Journal of Clinical and Experimental Cardiology

OPEN ACCESS Freely available online

Research Article

Heart Failure with Improved Ejection Fraction (HFiEF) in Afro Caribbean Population: Fact or Fiction? A Case Series and Review of the Literature

Felix Nunura[1*], Edwin Tulloch-Reid[2], Dainia S. Baugh[3], Ernest C Madu[1]

[1]Division of Cardiovascular Medicine, Heart Institute of the Caribbean, Kingston, Jamaica;[2]Department of Interventional Cardiology, Heart Institute of the Caribbean, Kingston, Jamaica;[3]Department of Medicine, Heart Institute of the Caribbean, Kingston, Jamaica

ABSTRACT

Background The group of Afro-Caribbean patients with HFrEF who experience improvement of LVEF to nearly normal or even normal levels (HFiEF) after Guideline-Directed Medical Therapy (GDMT) including ARNI (Sacubitril/Valsartan) represents a unique cohort of HF patients that has not been previously documented. Methods Case series, observational study of Afro-Caribbean outpatients with HFrEF from the Heart Institute of the Caribbean (Jamaica) that were treated with ARNI in addition of conventional GDMT (Beta Blockers, MRA). Clinical characteristics and echocardiographic and. factors associated with LVEF improvement were analyzed based on the rate of EF (>than 10% or <10%) improvement. Results 46 cases (age, 61 Â ± 12.1 years; male, 50%) with HFrEF were consecutively treated with conventional GDMT+Sacubitril-Valsartan for a mean of 28.1 Â ± 15.5 weeks (7Â ± 3.8 months). The underlying etiology of cardiomyopathy was non-ischemic in 83% of patients (history of MI 17%, LBBB 23%, and AFib 19.5%). All patients were responders (mean LVEF was 29.3% Â ± 6.4% before and 40.3% Â ± 10% after HF treatment ($p<0.0001$), however 63% (N=29) were super-responders as EF increased from 28.4% to 44.9%, a mean absolute increase of 16.6 Â ± 7.7% (>10% LVEF improvement) . This response trend ($p<0.05$) to be more related with female gender, hypertension history, absence of Diabetes, obesity, smaller baseline left ventricular end-diastolic dimension (LVEDD) and non-ischemic etiology. Conclusion Among Afro-Caribbean patients with HFrEF treated with conventional GDMT and ARNI therapy the rate of conversion from HFrEF to HFiEF was significant($p<0.01$) suggesting improvement in cardiac remodeling.

Keywords: Heart Failure (HF); Goal-Directed Medical Therapy (GDMT); ACE-inhibitors; Cardiomyopathy; Valsartan heart failure trial

INTRODUCTION

Among patients with Heart Failure with reduced Ejection Fraction (HFrEF), a subgroup experience the restoration of LVEF with Goal-Directed Medical Therapy (GDMT) and are classified as having HF with improved ejection fraction (HFiEF) [1]. Data on demographics, etiology, and prognosis of HFiEF remain scarce, especially in African descendant patients with Heart Failure. HFiEF is a unique disease entity that has superior clinical outcomes. Younger age, de novo HF, nonischemic heart disease, and a b-blocker prescription are independent predictors of HFiEF [2]. This improvement has been recently recognized as an important prognostic tool [3,4] and "Reverse Remodeling (RR)" is more often the result of evidence-based pharmacological and non-pharmacological therapies [5]. The classical medical management of HF is based on treatment with ACE-inhibitors/angiotensin receptor blockers-ARB, beta-blockers-BB and mineralocorticoid receptor antagonists (MRA) [6]. In a sizeable portion of patients (up to 15%), LVRR was pronounced enough to result in a normalization of both LVEF and LV diameters, in a process that has been referred to as "apparent healing" [7]. The mechanistic basis of apparent healing remains largely unknown. Recent work in animal models suggests gene expression changes [8], but data in humans are scarce, as our understanding of disparities of this process in different populations. There is insufficient evidence of the results of successful Heart Failure therapy-induced improving in the LVEF among Black African-descendant population. Hypertension, the most frequent Risk factor among African-descendant population, can be associated with increased wall tension, and we can see many Hypertensive Afro-Caribbean

Correspondence to: Felix Nunura, Division of Cardiovascular Medicine, Heart Institute of the Caribbean, Kingston, Jamaica, Tel: +18769062105; E-mail: fnunura@caribbbeanheart.com

Received: November 27, 2020**; Accepted:** December 11, 2020**; Published:** December 18, 2020

Citation: Nunura F, Tulloch-Reid E, Baugh DS, Madu EC (2020) Heart Failure with Improved Ejection Fraction (HFiEF) in Afro Caribbean Population: Fact or Fiction? A Case Series and Review of the Literature. J Clin Exp Cardiolog. 11: 693.

with a phenotype overlapping that of Dilated Cardiomyopathy (DCM). Several landmark studies and pharmacologic therapies that reduce neuro-hormonal activation have been shown to promote LVRR [9], accordingly Neuro-hormonal Blockade is the gold standard and first step to treat HFrEF. Pronounced effects on reverse remodeling with ACE inhibitors but also Beta-Blockers have been observed [10]. To name a few, in the Valsartan Heart Failure Trial (Val-HeFT, white race 90%) subjects who had higher blood pressure and those treated with a β-blocker or randomized to valsartan had greater odds of being in the HFiEF group, whereas those with an ischemic pathogenesis, a more dilated left ventricle, and a detectable hs-troponin had lower odds of an improvement in EF [11]. On the other hand, In an echocardiography sub-analysis of the A-HeFT (African-American Heart Failure Trial) population reported by Cohn et al. [12-14] the mean LVEF was significantly increased with the fixed dual combination ISDN/hydralazine (p=0.0025 vs. placebo) and LVEDD (mm) was significantly decreased (p=0.0062) after 6 months of therapy. More recently the EVALUATE-HF study investigators reported that In patients with HFrEF (27% Black race) treatment of with sacubitril-valsartan, compared with enalapril, did did significant reduced left ventricular end-diastolic and end-systolic volumes but no difference was noted in measures of contractile function (i.e LVEF). Again, data is scarce as African descendants have been underrepresented in most clinical trials [15]. In a real world small cohort study we have reported that Sacubitril/Valsartan was safe, and well tolerated among and Afro-Caribbean patients with HFrEF [16] and, of note, a significant functional improvement were noted. In the present study we hypothesized that some particular baseline regional clinical and echocardiographic features might predict the subgroup of best GDMT responders in the improvement of the LVEF and this data may guide our clinical management.

CASE SERIES

This is a Case series, non-comparative observational study in Afro-Caribbean outpatients with Heart Failure with reduced Ejection Fraction (HFrEF) from the Heart Institute of the Caribbean (HIC) in Jamaica. The records of cases with HF and documented LVEF<40% were reviewed for this study. Patients were excluded if no baseline transthoracic echocardiographic study was performed at our institution and patients with insufficient echocardiographic image quality for the measurements were excluded. All patients with documented HFrEF were consecutive included in the study and they got initial treatment with an ACEI (mostly Enalapril 5-20 mg bd or Ramipril 10 mg od) or ARB (mostly Valsartan 80-160 mg od or Candesartan 8-32 mg od), a Betablocker (mostly Carvelidol 3.125 – 25 mg BD or Bisoprolol 1.25-10 mg od) and a MRA (mostly spironolactone 25-50 mg od or eplenrenone 25-50 mg od). After a period of hemodynamic stabilization if no contraindicated (hyperkalemia or severe Kidney dysfunction) all patient with ACEI were switched to Sacubitril/Valsartan (available as Vymada® in Central America and the Caribbean) at initial doses of Sacubitril 24 mg/Valsartan 26 mg twice daily that was titrated to a target dosage of 97/103 mg twice daily in a period of two to four weeks in subjects without significant Hypotension (SBP<100 mmHg). Demographic (Age and Gender) and clinical features (history of Hypertension, Type 2 Diabetes, Obesity-BMI of 30 or greater m/h2, old myocardial infarction) and Adverse Reactions (when present) were registered in our Electronic Medical Records. All patients ECGs were registered in order to identify the presence of Q waves, atrial fibrillation (AFib) and Left Bundle Branch Block (LBBB). Reports from Myocardial perfusion scan (MPS) and/or Coronary angiography information was available in 50% of the cases. The cause of HF was considered ischemic on the basis of their clinical history of myocardial infarction (with ECGs evidence of old infarct) and/or abnormal Angiogram and/or MPS. Standard echocardiographic examinations with Doppler studies were performed using commercially available echocardiographic systems and stored digitally. Echocardiograms were systematically reviewed and measured by an experienced Physician. The parasternal images were used to measure LV end-diastolic (LVED) and end-systolic (LVES) dimensions. The 2- and 4-chamber images were used to calculate LV end-diastolic and end-systolic volumes, and LVEF was calculated using a modified biplane method. These echocardiographic data were collected at two time points; at baseline prior to initiating treatment and the most recently available test after a period of treatment. Although the primary focus was the change in LVEF to identify the subgroup with HFiEF over the two studied time points (baseline and post therapy), we looked to describe changes in left ventricular end diastolic dimension (LVEDD, mm) variation as a surrogate indicator suggestive of reverse remodeling however more sophisticated echocardiographic parameters like BSA-indexed measurements or 2-dimensional strain imaging were not available at the time of this analysis. Statistical were performed using MedCalc version 19.3.1. Continuous data were expressed as mean ± standard deviation and qualitative data by proportions. Comparisons were performed using a Student's t-test for paired and unpaired data, as appropriate in order to identify variables associated with the response. For all tests, P<0.05 was considered statistically significant.

RESULTS

Between October 6, 2017 and December 9, 2019 a total of 58 outpatients of the Heart Institute of the Caribbean in Jamaica with the diagnosis of heart failure with reduced ejection fraction (HFrEF) were treated according with the recommended GDMT that included Beta-blockers (BB, 90.9%), Mineralocorticoid Receptor Antagonist (MRA, 90.9%) and the fixed combination Sacubitril/Valsartan (ARNI, 100%) at initial doses of Sacubitril 24 mg/Valsartan 26 mg twice daily titrated to a target dosage of 97/103 mg twice daily (mean dose achieved was 166.7 mg twice a day). Twelve patients were excluded from this analysis because they lost the follow up or they showed poor adherence, accordingly the final analysis included 46 cases (age, 61 ± 12.1 years; male, 50%) with a mean follow-up time of 28.1 ± 15.5 weeks (7 ± 3.8 months). Patients had a Baseline mean Systolic Blood Pressure of 137 mm Hg, a mean Diastolic Pressure of 82 mm Hg, and a mean Pulse of 77.6 bpm. The NYHA functional Class was II in 92.5% and Class II in 7.5%. The mean Potassium level was 4.4 mmol/L and the mean eGFR was >73 mL/min/1.73 m^2 in. Just 17% of the patients showed Q waves and had a clear past medical history of Myocardial infarction consistent with ischemic etiology for the Heart Failure. Data from coronary angiograms or Myocardial Perfusion Scan was available in 23 cases (50% of the total) and from this subgroup just 39% showed abnormalities consistent with Angiographycally Obstructive Coronary Arteries (AOCA) for the ischemic etiology. All (n=46) patients were GMDT (including ARNI) responders as the baseline mean LVEF was 29.3% ± 6.4% and rose to 40.3% ± 10% after therapy (p<0.0001), however 63% (n=29) shown an improvement in LVEF more than 10% (Super responders, Group 1),Table 1 and Figure 1, from a mean of 28.4% at baseline to 44.9% (p<0.001). The remaining 37% (n=17) cases showed EF increases less than 10% (Responders Group 2), Table 1, from a mean EF

of 30.7% to 32.4% (p<0.05) The clinical and echocardiographic characteristics of both populations (>10% vs. <10% change in LVEF) are shown in Table 1. When both groups were compared according to Demographic features and associated comorbidities (Table 1) we found not statistically differences between both groups (p<0.05) however the cases in Group 1 (EF improvement>10%) trended to have smaller baseline LVEDD (66.8 mm vs. 70.3 mm), more likely to be females (59% vs. 35.3%), hypertensive (62% vs. 53%), non-diabetics (72.5% vs. 59%), obese (20.5% vs. 17.6%) , and have mostly non-ischemic etiology (13.8% vs. 17.6%). In addition, we observed more proportion of cases with AFib (20.6% vs. 5.8%)) and LBBB (24% vs. 17.6%) in this subgroup In the other hand following the treatment, Group 1 patients showed more significant (7.7 ± 6.5 mm, -10%, p<0.001) reduction of the LVEDD (from 66.8 mm at baseline to 60.1 mm at follow) that Group 2 responders, Table 1, in which there were not significant LVEDD changes (2.8 ± 3.3, -1%; from 70.3 mm at baseline to 69.1 mm at follow up (Table 2).

Table 1: Baseline clinical characteristics for the study population and comparative baseline and after therapy clinical characteristics according with the rate of response for the LVEF after Guidelines Directed Medical Therapy (GDMT).

Variable	All patients (N=46)	Group 1 EF improve>10 % (n=29)	Group 2 EF improve< 10 % (n=17)	Group 1 vs. 2
				P value
Demographic				
Age, y	61 ± 12	61 ± 11	60 ± 14	NS
Male,%	50	41.4	64.7	0.12
Past medical history				
Hypertension,%	60.8	62	52.9	0.56
Diabetes,%	32.6	27.5	41.1	0.35
Obesity,%		20.6	17.6	0.8
NYHA functional class				
II,%	92.5			
III,%	7.5			
ECG				
Myocardial Infarction,%		13.8	17.6	0.7
Atrial fibrillation,%	19.5	20.6	5.8	0.6
LBBB,%	23	24	17.6	0.1
Echocardiogram				
Mean baseline LVEDD, mm	68.1 ± 7.4	66.8 ± 6	70.3 ± 9.2	
After therapy LVEDD,mm	63.6 ± 10.1	60.1 ± 8.5	69.1 ± 9.8	
Mean change LVEDD, reduction, %	5.9	10	1.7	<0.05 (*)
Mean baseline LVEF,%	29.3 ± 6.4	28.4 ± 6.8	30.7 ± 5.6	
After therapy LVEF,%	40.3 ± 10	44.9 ± 8.5	32.4 ± 7	
Mean change LVEF increase,%	11	58	1	<0.001 (**)
Physical Examination				
SBP,mm Hg	137			
DBP,mm Hg	82			
Laboratory Examination				
Potassium level, mmol/L	4.4			
eGFR, mL/ min/1.73m^2	>73			
Medications				
Betablockers,%	90.9			
MRA,%	90.9			
Ivabradine,%	29.5			
ISBDN,%	77			
ARNI, mean daily doses, mg	333.4			
Median duration of treatment, weeks	28.1			

Note: (*) Mean change reduction in LVEDD, Group 1 vs. Group 2: p<0.05

(**) Mean change increase in LVEF, Group 1 vs. Group 2: p<0.001

Table 2: Logistic regression analysis between ventilatory and echocardiographic parameters and stress RV E/e'.

Univariable regression analysis	p-value	OR	95% CI
Ventilatory parameters			
FEV1, l	0.78	2.01	0.86-3.87
ICdyn, l	0.04	5.29	2.68-9.18
LV parameters			
Septum, mm	0.67	1.98	1.62-2.86
LVPWT, mm	0.81	2.17	1.93-4.49
E/A ratio at rest	0.94	0.99	0.80-1.23
E/e' ratio at rest	0.99	1.89	1.59-1.99
E/A ratio after stress	0.04	1.54	1.00-2.35
E/e' ratio after stress	0	4.07	1.75-12.47

RV parameters			
RV basilar diameter, mm	0	1.48	1.23-1.78
RVmedian diameter, mm	0	1.83	1.38-2.48
RVWT, mm	0.74	0.98	0.78-1.02
RAVI, ml/m^2	0	3.82	2.04-7.14
E/A ratio at rest	0	19.73	18.52-21.01
E/e' ratio>5.1 at rest	0.03	4.79	1.73-13.24
TAPSE, mm	0.37	21.56	1.20-38.91
S peak velocity, m/s	0.33	0.73	0.55-0.97
PASP, mmHg	0.12	0.7	0.07-75.08
AT, msec	0.49	2.39	0.20-28.67
Biomarkers			
Resistin, ng/ml	0.02	0.81	0.51-1.31
PG E2 , µmol/l/cre	0.04	0.7	0.34-1.07
Multivariable regression analysis			
E/e' ratio>5.1 at rest	0.02	9.03	1.32-63.73
RAVI, ml/m^2	0	2.27	1.40-3.68

Abbreviations: FEV1: Forced Expiratory Volume in 1 sec; ICdyn: Dynamic Hyperinflatio; RVDD: Right Ventricular Diastolic Dysfunction; LV: Left Ventricle; RV: Right Ventricle; LVPWT: Left Ventricular Posterior Wall Thickness; RVWT: Right Ventricular Wall Thickness; RAVI: Right Atrium Volume Index; AT: Acceleration Time; PASP: Pulmonary Arterial Systolic Pressure; AT: Acceleration Time; TAPSE: Tricuspidal Annular Plane Systolic Excursion; PG E2: Prostaglandine E2.

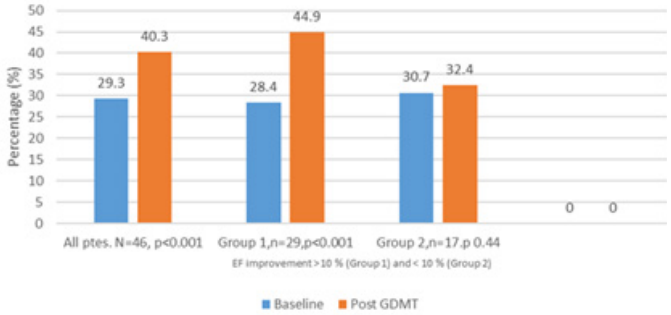

Figure 1: Mean ejection fraction (%) improvement at two points: baseline and post therapy (GDMT, including ARNI) in afro caribbean heart failure with reduced ejection fraction.

DISCUSSION

Before starting the discussion below are some cases with Afro-Caribbean Heart Failure that have been the subject of presentation at our HIC Heart failure Clinic monthly meetings with the Perelman Center for Advanced Medicine team (University of Pennsylvania) the past 2 years.

In this case series, we report for the first time to date in our region, the clinical and echocardiographic findings of 46 Afro-Caribbean patients with the diagnosis of HFrEF that were treated with Sacubitril/valsartan, an Angiotensin Receptor–Neprilysin Inhibitor (ARNI) in addition of the conventional GDMT (Beta Blockers and mineralocorticoid receptor antagonists [MRAs]. Although Sacubitril/valsartan was approved in July 2015 to reduce the risk of cardiovascular death and hospitalization for patients with HFrEF, it is available in the Caribbean region since 2017. Our case series highlights that in a significant proportion of the subjects (63%) the treatment led to marked improvements (>10% improvement) in the left ventricle systolic function (as assessed for EF changes) and the cardiac structure (as assessed for LVEDD changes) after a media of time of 28 weeks (about 7 months) however just low improvement was achieved in 37% of the subjects. Several important topics emerged from our case series that may provide important insight into the concept of the process of Left ventricle Ejection Fraction improvement and suggestive reverse remodeling (LVRR) among African-Caribbean population with Heart failure which may inform the clinician (Table 1).

Role of CAD in the etiology of Afro-Caribbean heart failure

Clinically, as it was documented in our previous observations [17] the majority of Afro-Caribbean patients with the diagnosis of Heart Failure (HF) an despite a history of systemic hypertension, type-2 Diabetes or both, do not have angiographically or by Nuclear imaging a demonstrated obstructive CAD or ischemic cardiomyopathy or evidence of an old Myocardial Infarction (MI). This is clearly different of the big epidemiological data that states that nearly 70% of all HF syndromes can be attributed to underlying Ischemic Heart disease (IHD) [18], namely that patients with an obstructive epicardial stenosis (eg, obstructive Coronary Artery Disease [CAD]) are more likely to develop HFrEF as a result of acute ischemic injury causing Myocardial infarction and subsequent scar formation but this pathophysiologic path seems not to be always fully applicable in this population which is consistent with epidemiological data that have shown that the role of CAD in HF varies based on geographic region: while only 10% of all HF cases in Sub-Saharan Africa can be attributed to CAD, as high as 50% to 70% of all cases in the United States and Europe, and 30% to 40% of all cases in Asia and Latin America, are caused by underlying CAD [19].

The microvascular dysfunction hypothesis

It is relevant that, after the treatment with conventional GDMT + ARNI therapy the best response in terms of improving the Ejection Fraction and reduction of the Left ventricle end diastolic dimension seems to be more associated with female gender, hypertension, non-diabetics, and obese. Association was also noted with Atrial Fibrillation and LBBB (Figure 1) but, of note, mostly in patients with Non-ischemic etiology of HF, raising the question if Coronary Microvascular Coronary Disease or other kind of ischemic or non-ischemic etiologies are a better target for therapies like ARNI agents. Sacubitril/valsartan consists of the neprilysin inhibitor sacubitril and the Angiotensin Receptor Blocker [ARB] valsartan. Neprilysin is a neutral endopeptidase that metabolizes endogenous vasoactive peptides, including natriuretic peptides, bradykinin (BK), and substance P into their inactive metabolites). BK stimulates endothelial cells to release a number of relaxing factors, such as NO, prostanoids (PGs), and an endothelium-derived hyperpolarizing factor (EDHF). Inhibition of neprilysin increases the levels of these substances leading to vasodilation, decreased vasoconstriction, decreased sodium retention,

abnormal growth, and remodeling. Moreover, angiotensin II, a potent vasoconstrictor, is also a substrate of neprilysin. Thus, the addition of an ARB (Valsartan) to the neprilysin inhibitor is necessary to prevent activation of the RAAS [20]. How important are myocardial endothelial and microvascular dysfunction in the pathogenesis of Afro Caribbean Heart Failure? What are the physiological and clinical consequences of myocardial endothelial and microvascular dysfunction in Afro Caribbean HF? There is an unmet need to classify HF patients based on their myocardial vasodilator response as well as characterize their ventricular mechanics, inflammatory and neuro-hormonal milieu, myocardial substrate, and overall outcomes. To date, no study has evaluated and phenotyped the myocardial substrate in patients with Afro-Caribbean HF and possible associated myocardial microvascular dysfunction. Identification and classification of HF based on the presence or absence of endothelial or microvascular dysfunction may identify high-risk subgroups that may benefit from therapy targeted to the endothelium and/or microvasculature [21] In this respect, the vasodilator actions of Renin-Angiotensin system blockers combined with Neprilysin Blockers would be of particular importance in the process of LV inverse remodeling since other vasodilator therapies (Nitrates/Hydralazine) have already shown that can improve LV structure and function and reduce mortality in self-identified black patients with symptomatic HF [22].

Afro Caribbean Heart Failure with Improved Ejection Fraction [HFiEF]

Although it is acknowledged that a distinct cohort of patients with improved or recovered LVEF exists, there is currently no consensus definition of this cohort. In 63% of our cases there was a well-defined improved ejection fraction after therapy (from 28.4 ± 6.8% at baseline to 44.9 ± 8.5% after therapy: a variation of + 16.6, a 58% improvement) Figure 1. HF with improved EF (HFiEF) has been proposed to define patients with LVEF >40% with a previously documented LVEF<35% [22]. We use the term "improved" rather than "recovered" because it highlights two important features of this clinical entity: 1) despite having very improved or even normalized LVEF, these patients may continue to have clinical HF and abnormal biomarker signs of functional impairment; and 2) the improvement experienced by these patients does not necessarily reflect "recovery" from their underlying structural cardiomyopathic process. Moreover, improvement in LVEF is generally considered a surrogate for the underlying process of reverse remodeling occurring at the myocardial and ventricular structural and functional levels, and, therefore, it should be accompanied by a reduction in LV volumes [23]. For some patients, such as those with stress cardiomyopathy (Takotsubo-like), LVEF improvement may occur rapidly, even in the absence of medical therapy. For others, medical therapy may be partially or wholly responsible for LVEF improvement. What is clear, however, is that the frequency of LVEF improvement depends on the cause of the underlying cardiomyopathy. In a comprehensive review, Givertz et al. [24] documented rates of LVEF improvement (to LVEF >50%) of 60% to 100% when considering causes of cardiomyopathy such as tachycardia, Takotsubo, and hyperthyroidism among patients with recent onset (<6 months) cardiomyopathy. Rates of LVEF improvement are lower in cohorts of patients with chronic HF. In a tertiary care center cohort of over 1,800 patients with HF, only 10% of patients had HFiEF (to LVEF ≥ 50%) [25]. Similarly, only 9% of the nearly 4,500 patients selected for analysis from Val-HeFT (Valsartan Heart Failure Trial) went on to experience LVEF improvement to ≥ 40% during the first 12 months of follow-up [11].

Baseline characteristics associated with LVEF improvement in Afro-Caribbean heart failure

Despite differences in HFiEF definition, several demographic and clinical characteristics are repeatedly identified as being associated with greater likelihood of improved LVEF. These include female sex, absence of Diabetes , nonischemic cause of HF, shorter duration of HF, and less severe adverse cardiac remodeling at initial evaluation, smaller LVEDD, smaller LA dimension, higher Blood pressure, higher LVEF [26] These factors have also been associated with "super-responders" to CRT [27] However, although the presence of left bundle branch block (LBBB) is also predictive of good CRT response, LBBB has also been associated with attenuated LVEF improvement or lack of LVEF improvement with optimal medical therapy alone. This discrepancy again highlights the importance of dyssynchrony in maintaining LV dysfunction in some patients. Our findings in these case series suggest that factors associated with a "super-response" among Afro-Caribbean population (Table 1, Figure 1) might be female sex, absence of Diabetes, Hypertension, and smaller baseline LVEDD although our small sample failed in show a clear significance. We also observed a trended association with 1-Obesity. In the longitudinal echocardiographic study of the Framingham population, an increase in BMI over time was closely related to increases in LV mass and volumes [28] and Left ventricular remodeling in patients with metabolic syndrome has been shown influenced for female gender [29]

2-Atrial Fibrillation : The weight of current evidence suggests that most cases of AF and HF result from exposure of the heart to a common set of systemic cardiovascular risk factors and that HF and AF share common genetic predictors as well as mechanisms of structural and electrophysiological remodeling and established risk factors and cardiac remodeling are essential for the development and maintenance of AF in many patients [30].

3-Non-Ischemic etiology: Only 14% of our "super responders" cases had history of previous Myocardial infarction (Table 1) and from our available cases (50%) with available reports of coronary angiogram/Myocardial persfusion scan and from this subgroup just 39% showed abnormalities. At this point is interesting to note that possibly some of these "non-ischemic" patients may fit in the definition of ischemia with non-obstructive coronary arteries (INOCA). INOCA patients present with a wide spectrum of symptoms and signs that are often misdiagnosed as non-cardiac leading to under-diagnosis/investigation and under-treatment. INOCA can result from heterogeneous mechanism including coronary vasospasm and microvascular dysfunction and is not a benign condition. Compared to asymptomatic individuals, INOCA is associated with increased incidence of cardiovascular events, repeated hospital admissions, as well as impaired quality of life and associated increased health care costs [31].

Racial differences in characteristics and outcomes of patients with heart failure

Black patients have a 50% higher incidence of HF that occurs at an earlier age than white patients with epidemiological studies suggesting are 30% to 50% hospitalized [32]. Epidemiological studies suggest more rapid progression of HF in black patients, and explanations have included higher prevalence of key risk factors such as hypertension, diabetes mellitus, and obesity; possibility of

disparate health care; worse socioeconomic status; and potential differences in physiological responses to elevated blood pressure among others [33]. More research is needed to fully understand pathophysiological disparities.

LIMITATIONS

This study observational has several limitations. First it is a relatively small sample for a single center. Second: the limited number of echocardiographic parameters assessed without the support of an Echocardiographic Core Lab. Third: insufficient resources to assess the Heart Failure etiology (such as universal access to Coronary angiograms, Myocardial Perfusion Scans, Cardiac MRI, or Intracoronary Imaging; however it is the first documentation about the topic of HFiEF in Afro Caribbean patients.

Although all the standards were not 100% met and there is certainly room for improvement, illustrating the importance of good clinical practice through audits and quality improvement projects highlights areas in clinical care that we as healthcare professionals must be mindful of. Additionally, presentation of this audit and the results obtained in a number of different clinical settings will contribute in improving the outcome and encourage others to view one aspect of medical care through our lens.

CONCLUSSION

This case series highlights the clinical and echocardiographic manifestations of Afro-Caribbean patients with HFrEF in association with their response to our current therapy options (GDMT+ARNI therapy). Our findings should serve for a better understanding of the phenomenon of therapy-induced EF improvement and, in some extension, of the with therapy-induced reverse of cardiac structure process, and also underscore the clinical profile of heart failure with improved ejection fraction (HFiEF) in this geographical region since so far there are not publications in this field. In this context this cases series intended to bring the attention to possible pathophysiologic mechanism why Afro-Caribbean patients seems to be particularly benefited from this type of therapy. Our findings also support our earlier work showing that Non-ischemic cardiomyopathy is the leading cause of Heart failure in Jamaica. The reversibility potential of certain types of HFrEF patients who progress to HFiEF status after GDMT includes Neprilysin inhibitors has been documented in this case series. Better designed and larger studies will be needed to gain insight into the different iterations of current medical therapies in this Caribbean region where the setting of not only preexisting hypertensive heart disease and Diabetes but also cardiac amyloidosis should not be underestimated.

CONFLICT OF INTEREST

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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