

A comprehensive review of chronic heart failure pharmacotherapy treatment approaches in African Americans

Frank Tillman^{ID}, Jennifer Kim, Tanya Makhlof and Leah Osae

Abstract

Background: Our aim was to review the published literature evaluating treatment approaches for chronic heart failure (HF), notably as it relates to African American patients.

Method: We undertook a comprehensive database search (1986–2017) of PubMed, EMBASE, and Ovid/MEDLINE utilizing terms 'African American', 'black', 'chronic heart failure', 'heart failure', 'medication', 'chronic therapy', and 'clinical trials'. Additional notable studies were obtained from ClinicalTrials.gov. Studies published in English that examine treatment modalities of chronic HF in African American and non-African American patients were included.

Results: Examples of current gaps worthy of investigation include whether to maximize thiazides and calcium-channel blockers prior to adding renin-angiotensin system (RAS) inhibitors or beta blockers in HF with preserved ejection fraction; whether hydralazine/isosorbide dinitrate (ISDN) should be initiated during earlier HF stages; whether to prioritize hydralazine/ISDN over other agents such as RAS inhibitors; varying response of African Americans to different agents within drug classes; and the role of mineralocorticoid receptor antagonists.

Conclusion: Further studies are needed in order for consensus guidelines to clarify how best to treat this population.

Keywords: chronic heart failure, African American, clinical trials, pharmacological treatment, under-representation

Received: 25 April 2018; revised manuscript accepted: 3 August 2018.

Introduction

Approximately half of all African American adults have some form of cardiovascular (CV) disease, with hypertension functioning as the major etiologic factor contributing to this trend.¹ African American patients experience a 50% higher incidence of heart failure (HF) relative to the general population, as well as an increased risk of mortality secondary to chronic HF (CHF) as compared with White patients.¹ Unfortunately, clinical trials supporting treatment recommendations for HF with preserved and reduced ejection fraction (HFpEF and HFrEF, respectively) considerably under-represent African Americans (Table 1).¹ The significant burden that this patient demographic assumes with HF has influenced a body of researchers to put forth a call to action in 2011 to advocate for higher racial equality in clinical trials, thus further emphasizing the significant gap

in care that these patients receive.² In this review, we aim to describe HF treatment specific to African American patients by evaluating existing literature to identify potential areas necessitating further research.

Heart failure in African Americans

In addition to the racial disparity regarding enrollment of African Americans into clinical trials, key etiological differences support the need for further research.^{3–5} A notable difference from other populations is that HF in African Americans is more strongly associated with a nonischemic etiology of left ventricular dysfunction, with the main culprit being hypertension.

In African Americans, hypertension pathophysiology is associated with increased sodium sensitivity,

Ther Adv Cardiovasc Dis

2019, Vol. 13: 1–9

DOI: 10.1177/
1753944719840192

© The Author(s), 2019.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:
Frank Tillman
University of North
Carolina Eshelman
School of Pharmacy, 301
Pharmacy Lane, Chapel
Hill, NC 27599-7360, USA
ftillman@email.unc.edu

Jennifer Kim
University of North
Carolina Eshelman
School of Pharmacy,
Chapel Hill, NC, USA
Cone Health Internal Medicine
Center, Greensboro, NC,
USA
Greensboro Area
Health Education Center,
Greensboro, NC, USA

Tanya Makhlof
University of North
Carolina Eshelman School
of Pharmacy, Chapel Hill,
NC, USA

Leah Osae
University of North
Carolina Eshelman School
of Pharmacy, Chapel Hill,
NC, USA

Table 1. Representation of Black patients in key heart failure clinical trials.

Abbreviated trial name	Intervention (mean dose)	NYHA class included	Mean baseline EF	Key treatment effects	Black patients included
CONSENSUS ⁶	Enalapril (18.4 mg daily) <i>versus</i> placebo	IV	Not specified	27% mortality RRR ($p = 0.003$)	Not reported
SOLVD ⁷	Enalapril (16.6 mg daily) <i>versus</i> placebo	I, II, III or IV	25%	16% mortality risk reduction ($p = 0.0036$); 26% hospitalization risk reduction ($p < 0.0001$)	15.4%
DIG ⁸	Digoxin (0.25 mg daily) <i>versus</i> placebo	I, II, III or IV	28.5%	No significant difference in all-cause or CV death; 22.8% HF hospitalization RRR ($p < 0.001$)	Not reported (85.4% White)
RALES ⁹	Spirololactone (26 mg daily) <i>versus</i> placebo	III or IV	25%	30% all-cause death RRR ($p < 0.001$); 31% CV death RRR ($p < 0.001$); 30% risk reduction in CV hospitalizations ($p < 0.001$)	Not reported (86.5% White)
CIBIS-II ¹⁰	Bisoprolol (8.6 mg daily) <i>versus</i> placebo	III or IV	27.5%	No significant difference in all-cause death; 32% CV hospitalization RRR ($p < 0.01$)	Not reported
Val-HeFT ¹¹	Valsartan (254 mg daily) <i>versus</i> placebo	II, III or IV	27%	13.2% risk reduction for combined morbidity/mortality ($p = 0.009$); 27.5% risk reduction for hospitalization ($p < 0.001$)	7%
BEST ¹²	Bucindolol (76 mg twice daily) <i>versus</i> placebo	II, III or IV	23%	No significant difference in all-cause death; 14% CV death RRR ($p = 0.04$); 17% hospitalization RRR ($p < 0.001$)	23%
COPERNICUS ¹³	Carvedilol (about 70% achieved target dose of 25 mg twice daily) <i>versus</i> placebo	Not specified	20%	13% mortality risk reduction ($p = 0.00014$); 24% combined death or HF hospitalization risk reduction ($p < 0.001$)	5%
CHARM ¹⁴	Candesartan (25 mg daily) <i>versus</i> placebo	II, III or IV	29%	23% combined CV death or HF hospitalization risk reduction ($p < 0.001$), and 20% all-cause mortality risk reduction at 2 years ($p < 0.001$)	3.6%
COMET ¹⁵	Carvedilol (41.8 mg daily) <i>versus</i> metoprolol (85 mg daily)	II to IV	26%	15% all-cause mortality RRR with carvedilol ($p = 0.0017$)	Not reported (99% White)
MERIT-HF ¹⁶	Metoprolol CR/XL (159 mg daily) <i>versus</i> placebo	II to IV	26%	34.5% all cause mortality RRR with metoprolol CR/XL ($p = 0.00009$)	5%
A-HeFT ¹⁷	ISDN/hydralazine (68% achieved target dose of 120 mg/225 mg) <i>versus</i> placebo	III or IV	24%	39% all-cause death RRR ($p = 0.02$); 33% reduction in HF hospitalization ($p = 0.001$)	100%
I-PRESERVE ¹⁸	Irbesartan (275 mg) <i>versus</i> placebo	II, III or IV	60%	No significant difference in outcomes (death from any cause, CV hospitalization, HF death or hospitalization)	2%
BEAUTIFUL ¹⁹	Ivabradine (6.18 mg twice daily) <i>versus</i> placebo	I, II, III	32.4%	Ivabradine did not affect composite primary endpoint (HR 1.00, $p = 0.94$) of CV death, admission to hospital for acute MI, and hospital admission for new-onset or worsening HF	0.1%

Table 1. (Continued)

Abbreviated trial name	Intervention (mean dose)	NYHA class included	Mean baseline EF	Key treatment effects	Black patients included
SHIFT ²⁰	Ivabradine (6.5 mg twice daily) <i>versus</i> placebo	II, III, IV	29%	HF death or hospitalization: ivabradine 793 (24%) <i>versus</i> placebo 937 (29%); HR 0.82; 95% CI 0.75–0.90; $p < 0.0001$	Not specified (89% White)
EMPHASIS-HF ²¹	Eplerenone (39.1 mg daily) <i>versus</i> placebo	II	26%	RRR: 29% combined CV death or HF hospitalization ($p < 0.001$); 20% CV death ($p = 0.01$); 16.5% HF hospitalization ($p < 0.001$)	2.5%
EPHESUS ²²	Eplerenone (42.6 mg daily) <i>versus</i> placebo	Not specified	33%	13.8% all-cause death RRR ($p = 0.008$); 11% combined CV death or hospitalization RRR ($p = 0.002$); RRR 15% for hospitalization ($p = 0.03$)	1%
PARADIGM-HF ²³	Sacubitril/valsartan (375 mg/300 mg daily) <i>versus</i> enalapril (18.9 mg daily)	II, III or IV	30%	RRR: 18% for combined CV death or HF hospitalization, 19% for CV death, 18% for HF hospitalization ($p < 0.001$ for all) in favor of sacubitril/valsartan	5.1%
PIONEER-HF ²⁴	Sacubitril/valsartan* (target dose, 97 mg/103 mg twice daily) <i>versus</i> enalapril (target dose, 10 mg twice daily)	Not specified; included patients with ADHF	24.5%	Time-averaged percent change in NT-proBNP -46.7% for sacubitril/valsartan and -25.3% for enalapril ($p < 0.001$); RRR 42% for HF rehospitalization	35.9%

*Mean dose not reported.
ADHF, acute decompensated heart failure; CI, confidence interval ; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HR, hazard ratio; ISDN, isosorbide dinitrate; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RRR, relative risk reduction.

relatively low renin activity, and possibly reduced nitric oxide production.³ Though renin–angiotensin system (RAS) abnormalities are pivotal in the pathogenesis of HF, impaired endothelial function is another major contributor in African Americans.^{3,4} Other contributing factors include higher burdens of chronic kidney disease and diabetes, genetic polymorphisms, lower socioeconomic status, and limited access to care. Of note, RAS inhibitors are generally avoided as monotherapy or first-line therapy for hypertension in African Americans due to lower efficacy compared with thiazides or calcium-channel blockers (CCBs), in addition to increased risks of angioedema.

For HF_pEF treatment, blood pressure control is recommended to prevent morbidity.^{25,26} In keeping with this recommendation, guideline-directed antihypertensives (thiazides or CCBs) are prioritized in African Americans with hypertension. RAS inhibitors and beta blockers (BBs) provide

additional therapy options for these patients although their effect on lowering blood pressure is weaker than those of thiazide diuretics or CCBs. Importantly, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found chlorthalidone to be more effective than lisinopril or amlodipine at reducing the occurrence of new-onset HF.²⁵ Also, chlorthalidone was similar to lisinopril in reduction of HF_rEF risk, and both chlorthalidone and lisinopril were found to be more effective than amlodipine.

For patients who develop HF_rEF, RAS inhibitors and BBs are generally recommended as first-line treatments. Other HF_rEF options include mineralocorticoid receptor antagonists (MRAs), angiotensin receptor–neprilysin inhibitors (ARNIs), hydralazine/isosorbide dinitrate (ISDN), digoxin, and ivabradine. As mentioned previously, many notable clinical trials that have served as the basis

for these recommendations have low proportions of African American patients.

Study selection and data extraction

A comprehensive database search (1986–2017) of PubMed, EMBASE, and OVID/Medline was conducted using the search terms ‘African American’, ‘black’, ‘chronic heart failure’, ‘heart failure’, ‘medication’, ‘chronic therapy’, and ‘clinical trials’. Additional hallmark studies contributing to the armamentarium of treatment approaches for CHF were obtained from ClinicalTrials.gov. Published literature in English language, primarily examining the treatment and management of CHF in patients with HF ν EF, was included. Ethical standards were upheld in the development of this review in accordance with the standards set forth by the institution Ethical Committee.

Review of notable clinical trials

The Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure (V-HeFT) trial was the first study to define benefits in mortality of any drug in HF patients.²⁷ This double-blind study randomized male patients with CHF, reduced exercise tolerance, left ventricular ejection fraction (LVEF) < 45% or evident vasodilation to one of three groups: hydralazine/ISDN, prazosin, or matched placebo. Hydralazine/ISDN was the only treatment that demonstrated a statistically significant reduction in mortality up to 2 years when compared with placebo ($p < 0.028$).²⁷ These results suggested further explanation behind the etiology of HF with regards to peripheral vasoconstriction. Of note, the study did not report the percentages of African American patients.

A later study, Comparison of Enalapril with Hydralazine/Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure (V-HeFT II), involved patients with evidence of cardiac dysfunction and reduced exercise tolerance.²⁸ Of note, 27% of the study participants were African American. Patients already taking digoxin and diuretics continued those therapies and were randomized to one of two treatment groups: enalapril 20 mg daily or hydralazine/ISDN 300–160 mg daily. Results revealed a significantly lower reduction in mortality after 2 years in the enalapril group compared with the hydralazine/ISDN group ($p = 0.016$). This outcome was attributed to the reduction in sudden

death in the enalapril group, which was most evident in patients with New York Heart Association (NYHA) class I–II HF. In contrast, body oxygen consumption at peak exercise was increased by hydralazine/ISDN treatment ($p < 0.05$), and LVEF increased more ($p < 0.05$) during the first 13 weeks in the hydralazine/ISDN group. This supports the need for additional trials that compare the efficacy of these two therapies in African American patients with NYHA class I–II HF, considering that evidence supports hydralazine/ISDN in this patient demographic for NYHA class III–IV. Doing so could enhance our understanding of targeted-therapy algorithms for African Americans.

An additional trial, The Studies of Left Ventricular Dysfunction (SOLVD), investigated the impact of enalapril on reducing mortality in patients with HF ν EF who were naive to any angiotensin-converting enzyme inhibitor (ACE-I).⁷ The primary objective was to assess the effect of enalapril on mortality. Secondary objectives included hospitalization for CHF, the incidence of myocardial infarction (MI), mortality due to specific causes, and a combined analysis of mortality and morbidity. Treatment with enalapril or placebo was initiated at 2.5 mg or 5 mg twice daily based on the physician’s clinical judgment and the patient’s condition, and the dose was maximally titrated to 10 mg twice daily when clinically feasible. The findings revealed a 16% risk reduction [95% confidence interval (CI) 5–26%; $p = 0.0036$] in all-cause mortality at the end of the scheduled follow up for patients in the treatment group. The most significant difference in mortality between treatment and placebo groups occurred within the first 24 months, whereas differences thereafter were similar. There was an 18% risk reduction (95% CI 6–28%) in the number of CV deaths in the treatment group, with the most significant difference in mortality attributed to progressive HF (22% risk reduction for enalapril group, 95% CI 6–35%). While this trial demonstrates a significant reduction in overall mortality and hospitalizations for CHF in patients treated with an ACE-I in addition to their conventional therapy, only about 15% of the study population comprised African American patients. Although there were no racial or ethnic differences in the efficacy of enalapril in reducing mortality and preventing the development of HF, African Americans were at a 44% increased risk of hospitalizations ($p < 0.005$) compared with White patients. This suggests a

strong need for additional prospective studies that examine CV outcomes for African Americans treated with an ACE-I for CHF.

Though not first line, MRAs are utilized in CHF therapy to aid in the reduction of worsening morbidity and mortality. Current guidelines recommend the use of these agents, namely spironolactone, in HF ν EF patients who are on maximally tolerated doses of conventional HF therapy and have mild to severe symptoms of CHF.^{25,26} Eplerenone, an additional MRA, is generally reserved for patients who are unable to tolerate spironolactone due to gynecostasia and sexual dysfunction but will not be discussed in detail in this review. Data on whether or not race influences the clinical efficacy of MRAs in patients with CHF are limited. The association between clinical efficacy in African Americans taking MRAs was studied in a double-blind, randomized, placebo-controlled trial that was designed to assess the efficacy of spironolactone on preventing all-cause mortality and cardiac-related hospitalizations in patients with NYHA class III–IV CHF.⁹ The findings revealed that spironolactone was associated with a 30% reduction in the risk for all-cause mortality [adjusted hazard ratio (HR) 0.70; 95% CI 0.59–0.82] and a 36% reduction in the risk for cardiac-associated death or hospitalization (adjusted HR 0.64; 95% CI 0.55–0.74) in non-African Americans. By contrast, spironolactone was associated with no clinically significant effect on all-cause mortality (adjusted HR 0.87; 95% CI 0.47–1.59) or cardiac-associated death or hospitalizations (adjusted HR 1.18; 95% CI 0.72–1.94) in African Americans. There was also no added benefit of spironolactone in African Americans even after making adjustments for covariate interactions.⁹ Changes in blood pressure from baseline were similar between African Americans and non-African Americans at the second follow up and throughout duration of the study. This trend suggests that blood pressure management alone does not suffice for the prevention of worsening morbidity and mortality, and that African Americans who remain symptomatic may be provided with limited benefit when spironolactone is added to their medication regimen. It is worth noting that this perceived lack of efficacy with spironolactone for African Americans may have been influenced by the study not achieving adequate power for the secondary analysis. In current practice, MRAs are often prioritized over other second-line agents, possibly an approach that does not garner the largest benefit for African

American patients based on findings from Pitt *et al.*⁹ Evidence from this trial demonstrates the need for additional adequately powered studies that provide for enhanced, tailored approaches of care for African Americans. Doing so is necessary to reduce their disproportionate burden of HF and resultant complications.

The Valsartan Heart Failure Trial (Val-HeFT) examined patients with history of NYHA class II–IV HF ν EF receiving at least 2 weeks of a fixed-dose regimen including ACE-Is, diuretics, digoxin, or BBs.¹¹ The primary endpoint was mortality, and the combined endpoint of mortality and morbidity was defined as cardiac arrest with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator drugs for 4 hours or more without hospitalization. Secondary endpoints included the changes from baseline in ejection fraction, NYHA functional class, quality of life, and signs and symptoms of HF after initiation of angiotensin-receptor blocker (ARB) therapy. The findings revealed that mortality between the two groups was similar, whereas the incidence of the combined endpoint was 13.2% lower with valsartan as compared with placebo (relative risk, 0.87; 97.5% CI 0.77–0.97; $p = 0.009$).¹¹ Of note, valsartan had favorable effects in patients receiving an ACE-I, BB, or neither but deleterious effects in patients receiving both. The Val-HeFT trial comprised a population of approximately 7% Black patients, and the effect of valsartan was not statistically significant in this subgroup (relative risk, 1.11; 95% CI 0.77–1.61). This further reiterates the need for additional prospective studies in this patient population.

The Beta-blocker Evaluation of Survival Trial (BEST) compared bucindolol with placebo in 2708 patients, 23% of which were African American.¹² This study included patients with NYHA class III–IV on optimal medical therapy and HF ν EF. The primary endpoint was the incidence of all-cause mortality. Patients were either randomized to placebo or bucindolol 3 mg twice daily, titrated to 50 mg twice daily or 100 mg twice daily for patients weighing greater than 75 kg. The primary outcome of all-cause mortality occurred in 30% of the bucindolol-treated patients and 33% of the placebo-treated patients ($p = 0.13$). What is of particular relevance to this review is that African American patients did not benefit from bucindolol (HR for death 1.17; $p = 0.27$) while non-African Americans

did demonstrate survival benefit (HR 0.82, $p = 0.01$). While the reason for the lack of benefit on the primary endpoint is uncertain, it is thought that the large proportion of African Americans in this trial may have influenced this result. In contrast, carvedilol was superior to placebo for each racial cohort ($p < 0.05$) in reducing risk for worsening HF and improving functional status, ejection fraction and global assessment in the US Carvedilol Heart Failure Trials Program.²⁹ This study included 217 Black and 877 non-Black patients (NYHA class II–IV with LVEF $< 35\%$) randomized to carvedilol (6.25–50 mg twice daily) or placebo for up to 15 months.²⁹ Although current guideline-directed medical therapy prioritizes BBs for patients with HF \neq EF, the discordant findings between BEST and the US Carvedilol Heart Failure study raise questions regarding whether the benefits seen with carvedilol would also be seen with other BBs (e.g. bisoprolol) in African Americans: A subgroup analysis of 207 Black patients in the Metoprolol CR/XL Randomized Intervention trial in Congestive Heart Failure (MERIT-HF) found no significant differences for various outcomes of all-cause and CV-related death ($p > 0.05$ for all).³¹ Furthermore, direct comparisons of BBs to other therapies such as hydralazine/ISDN in African Americans would provide more evidence and guidance for place in therapy of BBs.

While the previously discussed trials involve disproportionate inclusion of African Americans, the African American Heart Failure Trial (A-HeFT) is particularly notable because it provides the most robust evidence for African Americans with HF.¹⁷ A-HeFT compared hydralazine/ISDN ($n = 518$) with placebo ($n = 532$) as an adjunctive agent to conventional therapy. Patients were included if they self-identified as Black, had a diagnosis of NYHA class III–IV HF for at least 3 months, and were receiving standard CHF therapy (i.e. ACE-I/ARB or BBs) for at least 3 months prior to enrollment. The initial dose of hydralazine/ISDN was one tablet (20/37.5 mg) three times daily (TID) and was titrated to two tablets TID in select patients, based on tolerability. The primary endpoints were all-cause mortality, CHF hospitalizations during the 18-month study duration, and change from baseline in quality of life as measured by the Minnesota Living with Heart Failure questionnaire. The study was terminated prematurely due to significantly higher number of deaths in the placebo group (54 deaths in placebo group *versus* 32 deaths in hydralazine/ISDN group). The hydralazine/ISDN group demonstrated a 43%

improvement in survival ($p = 0.01$). Furthermore, the rate of first hospitalization in the hydralazine/ISDN group was reduced by 33% ($p = 0.001$) and quality-of-life scores were more significantly improved in the hydralazine/ISDN group as compared with placebo (-5.6 ± 20.6 *versus* -2.7 ± 21.2 ; $p = 0.02$). Treatment with the study medication also resulted in a reduction of systolic blood pressure (-1.9 mmHg, $p = 0.02$) and diastolic blood pressure (-2.4 mmHg, $p < 0.001$) when compared with placebo ($+1.2$ mmHg; $p = 0.02$ and $+0.8$ mmHg; $p < 0.001$, respectively). Of the patients in the treatment group, 21% discontinued the medication due to intolerable adverse effects as compared with 12% of patients in the placebo group. The major adverse events were headache (47.5% *versus* 19.2%; $p < 0.001$) and dizziness (29.3% *versus* 12.3%; $p < 0.001$). These findings support the use of hydralazine/ISDN in African Americans as an effective adjunctive, combination therapy for the management of NYHA class III–IV HF in terms of reducing hospitalizations and all-cause mortality. To date, there are no studies investigating use of hydralazine/ISDN in earlier stages of disease in African American patients.

In a subsequent subanalysis of the A-HeFT trial, Ghali and colleagues investigated the potential additive effects of ACE-I/ARBs and BBs with hydralazine/ISDN.³⁰ The percentages of patients managed on ACE-I was 78%, ARBs 28%, ACE-I and/or ARBs 93%, and BBs 87%. In the patients receiving treatment drug, the use of ACE-I and/or ARBs was not associated with a significant reduction in mortality or first CHF hospitalization (HR 0.72; 95% CI 0.35–1.37), whereas the use of BBs demonstrated a 38% reduction in mortality or first CHF hospitalization (HR 0.62; 95% CI 0.34–0.96).³⁰ There was a strong trend of reduction, although not statistically significant, in mortality or first CHF hospitalization among patients who were treated with ACE-I or ARB (HR 0.63; 95% CI 0.31–1.07), and a statistically significant 42% reduction among patients treated with BBs (HR 0.58; 95% CI 0.34–0.79). Furthermore, it was found that there was no significant effect within both the treatment and placebo groups for patients who were being managed on ACE-I or ARB in terms of the primary endpoint composite score of mortality, CHF hospitalization, and change in quality of life from baseline. The use of BBs did demonstrate significantly improved outcomes for the composite scores in both the treatment ($p = 0.016$) and placebo ($p < 0.001$) groups. It is important to note that the small sample size of individuals

not taking ACE-Is or ARBs poses a challenge to guaranteeing that any significant effect observed could be a result of chance and should therefore be viewed as hypothesis generating only. This study reveals the need to clarify whether BBs and hydralazine/ISDN should be prioritized over ACE-I or ARB therapy in African Americans with CHF, and whether earlier initiation of BBs or hydralazine/ISDN (e.g. CHF prevention and HFpEF) would be beneficial. Additional, prospective, randomized-controlled trials could expand the clinical utility of these medication therapies and potentially contribute to clinically meaningful reductions of the onset of CHF in this patient population. Studies that investigate this clinical question could contribute novel approaches to the management of CHF in African Americans, reduce the overall burden of the disease, and impose significant reductions in healthcare costs and resources.

Ivabradine is indicated to reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic CHF with LVEF $\leq 35\%$, and in sinus rhythm with resting heart rate ≥ 70 bpm. Two notable trials examining ivabradine use, Ivabradine in Patients with Stable Coronary Artery Disease and Left Ventricular Systolic Dysfunction (BEAUTIFUL) ($n = 10,917$) and Systolic Heart failure treatment with the If inhibitor Ivabradine Trial (SHIFT) ($n = 6558$), were 98.1% and 89% comprised of Whites, respectively.^{19,20} Overall, little evidence exists for African American HF r EF patients using ventricular rate-reducing agents, such as ivabradine and digoxin.^{25,26} The earlier Jackson Heart Study found that elevated heart rate is associated with increased HF hospitalizations in African Americans, thus conferring an even greater necessity to evaluate the clinical utility of nonbeta-blocking agents, particularly ivabradine.³¹ Considering the ambiguity of beta-blocker benefit to African American HF r EF patients as seen in the BEST Trial, further evaluation of alternate mechanisms of ventricular rate reduction is especially warranted in this population. Further evaluation of these rate-reducing agents is vital to the clinical understanding of reducing hospitalizations, improving symptomology, and enhancing quality of life in African American HF r EF patients, especially in patients with sustained elevated heart rate despite optimal beta-blocker therapy.

The United States Food and Drug Administration approved sacubitril–valsartan, an ARNI, in 2015

for the treatment of HF in patients with reduced ejection fraction and NYHA class II–IV symptoms based on findings from the PARADIGM-HF trial.²³ Sacubitril–valsartan is a combination medication containing a neprilysin inhibitor (sacubitril) and ARB (valsartan). Neprilysin is shown to be a potential therapeutic target in HF and hypertension due to its protective cardiorenal, vasodilatory, natriuretic, and diuretic properties.³² The PARADIGM-HF trial demonstrated a clinically significant reduction of 20% in CV-associated deaths and hospitalization when compared with enalapril, which was also found to be independent of age and severity of disease, but evaluated a population which was around 5% Black.²³ The rate of adverse events was comparable between treatment groups.

In PARADIGM-HF, enalapril was dosed at 10 mg twice daily, while the valsartan component of the combination with sacubitril was titrated to 160 mg twice daily. The PIONEER-HF trial compared a target dose of enalapril 10 mg twice daily to sacubitril/valsartan 97 mg/103 mg twice daily, but in acute decompensated HF.²⁴ This trial had a higher percentage of Black patients (about 36%). The primary outcome measure for PIONEER-HF was N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of neurohormonal activation, hemodynamic stress, and cardiovascular events. After 1 week of therapy, sacubitril/valsartan reduced NT-proBNP more than enalapril (time-averaged percent change -46.7% and -25.3% , respectively, $p < 0.001$). Rehospitalizations for HF were also lower for sacubitril/valsartan (8%) compared with enalapril (13.8%; HR 0.56; 95% CI 0.37–0.84). A subgroup analysis revealed more NT-proBNP lowering in Black patients with sacubitril/valsartan compared with enalapril (ratio of change 0.72; 95% CI 0.57–0.89), similar to the effect seen in White patients (ratio of change 0.68; 95% CI 0.58–0.80). Rates of worsening renal function, hyperkalemia, and symptomatic hypotension were similar between groups. There was one confirmed angioedema in a white patient taking sacubitril/valsartan, and there were six (all black patients) in the enalapril group, which is unsurprising given that ARBs tend to have lower rates of angioedema compared to ACE-Is. The PIONEER-HF study enhances our understanding of sacubitril/valsartan in African Americans, but it is still unclear how this novel therapy measures up against other treatments with established data in this population (e.g. hydralazine/ISDN) across the spectrum of NYHA classes.

Summarizing the gap

Many principles of HF treatment remain unclear for African American patients. For instance, some clinicians may be inclined to maximize thiazide and dihydropyridine-CCB therapy in African American patients with HFpEF if they demonstrate a favorable response for hypertension. This approach may prevent further cardiac remodeling from uncontrolled blood pressure and therefore obviate the need for RAS inhibitor or BB therapy at earlier stages of disease. However, further HFpEF research is needed, and the role of hydralazine/ISDN in HFpEF and NYHA classes I-II remains unclear.

In HFrEF patients, until further evidence is available, RAS inhibitor and BB therapy should remain a cornerstone of therapy. However, it is imperative for future research to question whether hydralazine/ISDN and BB optimization should precede RAS inhibitor or ARNI therapy in HFrEF African Americans, as suggested by Ghali *et al.*³⁰ As mentioned previously, MRAs, digoxin, and ivabradine have limited evidence for HF in the African American population.

Novel strategies for African American patients should be considered, such as targeting endothelial function abnormalities. Adequately powered studies, ideally, head-to-head trials, with higher percentages of African Americans, are needed to determine which agents confer harm, benefit, or neutral effect. Expert panels should consider recommending caution when selecting from drug classes in which specific agents have little evidence or have demonstrated lack of efficacy in African American patients. Moreover, it is imperative for clinicians to consider the demographics of signature HF trials when developing treatment plans for their patients, particularly those who are African American.

Conclusion

Further studies are needed for a more meaningful understanding of how best to treat HF in African American patients with multifactorial clinical approaches that fully consider higher burdens of certain comorbidities (e.g. chronic kidney disease, diabetes, hypertension), lifestyle differences, and physiological differences (e.g. RAS abnormalities) in this population.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Frank Tillman  <https://orcid.org/0000-0003-0920-2090>

References

1. Sidney S, Quesenberry C, Jaffe M, *et al.* Recent trends in cardiovascular mortality in the United States and public health goals. *JAMA Cardiol* 2016; 1: 594–599.
2. Mitchell J, Ferdinand K, Watson K, *et al.* Treatment of heart failure in African Americans—a call to action. *J Natl Med Assoc* 2011; 103: 86–98.
3. Franciosa J, Ferdinand K and Yancy C. Treatment of heart failure in African Americans: a consensus statement. *Congest Heart Fail* 2010; 16: 27–38.
4. Sharma A, Colvin-Adams M and Yancy C. Heart failure in African Americans: disparities can be overcome. *Cleveland Clin Joun Med* 2014; 81: 301–311.
5. Pickering T. Reflections in hypertension: heart failure and hypertension: the diastolic dilemma. *J Clin Hypertens (Greenwich)* 2004; 6: 647–650.
6. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987; 316: 1429–1435.
7. Bourassa G, Gurne O, Bangdiwala S, *et al.* Natural history and patterns of current practice in heart failure. The studies of left ventricular dysfunction (SOLVD) investigators. *J Am Coll Cardiol* 1993; 22(Suppl. A): 14A–19A.
8. England TN. The effect of digoxin on mortality and morbidity in patients with heart failure. Digitalis investigation group. *N Engl J Med* 1997; 336: 525–533.
9. Pitt B, Zannand F, Remme W, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med* 1999; 341: 709–717.
10. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353: 9–13.
11. Cohn J and Tognoni G. Valsartan heart failure trial investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345: 1667–1675.

12. Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, *et al.*; Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; 344: 1659–1667.
13. Packer M, Coats AJ, Fowler MB, *et al.* Carvedilol prospective randomized cumulative survival study group. *N Engl J Med* 2001; 344: 1651–1658.
14. Colombo G, Caruggi M, Ottolini C, *et al.* Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) and resource utilization and costs in Italy. *Vasc Health Risk Manag* 2008; 4: 223–234.
15. Poole-Wilson P, Swedberg K, Cleland J, *et al.* Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; 362: 7–13.
16. Hjalmarson Å, Goldstein S, Fagerberg B, *et al.* Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353: 2001–2007.
17. Taylor AL, Ziesche S, Yancy C, *et al.*; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; 351: 2049–2057.
18. Massie B, Carson P, McMurray J, *et al.* Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; 359: 2456–2467.
19. Ferrari R, Ford I, Fox K, *et al.*; Beautiful Study Group. The BEAUTIFUL study: randomized trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction - baseline characteristics of the study population. *Cardiology* 2008; 110: 271–282.
20. Swedberg K, Komajda M, Böhm M, *et al.* Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376: 875–885.
21. Zannad F, McMurray J, Krum H, *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11–21.
22. Pitt B, Remme W, Zannad F, *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348: 1309–1321.
23. McMurray J, Packer M, Desai A, *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004.
24. Velazquez EJ, Morrow DA, DeVore AD, *et al.* Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019; 380: 539–548
25. Whelton PK, Carey RM, Aronow WS, *et al.* ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2017; 7: S0735–S1097.
26. Yancy C, Jessup M, Bozkurt B, *et al.* 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; 70: 776–803.
27. Cohn J, Archibald D, Ziesche S, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; 314: 1547–1552.
28. Cohn J, Johnson G, Ziesche S, *et al.* A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325: 303–310.
29. Packer M, Bristow M, Cohn J, *et al.* The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349–1355.
30. Ghali J, Tam S, Ferdinand K, *et al.* Effects of ACE inhibitors or beta-blockers in patients treated with the fixed-dose combination of isosorbide dinitrate/hydralazine in the African-American Heart Failure Trial. *Am J Cardiovasc Drugs* 2007; 7: 373–380.
31. Parikh KS, Greiner MA, Suzuki T, *et al.* Resting heart rate and long-term outcomes among African Americans: insights from the Jackson Heart Study. *JAMA Cardiol* 2017; 2: 172–180.
32. Li B, Zhao Y, Helian M, *et al.* Safety of the neprilysin/renin-angiotensin system inhibitor LCZ696. *Oncotarget* 2017; 8: 83323–83333.