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Racial Differences in Trends and Prognosis of Guideline-Directed Medical Therapy for Heart Failure with Reduced Ejection Fraction: the Atherosclerosis Risk in Communities (ARIC) Surveillance Study

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Abstract

Background Racial disparities in guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) have not been fully documented in a community setting.

Methods In the ARIC Surveillance Study (2005–2014), we examined racial differences in GDMT at discharge, its temporal trends, and the prognostic impact among individuals with hospitalized HFrEF, using weighted regression models to account for sampling design. Optimal GDMT was defined as beta blockers (BB), mineralocorticoid receptor antagonist (MRA) and ACE inhibitors (ACEI) or angiotensin II receptor blockers (ARB). Acceptable GDMT included either one of BB, MRA, ACEI/ARB or hydralazine plus nitrates (H-N).

Results Of 16,455 (unweighted $n = 3{,}669$) HFrEF cases, 47% were Black. Only ~ 10% were discharged with optimal GDMT with higher proportion in Black than White individuals (11.1% vs. 8.6%, $p < 0.001$). BB use was > 80% in both racial groups while Black individuals were more likely to receive ACEI/ARB (62.0% vs. 54.6%) and MRA (18.0% vs. 13.8%) than Whites, with a similar pattern for H-N (21.8% vs. 10.1%). There was a trend of decreasing use of optimal GDMT in both groups, with significant decline of ACEI/ARB use in Whites (− 2.8% $p < 0.01$) but increasing H-N use in both groups (+ 6.5% and + 9.2%, $p < 0.01$). Only ACEI/ARB and BB were associated with lower 1-year mortality.

Conclusions Optimal GDMT was prescribed in only ~ 10% of HFrEF patients at discharge but was more so in Black than White individuals. ACEI/ARB use declined in Whites while H-N use increased in both races. GDMT utilization, particularly ACEI/ARB, should be improved in Black and Whites individuals with HFrEF.

Keywords Heart failure · Racial differences · Guideline-directed medical therapy · Pharmacoepidemiology · Health care quality

Abbreviations

ACEI	Angiotensin-converting-enzyme inhibitor
AF	Atrial fibrillation or flutter
ARB	Angiotensin-receptor blocker
ARIC	Atherosclerosis Risk in Communities Study
BB	Beta blocker

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BMI	Body mass index
CHD	Coronary heart disease
CKD	Chronic kidney disease
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
H-N	Hydralazine nitrate
HR	Heart rate
GDMT	Guideline-directed medical therapy
MMCC	Morbidity and mortality
MRA	Mineralocorticoid receptor antagonist
LVEF	Left ventricular ejection fraction
SBP	Systolic blood pressure
IABP	Intra-aortic balloon pump
LVAD	Left ventricular assist device
eGFR	Estimated glomerular filtration rate

Introduction

Heart failure (HF) is associated with substantial morbidity, mortality, and healthcare costs, with a 1- and 5-year mortality rate of 30% and 52% respectively after diagnosis [1–3]. Neurohormonal blocking medications reduce mortality and recurrent HF events from HF with reduced ejection fraction (HFrEF) [4]. The implementation of guideline-directed medical therapies (GDMT) in patients with HFrEF has contributed to a reduction in HF mortality rates in the USA [5]. However, these declines have not occurred uniformly across all racial groups [3, 6]. For example, Black individuals are more likely to develop HF from modifiable risk factors such as hypertension and diabetes compared to Whites [7–9]. Black people have a higher incidence of HF at younger ages [7], with Black men having the highest incidence of HF across all ages and racial groups [10]. Young Black men and women with HF have higher mortality compared to Whites with rising trends in mortality over the last few years [6]. Furthermore, there is data to suggest Black patients are less likely than non-Black patients to receive guideline-recommended cardiovascular diagnostic and therapeutic interventions including cardiac catheterization, revascularization after myocardial infarction, and cardiac rehabilitation [11–17]. With regard to HF, one study showed that Black patients with acute HF were less likely to be admitted to cardiology specialty services compared to White patients [18].

Guidelines on the use of contemporary neurohormonal therapies for HFrEF have been in place since 2005 [19]. Yet a substantial number of HFrEF patients are still not treated with GDMT [20–33]. Data from the CHAMP-HF registry (Change the Management of Patients with Heart Failure) demonstrated that 63%, 47%, and 33% of eligible patients were on angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA) respectively [27]. To the best of our knowledge, only one study has examined racial differences in utilization of HFrEF GDMT. Data from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry reported that Black patients received similar or higher proportions of GDMT than Whites [30]. While these findings were encouraging, this data was from a quality improvement registry and therefore it is important to confirm these findings in the community. Furthermore, there has not been a systematic examination of trends in GDMT use by race over time. Information on GDMT trends in community-settings and across racial groups would be a valuable addition to the literature.

Our objective was to examine the prescription patterns of GDMT at hospital discharge with HFrEF in the community and assess the 10-year temporal trends by race. In addition, we evaluated the association of GDMT with all-cause mortality among patients with HFrEF by race.

Methods

Setting

Between 2005 and 2014, the Atherosclerosis Risk in Communities (ARIC) Study conducted continuous community surveillance of hospitalized HF events of residents who were over the age of 55 years living in four US communities that differed by geography, race, and socioeconomic status: Forsyth County, North Carolina; Jackson, Mississippi; the suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The methods used for event surveillance have previously been described [3, 34, 35].

Eligible hospitalizations were selected from hospitals in the ARIC communities using algorithms based on (1) age $\geq$ 55 years, (2) home address within the boundaries of the ARIC communities, and (3) International Classification of Diseases, 9th Revision (ICD-9) discharge diagnosis codes for HF or HF-related conditions (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 415.0, 416.9, 425.4, 428.x, 518.4, 786.0x). The sampling scheme was targeted to achieve a balance in incident events between field center, sex, and race [34].

Medical Record Abstraction

The abstracters obtained data related to the hospitalization including history, physical exam, diagnostic studies, and medications. Cases were classified by algorithms and reviewed independently by two physicians in the ARIC Mortality and Morbidity Classification Committee (MMCC) and grouped into five categories: definite decompensated HF;

possible decompensated HF; chronic stable HF; HF unlikely; or unclassifiable. Disagreements between the cases reviewed by the two MMCC reviewers were adjudicated by the chair of the MMCC.

Study Population

We included definite and possible decompensated HF with left ventricular ejection fraction (LVEF) < 50% as HFrEF in this study, as has previously done in ARIC (including patients with recovered HF) [3]. We excluded Black individuals from the predominantly White communities of Minneapolis and Washington County, and individuals who were neither Black nor White due to small numbers (< 5%), as has been done in previous ARIC Surveillance analyses [3]. We also excluded patients who died prior to discharge, discharged to hospice, transferred to another facility, lost to follow-up, left against medical advice, and those missing key variables. Out of 23,409 adjudicated HF events, there were 3,669 HFrEF events ($n = 16,455$ weighted) for the final study sample (Fig. 1).

Independent Variable: Race

Race was obtained from chart abstraction from hospitalization records and characterized as Black or White.

Dependent Variable: GDMT

According to HF clinical guidelines at the time of data collection (2005–2014) [4], we defined optimal GDMT as the simultaneous use of ß-blockers (BB), angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonist (MRA). We defined acceptable GDMT as two of either ACEI/ARB, BB, MRA, or hydralazine plus nitrates (H-N). Inadequate GDMT was defined as the use of only one or no GDMT options.

Dependent Variable: Mortality

All-cause mortality at 28 days and 1 year after hospitalization was determined by linkage to the National Death Index (NDI). ARIC used standard algorithms based on patient identifiers captured in the surveillance of hospitalized events to determine if a match with the NDI was confirmed. Reported sensitivity of the NDI has ranged from 81.2 to 97.9% depending on the population studied and methodology [36, 37]. There were a minority of cases where vital status was unknown and was not submitted to the NDI (Table 1 N = 438) and these cases were excluded from our analysis.

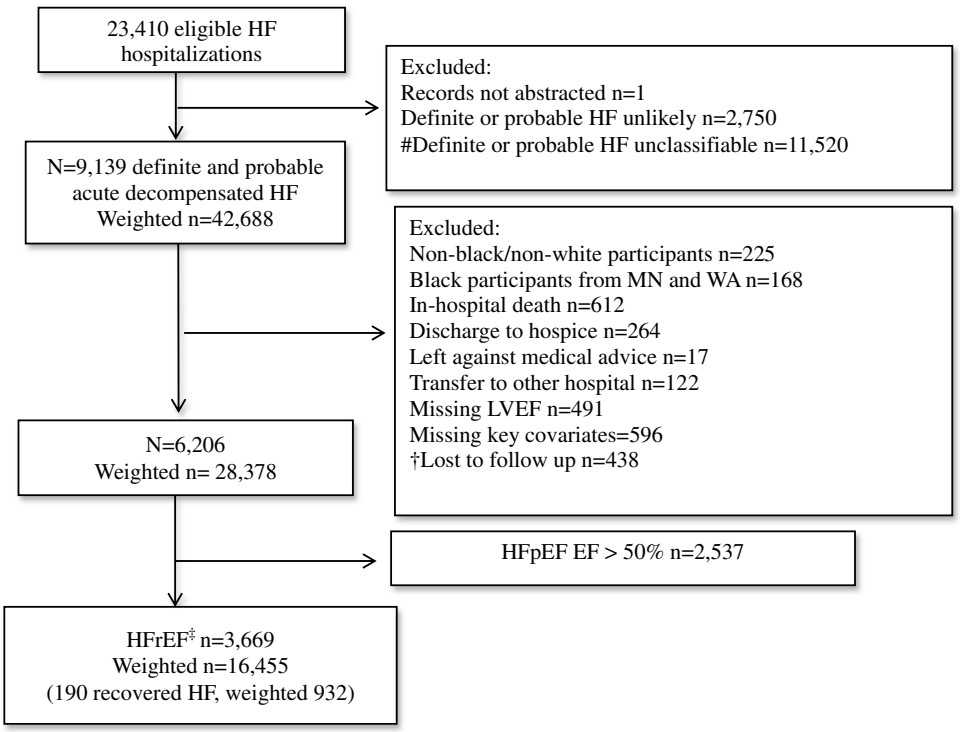

Fig. 1 Derivation of the study population, ARIC Study Community Surveillance 2005–2014. Abbreviations: HF heart failure, HFrEF heart failure with reduced ejection fraction, HFpEF heart failure with preserved ejection fraction, LVEF left ventricular ejection fraction, MN Minneapolis Suburbs, MN, WA Washington County, MD. # Unclassifiable HF (documentation not sufficient to make a clear diagnosis of whether HF present or absent). †Unknown vital status at 1 year, and not submitted to National Death Index. ‡ HFrEF (includes HFrEF and recovered HF)

Table 1 Hospitalization characteristics, ARIC Study Community Surveillance 2005–2014

	Overall population $N=16,455$	Black women $N=2,567$	Black men $N=3,155$	White women $N=4,264$	White men $N=6,469$	p value
Demographics						
Age, years, mean (SD)	72.9 (10.7)	70.8 (10.7)	67.5 (9.5)	78.2 (9.9)	75.7 (9.7)	$p<0.001$
Health Insurance (%)	95.8	98.2	92.1	97.4	97.6	$p<0.001$
Teaching hospital (%)	39.5	32.6	45.6	39.4	44.7	$p<0.001$
Clinical characteristics						
History of smoking (%)	18.8	17.1	29.2	8.6	13.1	$p<0.001$
Excess alcohol use (%)	10.4	4.4	18.7	2.5	9.6	$p<0.001$
Body mass index, kg/m^2,* mean (SD)	28.4 (9.5)	30.1 (8.6)	28.7 (12.3)	27.6 (7.8)	27.9 (8.1)	$p<0.001$
Prevalent CHD (%)	70.0	60.4	64.2	70.8	81.8	$p<0.001$
Atrial fibrillation (%)	32.8	21.5	22.9	40.0	45.0	$p<0.001$
Hypertension (%)	86.1	92.5	90.0	81.8	81.4	$p<0.001$
Diabetes (%)	48.3	56.1	50.4	42.3	48.2	$p<0.001$
COPD (%)	31.6	26.5	27.5	33.6	35.6	$p<0.001$
Hospitalization characteristics						
SBP on admission, mmHg, mean (SD)	142.1 (33.7)	149.9 (34.5)	146.6 (35.2)	140.4 (32.9)	134.8 (30.8)	$p<0.001$
HR on admission, beats per minute, mean (SD)	91.2 (24.0)	91.8 (24.0)	92.1 (24.0)	93.1 (24.4)	88.8 (23.6)	$p<0.001$
eGFR, ml/min/1.73m^2, mean (SD)	47.8 (23.9)	42.6 (23.9)	47.6 (24.5)	48.0 (21.9)	50.6 (24.1)	$p<0.001$
Left ventricular EF, %, mean (SD)	31.0 (11.7)	30.9 (11.9)	28.1 (11.7)	33.3 (11.4)	32.3 (11.3)	$p<0.001$
Length of stay, days, mean (SD)	8.2 (39.1)	7.5 (9.0)	7.6 (16.3)	7.8 (17.2)	9.5 (65.5)	$p=0.63$
Worst sodium, mg/dl, mean (SD)	135.8 (4.3)	136.3 (4.4)	136.0 (4.1)	135.8 (4.4)	135.5 (4.5)	$p=0.002$
IABP (%)	0.2	0.5	0.2	0	0.2	$p=0.091$
LVAD (%)	<1.0	0.4	0	0	0	$p<0.001$
Inotropes (%)	7.0	8.2	8.9	5.2	6.8	$p<0.05$
GDMT categories						
Optimal (%)	9.6	9.4	12.4	7.2	9.6	$p<0.001$
Adequate (%)	53.5	61.2	57.2	47.0	49.1	
Inadequate (%)	36.9	29.4	30.4	45.8	41.3	
Beta Blocker (%)	82.0	84.5	81.4	80.7	81.3	$p=0.33$
ACEI or ARB (%)	58.4	62.2	61.9	53.7	55.1	$p<0.05$
Hydralazine and Nitrate (%)	14.9	20.0	23.2	9.2	10.6	$p<0.001$
MRA (%)	15.6	15.2	20.2	11.0	15.7	$p<0.001$
Diuretics (%)	68.0	69.0	69.3	72.8	68.2	$p=0.13$

The p-value is for the comparison between race and sex groups. Abbreviations: *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate (ml/min/1.73m^2), *CHD* coronary heart disease, moderate *CKD* chronic kidney disease (eGFR estimated glomerular filtration rate <60 ml/min/1.73m^2), *COPD* chronic obstructive pulmonary disease, *IABP* intraortic balloon pump, *LVAD* left ventricular assist device, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *MRA* mineralocorticoid receptor antagonist. *Weighted totals with body mass index measured $n=14,385$

Covariates

Other characteristics at hospitalization including demographics (age, sex, insurance status, year of hospitalization); anthropomorphic characteristics (heart rate [HR] in beats per minute and systolic blood pressure [SBP] in mmHg at admission); social habits (current or past smoker, excess alcohol use [defined as "problematic drinking," "heavy alcohol use," alcohol abuse," or other term indicating a history of excess use of alcohol or alcoholism]); and lowest LVEF from echocardiogram or other imaging modality within 2 years of hospitalization, estimated glomerular filtration rate [eGFR] in ml/min/1.73m^2, and comorbidities (hypertension, diabetes, coronary heart disease [CHD], atrial fibrillation or flutter [AF]), were obtained from chart abstraction. Markers of disease severity including sodium, inotrope use, intra-aortic balloon placement (IABP), and left ventricular assist device

placement (LVAD) were also obtained. Chronic kidney disease (CKD) was defined as eGFR ≤ 60 ml/min/1.73m^2, and severe CKD was defined as eGFR ≤ 30 ml/min/1.73m^2).

Statistical Plan

All surveillance analyses were conducted using survey procedures and weighted by the inverse of the sampling probabilities to account for the sampling design [35, 38]. Hospitalization characteristics were compared across categories of race and sex using chi-square tests and one-way analysis of variance for categorical and continuous variables respectively.

We examined the proportions of GDMT stratified by race. We used ordered logistic regression to estimate the proportional odds and 95% confidence intervals of the association of race with GDMT. We also performed logistic regression for each individual therapy. The regression models were adjusted for demographics (age, sex, insurance status, teaching hospital status, ARIC center), clinical characteristics (BMI, current smoking, excess alcohol use, hypertension, CHD, AF, diabetes, eGFR), and markers of disease severity (SBP and HR at admission, sodium, LVAD, IABP, inotrope, LVEF and length of stay). We also estimated the average annual percent change of the prescription of GDMT between 2005 and 2014 using Poisson regression models adjusted for hospitalization characteristics as noted above [3]. We performed several sensitivity analyses, e.g., excluding cases with HR < 60 beats per min and SBP < 90 mmHg, excluding severe CKD (eGFR ≤ 30 ml/min/1.73m^2), and using the cutoff of LVEF < 40% as the definition for HFrEF.

We estimated the association of GDMT with 28-day and 1-year mortality using logistic regression models weighted by the inverse probability of treatment based on a propensity score [39, 40]. The propensity score comprised prognostically important variables that were related to treatment and potentially influenced the outcome [41, 42]. Our propensity score included GDMT status, age, sex, insurance status, teaching hospital, ARIC center, current smoking, excess alcohol use, CHD, AF, hypertension, diabetes, eGFR, SBP, HR, sodium, LVAD, IABP, inotrope, LVEF, and length of stay [41, 43, 44]. To account for extreme weights, we computed stabilized weights by multiplying the weights by the proportion of each treatment group [41]. We examined the distribution of baseline characteristics after weighting to ensure balance was achieved [41]. To account for the survey design of the ARIC Surveillance Study [35, 38], we combined the propensity score weight with the sampling probability weight to form a new weight used in the final analysis [45].

We performed sensitivity analyses using the cutoff of LVEF < 40% as the definition for HFrEF. A two-sided p-value of < 0.05 was considered statistically significant. Data analysis was performed using Stata Statistical Software: Release 15.1 (Stata Corp, College Station, TX). The Institutional Review Boards of all participating institutions approved the research protocol.

Results

Patient Characteristics

There were 42,688 (unweighted $n = 9{,}139$) definite or probable acute decompensated HF cases between 2005 and 2014, of which 38.5% were HFrEF. Of the 16,455 (unweighted n = 3,669) hospitalizations with acute decompensated HFrEF, 47% were Black and 39% were women. The mean age was 72.9 (standard deviation 10.7). 4.3% died within 28 days of hospitalization; 28.7% died within 1 year. In addition, 48.3% had diabetes and 86.1% had hypertension. Black men had the lowest age at hospitalization with a mean of 67.5 years, were less likely to have insurance, were more likely to smoke and use excess alcohol, and were more likely to have hypertension, diabetes, lower LVEF, and require inotropes than their White counterparts. Black women were less likely to be hospitalized in a teaching hospital, and had the highest proportion with hypertension (92.5%), diabetes (56.1%), lowest eGFR, highest SBP, and highest BMI. White men had the highest proportion with CHD (81.8%) and AF (45.0%) (Table 1).

GDMT Prescription

Only 9.6% were discharged on combination optimal GDMT (BB, ACE/ARB, and MRA), while 53.5% were discharged on acceptable GDMT (at least 2 therapies). There were more Black than White individuals on optimal GDMT (11.1% vs. 8.6%, $p < 0.001$), with 59.0% and 48.3% on acceptable GDMT, and 30.0% vs 43.1% on inadequate GDMT respectively (Fig. 2). BB was frequently used in both races (82.8% vs. 81.1%), but ACEI/ARB (62.0% vs. 54.6%), MRA (18.0% vs. 13.8%), and especially H-N (21.8% vs. 10.1%) were used more frequently in Black patients than in White patients (all $p < 0.001$) (Fig. 2). When we included only those with LVEF < 40% and those eGFR ≥ 30 ml/min/1.73m^2, the proportions on GDMT were slightly higher (Supplemental Fig. 1 and 2).

In adjusted analyses, the proportional odds of being on optimal or acceptable therapy was OR 1.42 (95% CI 1.15–1.76) in Black individuals compared to Whites (Table 2). For individual GDMT, ACEI/ARB, H-N and diuretics were more likely to be prescribed to Black compared to White patients in fully adjusted models, and BB in model 1. Our findings were consistent even

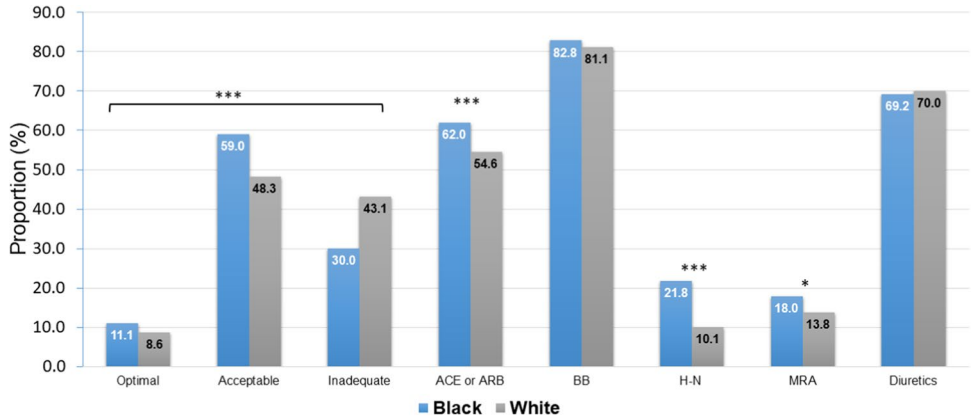

Fig. 2 Proportion on guideline-directed medical therapy by race in the ARIC Study Community Surveillance 2005–2014. Comparison of proportions of each of the GDMT by race using *t*-tests. *p*-value is for the comparison between Blacks and Whites for the specified therapy. Definitions: Optimal GDMT defined as ß blockers, ACEI/ARB and MRA; acceptable GDMT defined as any two of either ACEI/ARB, BB, MRA or H-N; inadequate defined as one or less of GDMT medications. $*p<0.05$, $**p<0.01$, $***p<0.001$. Abbreviations: ACE angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, H-N hydralazine and nitrates, MRA mineralocorticoid receptor antagonists

Table 2 The odds ratio and 95% CI of the association of Black race (vs. White race) with the prescription of guideline-directed medical therapy at heart failure hospital discharge, ARIC Study Community Surveillance 2005–2014

Overall	Optimal or acceptable	ACEI/ARB	BB	H-N	MRA	Diuretics
Model 1	**1.72 (1.40, 2.12)**	**1.48 (1.20, 1.82)**	**1.35 (1.05, 1.74)**	**1.90 (1.44, 2.52)**	1.03 (0.80, 1.34)	**1.30 (1.04, 1.62)**
Model 2	**1.42 (1.15, 1.76)**	**1.24 (1.01, 1.54)**	1.17 (0.90, 1.52)	**1.67 (1.25, 2.24)**	0.93 (0.71, 1.23)	**1.34 (1.07, 1.68)**
LVEF < 40% (n = 14,171)						
Model 1	**1.69 (1.35, 2.12)**	**1.35 (1.08, 1.68)**	**1.38 (1.05, 1.81)**	**1.96 (1.44, 2.67)**	1.00 (0.76, 1.32)	**1.40 (1.10, 1.77)**
Model 2	**1.41 (1.12, 1.77)**	1.16 (0.92, 1.45)	1.22 (0.92, 1.61)	**1.74 (1.26, 2.39)**	0.92 (0.70, 1.23)	**1.45 (1.13, 1.86)**
eGFR > 30 ml/min/1.73m^2 (n = 12,328)						
Model 1	**1.80 (1.42, 2.28)**	**1.54 (1.22, 1.95)**	**1.37 (1.03, 1.83)**	**2.26 (1.60, 3.20)**	1.07 (0.81, 1.42)	**1.40 (1.08, 1.81)**
Model 2	**1.46 (1.15, 1.86)**	**1.28 (1.01, 1.63)**	1.19 (0.89, 1.59)	**1.98 (1.38, 2.85)**	0.98 (0.73, 1.32)	**1.48 (1.14, 1.93)**
HR > 60 and SBP > 90 (n = 14,986)						
Model 1	**1.74 (1.40, 2.16)**	**1.48 (1.19, 1.83)**	**1.39 (1.06, 1.81)**	**1.81 (1.36, 2.42)**	1.05 (0.80, 1.37)	**1.31 (1.04, 1.64)**
Model 2	**1.42 (1.14, 1.77)**	**1.24 (1.00, 1.55)**	1.20 (0.92, 1.58)	**1.56 (1.16, 2.11)**	0.94 (0.71, 1.25)	1.35 (1.07, 1.72)

Ordered logistic regression to estimate the proportional odds and 95% confidence intervals of the association of race with Optimal, Acceptable, and Inadequate GDMT, and logistic regression of the association of race with each individual therapy. White race was used as the reference group. Bolded text indicates statistical significance

Model 1: adjusted for age, sex, insurance status, teaching hospital status, ARIC center smoking history, excess alcohol use, body mass index, previous CHD, atrial fibrillation, hypertension, diabetes, COPD, eGFR

Model 2: additionally, adjusted for heart rate and blood pressure on admission, ejection fraction, length of stay, sodium, inotrope, LVAD

Abbreviations: *ACE* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *H-ISDN* hydralazine and nitrates, *MRA* mineralocorticoid receptor antagonists, *eGFR* estimated glomerular filtration rate < 60 ml/min/1.73m^2, *LVEF* left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *HR* heart rate, *SBP* systolic blood pressure

Definitions: Optimal GDMT defined as ß blockers, ACEI/ARB and MRA; adequate GDMT defined as any two of either ACEI/ARB, BB, MRA or H-N; inadequate defined as one or less of GDMT medications. Inadequate GDMT is the reference group

after including those with LVEF < 40%, eGFR > 30 ml/min/1.73m^2, and excluding those with low HR and BP on admission (Table 2).

There was a declining trend in the average annual percent change in GDMT over the 10-year period. Between 2005 and 2014, there was a trend to lower optimal GDMT in White and Black individuals but it did not reach statistical significance (Fig. 3). Key GDMT therapies were notable for a significant decrease in ACEI/ARB use in Whites (− 2.8% per year $p < 0.007$) but not Black individuals (− 1.1% per year $p = 0.13$), and a significant increase in H-N (+ 6.5% per year $p < 0.009$ and + 9.2%

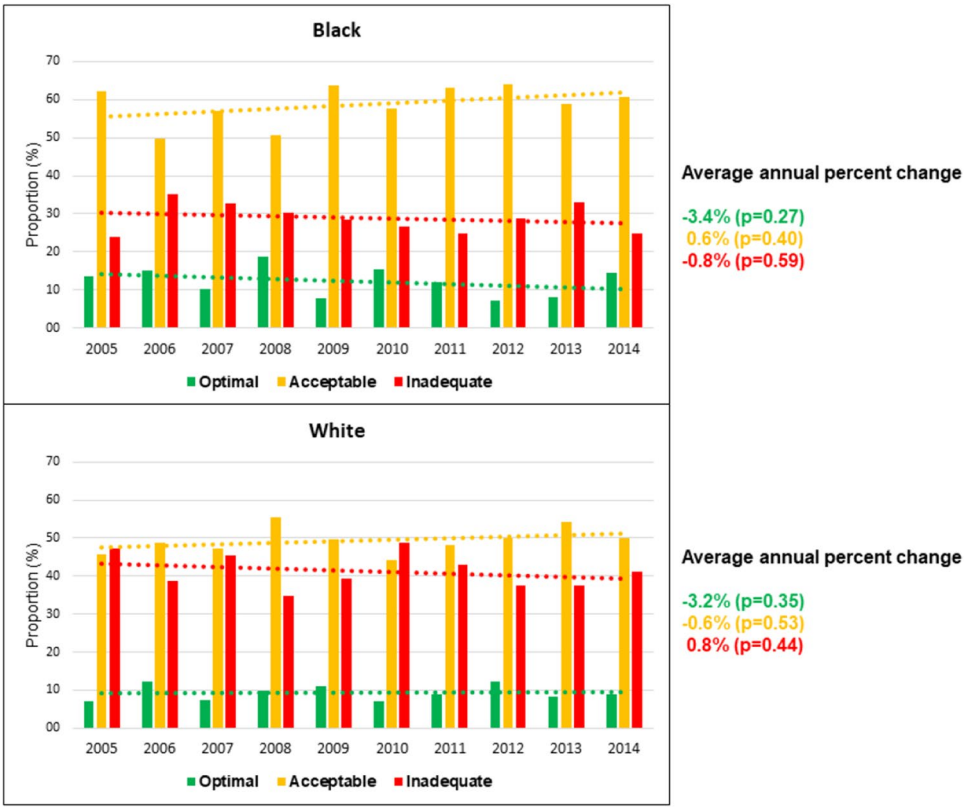

Fig. 3 Proportion and trends in the prescription of guideline-directed medical therapy by race in the ARIC Study Community Surveillance 2005–2014. Proportions on GDMT and the 10-year trends (average annual percent change) between 2005 and 2014 using Poisson regression models adjusted for hospitalization characteristics: ARIC Study Community Surveillance 2005–2014. Analysis adjusted for age, sex, insurance status, teaching hospital, ARIC center, current smoking, excess alcohol use, coronary heart disease, atrial fibrillation, hypertension, diabetes, estimated GFR, systolic blood pressure, heart rate, sodium, left ventricular assist device use, intra-aortic balloon pump, inotropes, left ventricular ejection fraction, length of stay. Definitions: Optimal GDMT defined as ß blockers, ACEI/ARB and MRA; acceptable GDMT defined as any two of either ACEI/ARB, BB, MRA or H-N; inadequate defined as one or less of GDMT medications. Abbreviations: ACE angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, H-N hydralazine and nitrates, MRA mineralocorticoid receptor antagonist

per year $p = 0.003$) for both Black and White individuals respectively (Fig. 4). BB use slightly increased for both races and but was significant for Whites (+ 1.3% per year $p = 0.005$). Our results were consistent when we examined those with EF < 40% (Supplemental Fig. 3). Lastly, to explore whether trends in GDMT may have been affected by changes in kidney function, we examined the mean eGFR over each of the 10 years (Supplemental Fig. 4) and found no significant difference.

GDMT-Mortality Relationship

We achieved balance in the means and proportions of the baseline characteristics by treatment status after inverse probability weighting, with a distribution that showed no extreme weights (Supplemental Table 1). We found a lower adjusted odds ratio of mortality in those prescribed optimal and acceptable GDMT compared to inadequate GDMT (Table 3). The 1-year odds of mortality for optimal GDMT was lower in both White (OR 0.55, 95% CI 0.32–0.96) and Black individuals (0.56, 95% CI 0.32–0.98). Similarly, the odds of mortality were lower for both White (OR 0.77, 95% CI 0.60–0.97) and Black individuals (OR 0.70, 95% CI 0.52–0.94) on acceptable GDMT. ACEI/ARB and BB were both associated with lower 1-year mortality in both groups (Table 3). Diuretics were associated with higher mortality in both groups as well.

Twenty-eight-day mortality was also lower for both Black and White individuals on GDMT (Table 3). Optimal GDMT was associated with lower mortality in Black individuals (OR 0.19, 95% CI 0.05–0.67). Acceptable GDMT was associated with lower mortality in both groups. ACEI/ARB and BB were associated with lower mortality in both groups. MRA was associated with lower mortality in Black individuals only (OR 0.31, 95% CI 0.10–0.96) (Table 3).

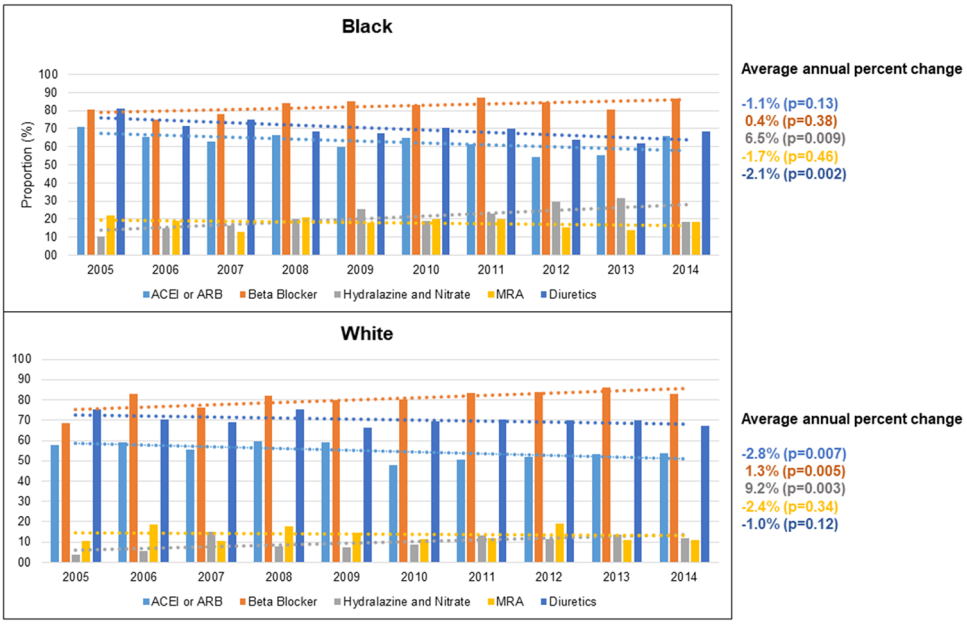

Fig. 4 Proportion and trends in the prescription of individual guideline-directed medical therapy by race in the ARIC Study Community Surveillance 2005–2014. Proportions on individual GDMT and the 10-year trends (average annual percent change) between 2005 and 2014 using Poisson regression models adjusted for hospitalization characteristics: ARIC Study Community Surveillance 2005–2014. Analysis adjusted for age, sex, insurance status, teaching hospital, ARIC center, current smoking, excess alcohol use, coronary heart disease, atrial fibrillation, hypertension, diabetes, estimated GFR, systolic blood pressure, heart rate, sodium, left ventricular assist device use, intra-aortic balloon pump, inotropes, left ventricular ejection fraction, length of stay. Abbreviations: ACE angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, H-N hydralazine and nitrates, MRA mineralocorticoid receptor antagonist

Table 3 The odds ratio and 95% CI of the association of guideline-directed medical therapy with mortality at 28 days and 1 year after hospitalization, ARIC Study Community Surveillance 2005–2014

	28-day mortality			1-year mortality		
	Black	White	*p* for interaction	Black	White	*p* for interaction
Inadequate	Reference	Reference		Reference	Reference	
Acceptable	**0.33 (0.16, 0.68)**	**0.49 (0.29, 0.81)**		**0.70 (0.52, 0.94)**	**0.77 (0.60, 0.97)**	
Optimal	**0.19 (0.05, 0.67)**	0.68 (0.27, 1.72)	0.17	**0.56 (0.32, 0.98)**	**0.55 (0.32, 0.96)**	0.27
ACEI/ARB	**0.35 (0.17, 0.73)**	**0.41 (0.25, 0.67)**	0.93	**0.60 (0.45, 0.79)**	**0.57 (0.46, 0.72)**	0.57
BB	**0.29 (0.15, 0.59)**	**0.47 (0.27, 0.82)**	0.18	**0.57 (0.41, 0.80)**	**0.53 (0.40, 0.71)**	0.83
H-N	0.64 (0.25, 1.68)	0.40 (0.13, 1.25)	0.78	1.12 (0.81, 1.56)	1.20 (0.76, 1.87)	0.58
MRA	**0.31 (0.10, 0.96)**	1.31 (0.66, 2.60)	0.04	0.87 (0.60, 1.28)	1.11 (0.77, 1.60)	0.39
Diuretics	1.25 (0.59, 2.66)	**1.99 (1.11, 3.56)**	0.2	**1.35 (1.00, 1.83)**	**1.96 (1.50, 2.56)**	0.02

Multivariable logistic regression of the association of GDMT with mortality using inverse probability weighting by a propensity score. Propensity scores include age, sex, insurance status, teaching hospital, ARIC center, current smoking, excess alcohol use, coronary heart disease, atrial fibrillation, hypertension, diabetes, estimated GFR, systolic blood pressure, heart rate, sodium, left ventricular assist device use, intra-aortic balloon pump, inotropes, left ventricular ejection fraction, length of stay. Bolded text indicates statistical significance. Abbreviations: *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *H-ISDN* hydralazine and nitrates, *MRA* mineralocorticoid receptor antagonists, *H-N* hydralazine and nitrates, *MRA* mineralocorticoid receptor antagonists, *eGFR* estimated glomerular filtration rate < 60 ml/min/1.73m^2

Definitions: Optimal GDMT defined as ß blockers, ACEI/ARB and MRA; adequate GDMT defined as any two of either ACEI/ARB, BB, MRA or H-N; inadequate defined as one or less of GDMT medications. Inadequate GDMT is the reference group

There was an interaction in the association with race and MRA use for mortality (Table 3).

Discussion

Only 8.6% and 11.1% of White and Black individuals respectively, hospitalized with HFrEF in the community were prescribed optimal combination therapy of BB, ACEI/ARB, and MRA at discharge. Furthermore, 48.3% and 59.0% of White and Black individuals respectively were prescribed acceptable GDMT (any 2 GDMT therapies) at discharge. Overall Black individuals were more likely to be prescribed ACEI/ARB, MRA, H-N compared to Whites. Over a 10-year period, there was a decline in the prescription of ACEI/ARB in Whites while H-N use increased in both races. The use of GDMT, specifically BB and ACEI/ARB, was associated with both lower 28-day and 1-year mortality in both racial groups.

In this community surveillance of HFrEF hospitalizations, we found higher GDMT prescription among Black compared to White individuals overall, as well as in adjusted analysis. Black individuals were more likely to be discharged on optimal and acceptable GDMT, ACEI/ARB, and H-N in fully adjusted analyses compared to Whites. Our findings were similar to the OPTIMIZE-HF performance improvement inpatient registry, which showed higher ACEI use among Black patients [30]. However, our results are reflective of real-world clinical practice, and went a step further by showing that combination therapy (ACEI/ARB, BB, MRA), and individual therapies of ACEI/ARB, H-N, and MRA were also more likely to be prescribed to Black individuals.

Our observations are important because data in the past has shown lower quality of care in hospitals that disproportionately care for Black patients [46]. And more recent data suggest widening disparities in HF outcomes by race [6]. Quality of care may be an explanation for racial disparities in HF outcomes; however, we did not find lower quality of care among Black patients at hospital discharge. Encouragingly, the use of GDMT was associated with better short- and long-term outcomes among both White and Black individuals. One possible explanation for higher GDMT among Black individuals with HFrEF could reflect more comorbidities including hypertension (> 90%) and diabetes (> 50%), and more severe HFrEF presentation with lower LVEF, and more likely to require inotropes.

We also found that optimal or acceptable GDMT were prescribed in only half of HFrEF patients. While BB prescription was high (~ 82%), ACEI/ARB, MRA, and H-N use was suboptimal at < 58%, < 16%, and < 15% respectively. Our findings of low ACEI/ARB differed from previously published quality improvement registry data showing the use of ACEI/ARB at 94.2% among 150,000 patients in *Get with the Guidelines* (GWTG) [28], a multicenter quality improvement inpatient registry [47]. Our estimates for ACEI/ARB prescription were similar to the findings from the CHAMP-HF registry, another multicenter quality improvement registry of outpatients with HF [26]. Furthermore, our findings of low MRA prescription were similar to national estimates using claims data [28, 48]. The low prescription of GDMT at hospital discharge is a concerning statistic as clinical trials have shown that these therapies reduce mortality and recurrent HF hospitalizations and improve symptoms [49–54]. However, both ACEI/ARB and MRA may be associated with hyperkalemia and physicians may be hesitant to discharge patients on these drugs despite their mortality benefits [49, 55, 56]. While discharge prescriptions may not indicate actual adherence, research has shown that patients who are not prescribed GDMT at hospital discharge are not always initiated on therapy, or have therapy augmented in the outpatient setting [23, 26].

A discouraging statistic was that we also found a non-statistically significant decreasing trend in optimal GDMT use in both White and Black individuals, and a statistically significant decline in ACEI/ARB use for Whites even after adjustment for comorbidities and disease severity. One hypothesis was worsening kidney function. While we did not have data on potassium levels or rates of hyperkalemia in our cohort, we were able to show that, over the 10-year period, eGFR did not differ significantly by race. The benefits of ACEI and ARB are unquestionable with randomized clinical trials in patients with HFrEF showing a 16% and 13% reduction in death respectively, [50, 54] and our results confirm their benefits. Efforts to increase awareness in the medical community and improve implementation of these therapies are urgently needed.

Interestingly, we found an increase in the prescription of H-N for both groups over the 10-year period. Clinical trials have shown that the morbidity, mortality, and quality of life benefit by the addition of H-N to optimal GDMT in Black patients with HFrEF, but this benefit did not extend to non-Black patients [52, 57, 58]. Of note, we did not find a long-term mortality benefit for H-N in either group. Our findings underscore the importance of managing all HFrEF patients with ACEI/ARB and BB, unless contraindications exist, and then consider H-N.

What can we do to increase GDMT utilization? Understanding the barriers to GDMT prescription is an important step in developing measures to improve GDMT utilization. In our study we hypothesized that race would be a factor impacting the prescription of GDMT at hospital discharge;

however, contrary to our expectations, we did not find that Black patients were less likely to receive GDMT prescription. Future studies are needed to specifically explore other barriers to optimal GDMT prescription, e.g., physician perceptions, awareness of the importance of GDMT, patient factors, or time constraints. Furthermore, there are a few potential strategies that might be used to increase the utilization of GDMT. For example, the use of incentives for providers when HF performance measures are met in both the inpatient and outpatient settings could be an option. [4, 59] Another important strategy is early outpatient follow-up, which can ensure GDMT is being well-tolerated with further optimization. Also, clinical decision support tools for providers using electronic health records during admission, especially at the discharge transition, would be helpful [60].

Limitations

We had a few limitations in our study including lack of information on medication doses, and contraindications. However, sensitivity analyses excluding patients who had HR < 60 bpm, SBP < 90 mmHg, and eGFR < 30 ml/min/1.73m^2 yielded consistent results. Another limitation was the potential for residual confounding despite adjustment for known confounders. Lastly, our definition of GDMT included standard neurohormonal blocking therapies that were recommended by guidelines since 2005 [19] through when the data was collected (2005–2014). We recognize that newer therapies including angiotensin receptor-neprilysin inhibitors (ARNI) have now been included in the HFrEF management guidelines [4] and future studies on contemporary prescription patterns of GDMT including ARNI are needed.

Conclusions

Among HFrEF patients in the community, optimal GDMT was only prescribed at discharge in approximately 10%, but more Black than White individuals received optimal GDMT, ACEI/ARB, MRA, and H-N. ACEI/ARB use declined over a 10-year period in Whites, while the use of H-N increased in both races. Prognostic benefit was seen only for ACEI/ARB and BB. Efforts at increasing implementation of GDMT among all HFrEF patients at hospital discharge are needed.

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Author Contribution Lena Mathews: conceptualization, methodology, formal analysis, writing—original draft; Ning Ding: formal analysis; Yingying Sang: formal analysis; Laura R. Loehr: conceptualization, methodology; Jung-Im Shin: conceptualization, methodology; Naresh M. Punjabi: conceptualization, methodology; Alain G. Bertoni: conceptualization, methodology; Deidra C. Crews: conceptualization, methodology; Wayne D. Rosamond: conceptualization, methodology; Josef Coresh: conceptualization, methodology; Chiadi E. Ndumele: conceptualization, methodology, writing—original draft, supervision; Kunihiro Matsushita: conceptualization, methodology, writing—original draft, supervision; Patricia P. Chang: conceptualization, methodology, writing—original draft, supervision.

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Data availability ARIC data is available through the NHLBI BioLINCC (https://biolincc.nhlbi.nih.gov/home/) or the ARIC Data Coordinating Center at the University of North Carolina (details can be found at https://sites.cscc.unc.edu/aric/distribution-agreements).

Code Availability Custom code is available upon request.

Declarations

Conflict of Interest The authors declare no competing interests.

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Participating Institutions.

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