-ISMN+HYD cohort, a percentage difference of 29%.

For the FDC-ISDN/HYD and OLC-ISDN+HYD matched cohorts during the single years of medication adherence, the Kaplan-Meier estimates of 1-year overall survival were 87.9% (95% CI 85.6–89.9%) for the patients receiving FDC-ISDN/HYD versus 83.0% (95% CI 80.3–85.3%) for the patients receiving OLC-ISDN+HYD group (Fig. 1). For the FDC-ISDN/HYD and OLC-ISMN+HYD matched cohorts during the single years of medication adherence, the Kaplan-Meier estimates of 1-year overall survival were 88.2% (95% CI 85.9–90.2%) for the FDC-ISDN/HYD group and 84.8% (95% CI 82.2–87.0%) for the OLC-ISMN+HYD group (Fig. 2). The log-rank test revealed a statistically significant difference for 1-year overall survival between patients adherent to FDC-ISDN/HYD and patients adherent to OLC-ISDN+HYD ($p = 0.0024$) and between patients adherent to FDC-ISDN/HYD and patients adherent to OLC-ISMN+HYD ($p = 0.0320$).

DISCUSSION

This retrospective propensity-matched analysis of black Medicare beneficiaries with HF has

Table 3 After propensity-score matching: demographic and clinical characteristics of the propensity-matched composite cohorts of black Medicare beneficiaries found adherent to FDC-ISDN/HYD or OLC-ISDN+HYD

Variables	FDC-ISDN/HYD adherent (n = 886)	OLC-ISDN+HYD adherent (n = 886)	Standardized mean difference	p value
Age, years (mean ± SD)	77.0 ± 7.7	77.0 ± 7.5	0.000	0.953
Sex, n (%)				
Male	287 (32.4%)	275 (31.0%)	0.030	0.540
Female	599 (67.6%)	611 (69.0%)		
Medical conditions, n (%)				
Acute myocardial infarction	40 (4.5%)	45 (5.1%)	0.028	0.578
Atrial fibrillation	131 (14.8%)	132 (14.9%)	0.003	0.947
Chronic kidney disease	665 (75.1%)	659 (74.4%)	0.016	0.743
Chronic obstructive pulmonary disease	246 (27.8%)	257 (29.0%)	0.027	0.562
Diabetes	651 (73.5%)	645 (72.8%)	0.016	0.748
Ischemic heart disease	773 (87.2%)	769 (86.8%)	0.012	0.777
Stroke or transient ischemic attack	90 (10.2%)	91 (10.3%)	0.003	0.938
Any cancer	47 (5.3%)	44 (5.0%)	0.014	0.747

Adherence was defined as a proportion-of-days covered (PDC) score ≥80%
FDC-ISDN/HYD fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride, *OLC-ISDN+HYD* off-label combination use of isosorbide dinitrate and hydralazine hydrochloride

found a suggestive significant 1-year survival difference between black Medicare beneficiaries with HF who received and were adherent to FDC-ISDN/HYD and black Medicare beneficiaries with HF who received and were adherent to either of the two off-label generic combinations. This finding lends support to the FDA Orange Book assertion that there is no therapeutic equivalent for the fixed-dose combination (the off-label combinations are not therapeutically equivalent) and should lead to prospective investigation.

The adherent black beneficiaries with HF in this study database were older and had a significantly higher burden of comorbid disease than the self-identified African American patients enrolled in the A-HeFT trial (mean age 57 years)—a difference to be expected between a real-world setting, consisting of Medicare patients, and a controlled clinical trial. Khazanie et al. identified 316 Medicare patients who had been discharged from hospital with a prescription for ISDN/HYD using the Get with the Guidelines registry linked with Medicare claims [14]. The Medicare patients identified in the current study and those identified by Khazanie et al. were of similar age (approximately 77 versus 75.3 years). But those in the current study were also predominantly female (66.7% versus 43.9%) and had a higher incidence of diabetes (70.9% versus 50.3%) and chronic kidney disease (74.9% versus 25.9%).

Khazanie et al. found that only 46% of black Medicare patients discharged with a prescription for ISDN/HYD filled the prescription within 90 days [14]. In the current analysis, in which adherence was defined as a PDC score ≥80%), the rate of adherence across the drug

Table 4 After propensity-score matching: demographic and clinical characteristics of the propensity-matched composite cohorts of black Medicare beneficiaries found adherent to FDC-ISDN/HYD or OLC-ISMN+HYD

Variables	FDC-ISDN/HYD adherent (n = 868)	OLC-ISMN+HYD adherent (n = 868)	Standardized mean difference	p value
Age, years (mean ± SD)	76.8 ± 7.5	76.9 ± 7.5	0.013	0.845
Sex, n (%)				
Male	277 (31.9%)	272 (31.3%)	0.013	0.796
Female	591 (68.1%)	596 (68.7%)		
Medical conditions, n (%)				
Acute myocardial infarction	53 (6.1%)	54 (6.2%)	0.004	0.921
Atrial fibrillation	115 (13.2%)	120 (13.8%)	0.018	0.726
Chronic kidney disease	650 (74.9%)	648 (74.7%)	0.005	0.912
Chronic obstructive pulmonary disease	227 (26.2%)	246 (28.3%)	0.047	0.306
Diabetes	657 (75.7%)	656 (75.6%)	0.002	0.955
Ischemic heart disease	775 (89.3%)	782 (90.1%)	0.026	0.581
Stroke or transient ischemic attack	102 (11.8%)	103 (11.9%)	0.003	0.941
Any cancer	50 (5.8%)	54 (6.2%)	0.017	0.686

Adherence was defined as a proportion-of-days covered (PDC) score ≥80%
FDC-ISDN/HYD fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride, *OLC-ISMN+HYD* off-label combination use of isosorbide mononitrate and hydralazine hydrochloride

groups for the respective analysis years was approximately 33%. Adherence to the fixed-dose and off-label combinations of ISDN and HYD is known to be poor and is generally explained by the large number of tablets required, the frequency of administration (three times a day dosing), and the incidence of possible adverse reactions, such as headache, dizziness, and gastrointestinal complaints [5, 14, 15]. Titration of the drug is recommended to enhance tolerance of therapy [1, 4].

Evidence-based medicine is built upon the foundation that evidence derived from randomized trials is more highly valued than expert opinion. Unfortunately, owing in part to the overriding of A-HeFT results by expert opinion, African Americans with HF do not routinely receive FDC-ISDN/HYD as standard-of-care medicine [16]. Since approval of FDC-ISDN/HYD by the FDA, critics have questioned the integrity of the results of A-HeFT; because no white patients were enrolled in A-HeFT, it was concluded by some that use of FDC-ISDN/HYD for treatment of HF in African Americans must promote "race" medicine [17]. These critics asserted that OLC-ISDN+HYD is a generic form of FDC-ISDN/HYD and state that FDC-ISDN/HYD is merely a more convenient preparation of ISDN and HYD that reduces every two pills of OLC-ISDN+HYD to the single pill of FDC-ISDN/HYD. Consequently, use of FDC-ISDN/HYD must "take advantage of" African Americans with HF because OLC-ISDN+HYD is available and less expensive than FDC-ISDN/HYD. Making assumptions about ability to pay for a

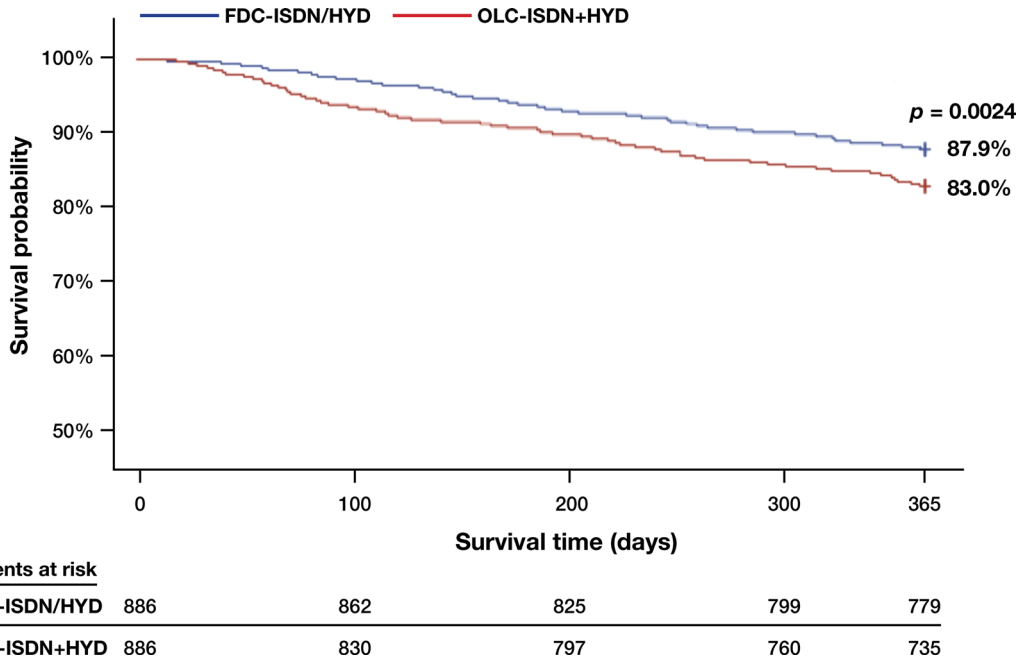

Fig. 1 Survival analysis for propensity-matched composite cohorts of black Medicare beneficiaries found adherent to the fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride (FDC-ISDN/HYD) or to the off-label combination use of isosorbide dinitrate and hydralazine hydrochloride (OLC-ISDN+HYD). Adherence was defined as a proportion-of-days-covered score ≥80%

unique and approved medication based on ethnicity has no scientific or ethical merit.

The substitution of OLC-ISDN+HYD finds support in the medical community among those who disregard the FDA-approval process and FDA labeling, which has consistently maintained since 2005 that FDC-ISDN/HYD is a unique drug with no therapeutic equivalent [2]. No published studies have supported claims that FDC-ISDN/HYD and OLC-ISDN+HYD are therapeutically equivalent.

It has also been suggested that HYD plus any nitrate (H+N) can be substituted for FDC-ISDN/HYD [5, 16]. In their analysis, Khazanie et al. defined "H-ISDN therapy" as "prescriptions filled for hydralazine nitrate combinations (i.e., fixed-dose combination of hydralazine and isosorbide dinitrate, hydralazine and isosorbide mononitrate, or hydralazine and isosorbide dinitrate), as well as mineralocorticoid antagonists" [14]. They reported that "for both black patients and patients of other races, there were no differences in outcomes between those treated [with H-ISDN therapy] and untreated at discharge." In fact, no published clinical study has supported H+N as a substitute for FDC-ISDN/HYD, although Khazanie et al. lead physicians and patients to assume that in clinical settings "H-ISDN therapy" is ineffective.

Fonarow et al. have estimated that following clinical guidelines, about 27% of African Americans with HF in the US are eligible to receive FDC-ISDN/HYD, but they have observed that compliance with these guidelines is poor [18]. These investigators concluded that appropriate use of ISDN/HYD could prevent 6655 premature deaths annually [18]. By their estimate, 75,000 black Medicare beneficiaries died prematurely between the years of 2007 and 2015 because they did not receive this standard of care.

FDC-ISDN/HYD was the first drug that the FDA approved to treat a disease in a specific racial group. Neither the manufacturer nor the FDA asserted that racial differences explained the effectiveness of FDC-ISDN/HYD in self-identified African Americans, but the science was clear: FDC-ISDN/HYD produced a 43%

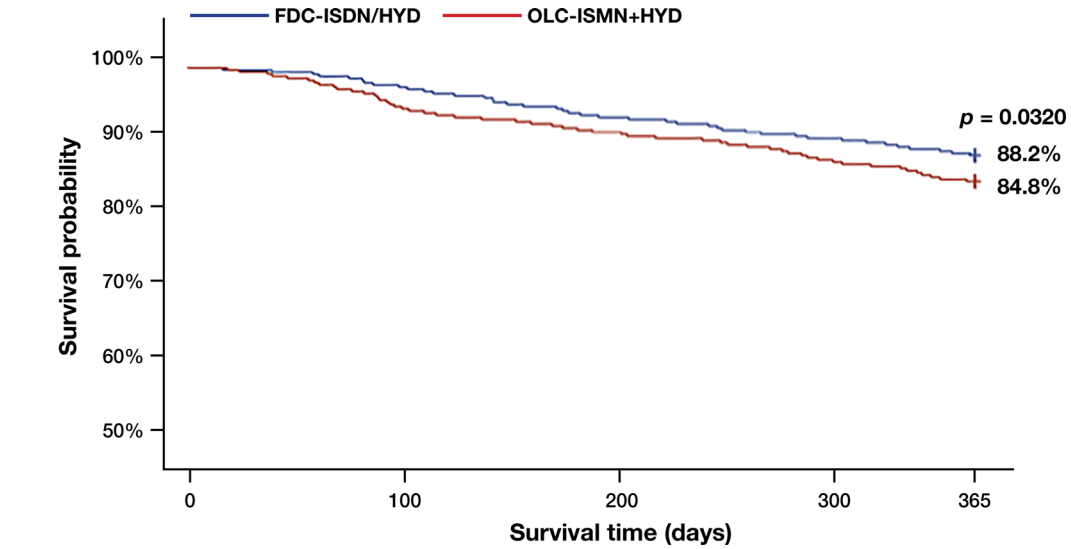

Fig. 2 Survival analysis for propensity-matched composite cohorts of black Medicare beneficiaries found adherent to the fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride (FDC-ISDN/HYD) or to the off-label combination use of isosorbide mononitrate and hydralazine hydrochloride (OLC-ISMN+HYD). Adherence was defined as a proportion-of-days-covered score ≥80%

reduction in mortality for self-identified African Americans with HF [1]. This compelling mortality benefit warranted FDA approval of the medication. In the absence of more specific indicators, the appropriate clinical approach is to heed evidence in prescribing a life-saving therapy.

A recent investigation based on data drawn from A-HeFT suggested that a functional polymorphism of the guanine nucleotide-binding protein beta polypeptide 3 subunit (GNB3) influenced the therapeutic efficacy of FDC-ISDN/HYD [19]. The Genomic Response Analysis of Heart Failure Therapy in African Americans (GRAHF-2) study (NCT02305095) is now underway in 500 self-identified African Americans with HF to confirm whether subjects with the GNB3 TT genotype have better outcomes with FDC-IDSN/HYD. Future research may find that non-African Americans with HF who have that genotype may also benefit from FDC-ISDN/HYD, making FDC-ISDN/HYD the first precision medicine for HF.

To redress the imbalance between science and opinion regarding FDC-ISDN/HYD, the National Minority Quality Forum (NMQF) submitted an HF performance measure to the National Quality Forum (NQF), which is recognized by the US Congress as a consensus organization whose mission is to endorse performance measures. Performance measures tie clinician reimbursement to specific performance criteria to ensure the delivery of quality care. The NMQF HF performance measure prescribes FDC-ISDN/HYD for self-identified African Americans who remain symptomatic while on angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or beta blockers. In reviewing the evidence, the NQF determined that African Americans are not receiving the standard of care, that there is a need for such a performance measure, and that the science does not support the substitution of OLC-ISDN+HYD or OLC-ISMN+HYD for FDC-ISDN/HYD [20].

The results in this study must be interpreted with caution owing to the limitations of the Medicare databases. Medicare claims data offer documentation that a beneficiary has been

treated for HF, what treatments the beneficiary received, who provided care, the cost of care, and the rates of acute events (inpatient stay, outpatient visits, and death), but they do not record the beneficiary's symptoms, the actual condition of the heart, or clinically relevant description of disease intensity. For example, it is unknown whether the black Medicare patients with HF identified in this study as receiving FDC-ISDN/HYD or the off-label combinations have preserved or reduced EF. In the ACCF/AHA 2013 HF guideline, the combination of ISDN and HYD is recommended only for self-described African American patients with reduced EF [4]. However, there is no evidence to support the use of combination therapy with these drugs—or of any nitrate alone or of HYD alone—for treatment in HF patients with preserved ejection fraction [21, 22]. The assumption can thus be made that the black Medicare patients with HF identified as receiving the different combinations in this study had reduced EF, but of course that assumption cannot be verified.

Medicare Part D data provide information about prescription refills, but they do not indicate what the medications are prescribed for. In this study, we assumed that if the separate drugs ISDN and HYD or the separate drugs ISMN and HYD were prescribed within 30 days of each other, the separate prescriptions were intended to be combined as generic substitutes for FDC-ISDN/HYD; however, that interpretation cannot be validated. In the ACCF/AHA 2013 HF guideline, the combination of ISDN and HYD is recommended for self-described African American HF patients "receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated" [4]. A criterion for this study's analysis database was treatment adherence as measured by the PDC method; it was impossible to add other drugs to qualify the patient set because the resulting number of patients was insufficient for survival analysis after propensity-matched scoring. With respect to the same criterion, it was impossible to extend the survival analysis beyond a single year because there were too few adherent beneficiaries after the first year of prescribed treatment.

CONCLUSION

In this retrospective propensity-matched analysis of black Medicare beneficiaries with HF who were medication adherent, there was a 1-year survival advantage for FDC-ISDN/HYD compared with the off-label combinations, suggesting a genuine difference between these medications. Despite the limitations of the Medicare databases, they can provide useful signals about the patterns and variations in care that African Americans with HF do or do not receive.

ACKNOWLEDGEMENTS

Sponsorship for this study, the article-processing charges, and the open-access fee were funded by Arbor Pharmaceuticals, LLC. Medical writing support was provided by representatives of Galen Press, Inc., and was funded by Arbor Pharmaceuticals, LLC. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval of the version to be published. The content of the manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures. Liou Xu is an employee of the National Minority Quality Form, which has received funding from Arbor Pharmaceuticals, LLC. Gary Puckrein is an employee of the National Minority Quality Form, which has received funding from Arbor Pharmaceuticals, LLC. Elizabeth Ofili is employed by Morehouse School of Medicine and receives research support from the National Institute on Minority Health and Health Disparities of the National Institutes of Health under Award Numbers U54MD008149, U54MD007588, and U54MD008173, also from the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454. Inder Anand, Richard

Allen Williams, and Ola Akinboboye have nothing to disclose.

Compliance with Ethics Guidelines. This article was based on an analysis of publically available US Medicare data and does not involve any studies in humans or animals performed by the authors.

Data Availability. The data sets analyzed for the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–57.

2. United States Food and Drug Administration. Orange book: approved drug products with therapeutic equivalence evaluations. http://www.accessdata.fda.gov/scripts/cder/ob/. Accessed May 5, 2017.

3. Tam SW, Sabolinski ML, Worcel M, Packer M, Cohn JN. Lack of bioequivalence between different formulations of isosorbide dinitrate and hydralazine and the fixed-dose combination of isosorbide dinitrate/hydralazine: the V-HeFT paradox. Clin Pharmacokinet. 2007;46:885–95.

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147–239.

5. Cole RT, Kalogeropoulos AP, Georgiopoulou VV, Gheorghiade M, Quyyumi A, Yancy C, et al. Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and future directions. Circulation. 2011;123:2414–22.

6. Centers for Medicare and Medicaid Services. Chronic conditions data warehouse. Medicare Administrative Data User Guide: Version 3.1, March 2015. https://www.ccwdata.org/cs/groups/public/documents/document/ccw_userguide.pdf. Accessed May 5, 2017.

7. Centers for Medicare and Medicaid Services. Chronic condition data warehouse: CCW Medicare Part D Data User Guide: Version 5.2, October 2015. https://www.ccwdata.org/cs/groups/public/documents/document/ccw_partddata_userguide.pdf. Accessed May 5, 2017.

8. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Pharmacy Quality Alliance. Medication Adherence Resource Center. http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf. Accessed May 5, 2017.

9. Rosenbaum PR, Rubin DB. The central role of the propensity score: relating theory to practice. Biometrika. 1983;70:41–55.

10. Rubin DB, Thomas N. Matching using estimated propensity score: relating theory to practice. Biometrics. 1996;52:249–64.

11. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci. 2010;25:1–21.

12. Hardis Fraeman K, Malley KG. Dynamic generation of SAS data step programming from an Excel data dictionary. 2010. http://www.lexjansen.com/nesug/nesug99/po/po096.pdf. Accessed May 5, 2017.

13. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158:111–7.

14. Khazanie P, Liang L, Curtis LH, Butler J, Eapen ZJ, Heidenreich PA, et al. 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. Circ Heart Fail. 2016;9:e002444.

15. Eapen ZJ, Hammill BG, Setoguchi S, Schulman KA, Peterson ED, Hernandez AF, et al. Who enrolls in the Medicare Part D prescription drug benefit program? Medication use among patients with heart failure. J Am Heart Assoc. 2013;2:e000242.

16. Golwala HB, Thadani U, Liang L, Stavrakis S, Butler J, Yancy CW, et al. Use of hydralazine-isosorbide dinitrate combination in African American and

other race/ethnic group patients with heart failure and reduced left ventricular ejection fraction. J Am Heart Assoc. 2013;2:e000214.

17. Kahn J. Race in a bottle: the story of BiDil and racialized medicine in a post-genomic age. New York: Columbia University Press; 2013.

18. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J. 2011;161(1024–30):e3.

19. McNamara DM, Taylor AL, Tam SW, Worcel M, Yancy CW, Hanley-Yanez K, et al. G-protein beta-3 subunit genotype predicts enhanced benefit of fixed-dose isosorbide dinitrate and hydralazine: results of A-HeFT. JACC Heart Fail. 2014;2:551–7.

20. National Quality Forum. NQF-endorsed measures for cardiovascular conditions, 2015–2016: final report, May 3, 2016. Washington, DC; National Quality Forum. https://www.qualityforum.org/Publications/2016/05/Cardiovascular_Conditions,_2015-2016_-_Final_Report.aspx. Accessed May 5, 2017.

21. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med. 2015;373:2314–24.

22. Zamani P, Akers S, Soto-Calderon H, Beraun M, Koppula MR, Varakantam S, et al. Isosorbide dinitrate, with or without hydralazine, does not reduce wave reflections, left ventricular hypertrophy, or myocardial fibrosis in patients with heart failure with preserved ejection fraction. J Am Heart Assoc. 2017;6.