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REVIEW ARTICLE

Simultaneous initiation of quadruple therapy for heart failure with reduced ejection fraction: initial experience in Afro Caribbean Jamaican population

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ABSTRACT

Background: Among Afro Caribbean Jamaican patients with heart failure with reduced ejection fraction (HFrEF), improvements in cardiac function associated with simultaneous initiation of quadruple therapy, have not been previously reported and we aimed to assess this special population.

Methods: Combined quadruple therapy (angiotensin-receptor neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonist, and Sodium-glucose cotransporter-2 inhibitors) was simultaneously initiated in 120 Afro Jamaican patients with HFrEF from the Heart Institute of the Caribbean. Patient data was consecutively recorded in our electronic medical records. Changes in Ejection fraction (EF) and N-terminal pro b-type natriuretic peptide (NT-ProBNP) levels, were evaluated after 90 days and statistically analysed during this two-year study.

Results: Patient mean age was 63 ± 12.7 years old, 68% male, with mean Body Mass index (BMI) 32.2±6.7 Kg/m2. Hypertension was observed in 62.5 %, T2Diabetes Mellitus in 31.7%, and history of old myocardial infarction in 15.7 %. Atrial fibrillation was present in 7.8% and left bundle branch block in 16.5 %. Other cardiomyopathies (idiopathic, peripartum and non-compaction) were noted in 16.6 %. After the quadruple therapy for a median follow-up period of 90 days, significant improvements of cardiac function were achieved. The mean NT pro-BNP level was significantly decreased from a Baseline of 3111.21 pg/mL ± 4535 to 1806.6 ± 2265.3 pg/ml. A mean change in NT Pro BNP of 1305 pg/mL ± 5069 ($p < 0.001$). The mean left ventricle ejection fraction (LVEF) improved from a baseline of 33.4 % ± 7.8 to 44.4 % ± 10.9. A mean change in LVEF of 11.3% ± 9.1 ($p <0.001$). Notably, an improvement of >10% in the LVEF was observed in 41.5% of the total population. In a separate analysis, the subgroup with T2 Diabetes mellitus showed more pronounced (mean change in EF 9.1% ± 11.0) improvement in LVEF than the non-diabetic (mean change in EF 7.7% ± 11.7) but no significant differences in the change of the NT pro-BNP levels were noted between both subgroups. The most frequent therapy adverse effect was hypotension (13.63%) followed by cough (6.81%) and kidney dysfunction (2.27%) but none of the patients presented Angioedema.

Conclusion: Among Afro Caribbean Jamaican patients with heart failure and reduced ejection fraction, simultaneous initiation of the quadruple therapy was demonstrated to be feasible, well tolerated and associated with significant functional improvement.

Key words: Heart Failure. Therapy. Afro Jamaican.

Introduction

In the last four years much research has focus on the comprehensive disease-modifying medical therapy, CDMMT (angiotensin-receptor neprilysin inhibitor,ARNI; beta-blocker,BB; mineralocorticoid receptor antagonist,MRA; and Sodium-glucose cotransporter-2 inhibitors,SGLT2i) , the so-called Fantastic four or the Four Pillars. This quadruple therapy has been established as the mainstays of heart failure with reduced ejection fraction (HFrEF) care, with estimates suggesting that compared to limited conventional therapy with an ACEI/ARB + BB, use, could further reduce cardiovascular mortality in HFrEF by 50%[1]. Accordingly it has become the new standard of care for patients with HFrEF. The effects of empagliflozin and dapagliflozin on hospitalisations for heart failure have been consistent in the two independent trials DAPA-HF (assessing dapagliflozin) and EMPEROR-Reduced (assessing empagliflozin) regardless of diabetes status, and it has been reported that these agents also improve renal outcomes and reduce all-cause and cardiovascular death in patients with HFrEF[2]. The estimated cumulative effect of these four medications includes a 73% relative reduction in mortality over 2 years[3]. However, despite these incredible advances in HFrEF treatment and the high incidence and hospitalization rate of Heart Failure in African-descendant, racial/ethnic inequities in heart failure burden, access to therapies, and outcomes persist, and this special population has remained underrepresented in pivotal landmark trials that form the foundational quad-therapy for HFrEF management in the modern era, and often comprise less than 5.5% of the treatment group[4]. In the PARADIGM Trial (sacubitril-valsartan) and in the DAPA-HF (Dapagliflozin) just 5% and 15.1 %, respectively, were black patients and notably, only a minority of these patients received both, a SGLT2i and an ARNI therapy[5,6]. Accordingly, the data about the impact of these new therapies in black population including Jamaican Afro Caribbean is very limited. Although researchers have called for more inclusivity and equity in heart failure clinical trials[7], there is a dearth of clinical studies focusing on the African descendant community from the Caribbean region affected with heart failure and the role of this ethnicity in cardiovascular risk and disease is still not fully understood. A higher prevalence of hypertension, elevated body mass index, and diabetes mellitus has been recognized and the mortality from stroke in people of Afro-Caribbean origin has been recognized to be twice the average for England and Wales patients[8]. In addition, a study in 211 Afro-Caribbean with Heart Failure living in United Kingdom has shown that non-ischemic dilated cardiomyopathy is the main cause of Heart Failure in 87 % of the cases and cardiac amyloidosis secondary to variant ATTR V122I is present in 8.5 %[9]. In a similar way, we have previously documented that Jamaican Afro-Caribbean, 92% of them self-identified as black[10], are mainly hypertensive with or without associated Diabetes Mellitus and most of them develop angiographycally proven non Ischemic Dilated Cardiomyopathy[11,12]. On the other hand, although indirect estimate suggests that the combination of both, simultaneously, dapagliflozin and sacubitril/valsartan would yield additive benefits[13], data about the real

word effect of this combination treatment in HFrEF has not been widely reported. A total of 508 patients (10.7%) enrolled in DAPA-HF were treated with sacubitril/valsartan at baseline and it has been reported that Dapagliflozin was similarly efficacious and safe in patients who were and who were not taking sacubitril/valsartan in the DAPA-HF trial, which suggest that the use of both agents together could further lower morbidity and mortality in patients with HFrEF[13]. Studies in Chinese and Croatia patients have shown that the concurrent use of sacubitril/valsartan and dapagliflozin is linked with improved cardiac function and greater reductions in NT-proBNP levels compared to sacubitril/valsartan monotherapy[14,15]. However, although the therapeutic response to angiotensin receptor/neprilysin inhibitor, ARNI, has been previously described in Afro Caribbean Jamaicans, the utilization of SGLTi has not yet been reported[16]. Moreover, data on the improvements in the cardiac function with the utilization of the combined quadruple therapy in patient with HFrEF is scarce and it has not been previously reported in African descendant population In addition, an alternative strategy to improve the utilization of the comprehensive disease modifying medical therapy, namely the quadruple therapy, consisting in the simultaneous/ rapid sequence initiation followed by titration of HFrEF medications, as tolerated, has been described[27,49]. Accordingly, this approach must be evaluated in Jamaican Afro Caribbean population because the simultaneous/rapid sequence initiation of all medications – as opposed to the slower serial stepwise approach – should be the preferred in order to reduce the Heart Failure associated risk as quickly as possible. Hence, the purpose of this study was to assess the real-world benefit of the quadruple therapy namely angiotensin receptor-neprilysin inhibitors (ARNI), sodium-glucose cotransporter 2 inhibitors (SGLT2i), BBs, and MRAs, simultaneously initiated , on cardiac function, in this special population.

Method

STUDY POPULATION

This study was designed as a single-center, prospective, observational study. The study was conducted at the Heart Failure Clinic of the Heart Institute of the Caribbean, Kingston and Manchester ,Jamaica ,from February 2021 to July 2023. Patients were referred to our Institution from local Medical Practitioners or the Regional Hospital.

Patients were included if they were at least 18 years of age, had New York Heart Association (NYHA) functional classes II to IV, the presence of symptoms and/or signs of heart Failure (HF) and LVEF ≤ 40% by echocardiography. The exclusion criteria were as follows: (1) patients lost to any follow-up, (2) if sacubitril/valsartan and/or dapagliflozin were discontinued at follow-up, (3) HF primarily resulting from right ventricular failure, pericardial disease, severe valvular heart disease or congenital heart disease. We consecutively enrolled 120 outpatients with HFrEF and the data was recorded in our Electronic Medical records (SMART EMR)

THERAPY

Unless contraindicated or not tolerated all patients were simultaneously initiated with the Quadruple therapy, namely: 1- The angiotensin receptor-neprilysin inhibitor

(ARNI). Sacubitril/valsartan (Vymada®) 2- A beta-blocker (mostly bisoprolol) 3- A mineralocorticoid receptor antagonists (MRA), mostly eplerenone, and 4- the sodium-glucose co-transporter 2 (SGLT2) inhibitor (mostly dapaglifozine) . While the study was ongoing in September 2021, new ESC guidance was published recommending the use of SGLT2 inhibitors as a foundational drug in HFrEF management (class recommendation IA)[19]. Based on the initial clinical assessment that included level of Blood Pressure, Heart Rate, Potasium level and the estimated glomerular filtration rate (eGFR) these drugs were started at the most appropriate dose according to the patient's individual profile, that is, in some cases with the minimum dose or in others with the maximum available dose. The blood pressure level was the most determining factor for the initial dose of Sacubitril/Valsartan and the heart rate for the dosage of the sympathetic beta blocker or the addition of the sinus node modulator Ivabradine. This was followed by a progressive up titration in the following days or weeks to the maximally tolerated evidence-based doses when possible. The starting dose /target dose was as follow: Sacubitril/ Valsartan 49/51 mg b.i.d./ 97/103 mg b.i.d.; Bisoprolol 1.25 mg o.d/10 mg o.d. or Carvedilol 3.125 mg b.i.d./25 mg b.i.d; Spironolactone 25 mg o.d./50 mg o.d. or Eplerenone 25 mg o.d./50 mg o.d. and Dapaglifozin 10 mg o.d./10 mg o.d. If the patient was on ACEI it was replaced for ARNI allowing at least a 36-hour washout period from an ACEI before starting sacubitril/ valsartan. Other pharmacological treatments (Loop Diuretics, Ivabradine, isosorbide dinitrate and Digoxin) were indicated in selected patients with specific indications.

FOLLOW UP

All patients, even if symptoms were well controlled and stable, had a follow-up in our Clinic to ensure adequate medication adherence and compliance and continued individualized optimization of therapy, in order to detect asymptomatic or symptomatic progression of heart failure or its comorbidities and to discuss any new recommendation in care. We follow-up our patients at intervals no longer than one month to check symptoms, heart rate and rhythm, BP, electrolytes, and renal function. For patients recently discharged from hospital, or in those undergoing up titration of medication the follow-up intervals were more frequent. An echocardiogram was advised every 3 months after optimization of the indicated therapies to determine the efficacy of the pharmacological agents.

STUDY PARAMETERS AND DATA COLLECTION

The data used for this study was collected by Clinical characteristics, including age, gender, Body Mass Index, history of Hypertension, history of T2Diabetes, History of Ischemic Heart disease and old myocardial infarction, and other possible HF aetiologies were registered at baseline. Body Mass Index, Blood pressure, Heart Rate, heart rhythm, and NYHA functional class were recorded at baseline and during each follow up visit. Echocardiography and Laboratory (eGFR, N-terminal pro b-type natriuretic peptide and Potassium level) were recorded at baseline and every 3 to 6 months. Therapeutic drugs doses were also collected at baseline and during follow-up in order to evaluate efficacy and safety.

STATISTICAL ANALYSES

The SPSS v. 23 statistical tool was used to analyse data for the study. Mean values were

generated about the summary clinical characteristics. At the time that this analysis was started, of the 120 patients 68.3 % of them had available both baseline and post therapy ejection fraction (EF) values, while 55 % had available baseline and post therapy NT-pro BNP level values. The post-therapy ejection fraction value used for the analysis was the most recent obtained and first post-therapy (average 3 months after therapy). NT pro BNP levels results were available up to one year after therapy initiation. EF variables met assumptions of normality; however the NT pro BNP variables did not meet the assumption of normality until a logarithmic mean was created. The parametric tests; independent sample t-test and paired sample t-test were used to determine the statistical significance of the EF and the logarithmic mean of BNP variables. There was disaggregation of the sample by the diagnosis of diabetes mellitus in order to determine if there was any significant difference in the mean change of EF or levels of NT Pro BNP within this group in comparison with Non diabetics after the Quadruple therapy.

Results

A total of 120 jamaican patients with HFrEF were consecutively enrolled in the study. As it can be seen in Table 1 (Baseline characteristics) the patients were averaged age 63 years old, mostly male, hypertensive, with elevated Body Mass Index, and 31.7 % were Diabetic however only 15% had a history of an old myocardial infarction. Other dilated cardiomyopathies (idiopathic, peripartum and noncompaction) were identified in 16.6 %. Most patient were in sinus rhythm but Atrial Fibrillation (AFib) was noted in 7.8% and Left Bundle Branch Block (LBBB) was recorded in 16.5%.

Table 1. Baseline characteristics of the study population (n=120)

Variable	n (%) or Mean±SD
Age (years)	63±12
Male, n (%)	66 (55)
Hypertension, n (%)	75 (62.5)
T2 Diabetes, n (%)	38 (31.7)
Dyslipidaemia, n(%)	16 (38.1)
Old Myocardial Infarction, n (%)	18 (15)
Atrial Fibrillation, n(%)	9 (7.8)
Left Bundle Branch Block, n(%)	19 (16.5)
Mean BMI (kg/m^2)	32±6
Mean SBP (mmHg)	135.6 ±25.8
Mean DBP (mmHg)	83.2±21.8
Mean Heart Rate (bpm)	83±20
Mean eGFR (mL/min/1.73m2)_	60.5±11.7

THERAPY AND TOLERANCE

All patients were simultaneous initiated with the four pillars regimen (ARNI, BBs, MRAs and SGLT2i) from the first visit, and these drugs were titrated on an individualized basis, to the maximum tolerated daily dose. The mean doses for Sacubitril/Valsartan (n-120) was 177.27 mg. b.i.d., for Dapaglifozin (n=120) was 10 mg. o d, for Eplerenone (n= 114) was 35 mg o.d, for Spironolactone (n=6) was 25 mg o.d., for Bisoprolol (n=116) was 9.0 mg. o.d, and finally, for carvelidol (n=6) was 18.75 mg b.i.d. Other medications: Nitrates (ISBDN 10-20 mg BD/TD or Nitro 2.6 mg BD) and Ivabradine 5 to 7.5 mg BD were recommended in 48 % and 28.6 % respectively. The frequency of Prospective Identified Adverse Events (PIAE) was Hypotension (13.6%), Cough (6.81%), and kidney dysfunction (2.27%). No patient developed angioedema

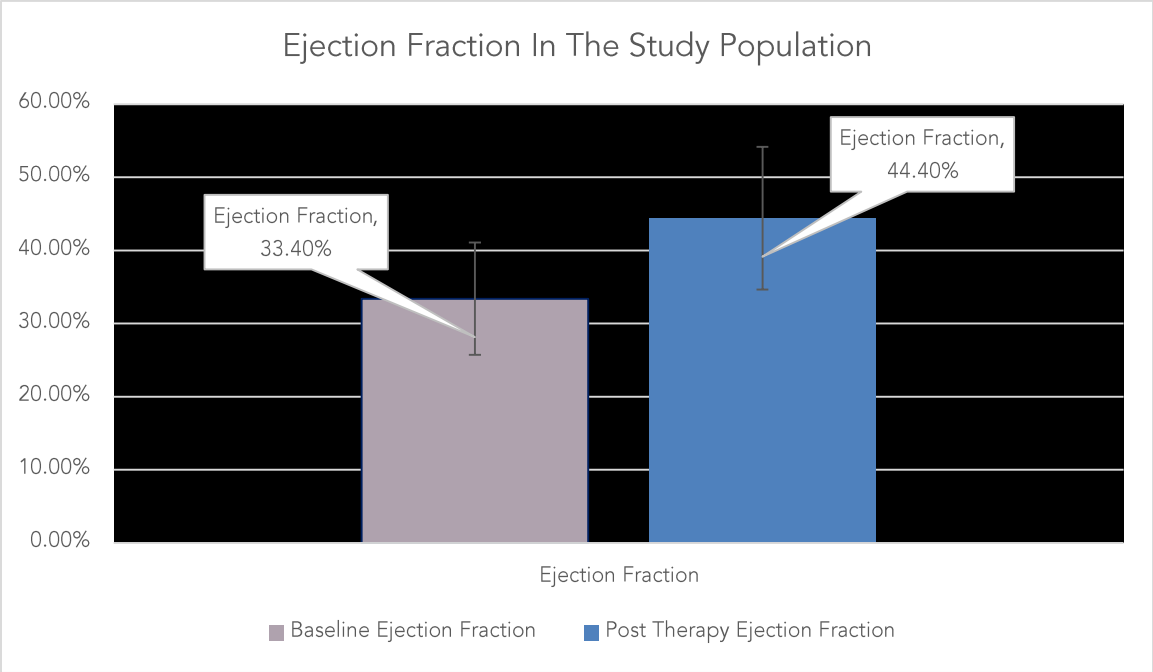
LEFT VENTRICULAR SYSTOLIC FUNCTION

As can be seen in table 2 and figure 1 and 2, significant improvement in the Ejection Fraction (EF) from baseline to follow-up was observed in the entire cohort. The mean change in EF was 11.3% ±9.1 consistent with a statistically significant 32.93% increase in EF after therapy administration in this study population (95% CI: 13.2 to 8.9, t = 10.194, df = 81, p = 0.001). In addition, It was observed that 41.5% of the patients had an increase in EF of ≯0% within 6 months of beginning the guidelines-directed medical therapy (t=-10.955 df=80 p=.001 95%CI -10.09 to -14.57) and 57.3% of the study population had an increase in EF of > 10% within 6 months and 1 year of Quadruple therapy (t=-10.396 df=79.255 p=.001 95%CI -10.99 to -16.20).

Table 2: Changes in Ejection Fraction and NT pro BNP Values (n=120)

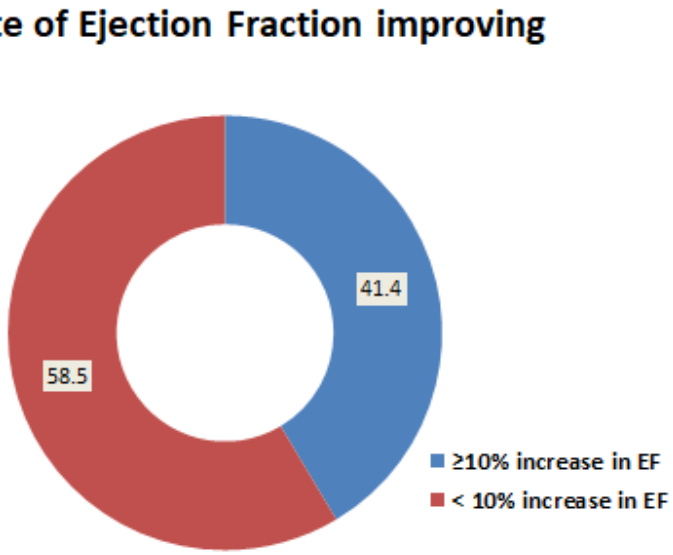
Variables	Mean ± SD
Baseline Ejection Fraction (%)	33.4 ± 7.8
Post Therapy Ejection Fraction (%)	44.4 ± 10.9
Change in Ejection Fraction (%)	11.3 ± 9.1
Percentage increase in EF	32.93%
Baseline NT pro BNP (pg/ml)	3111 ± 4535
Post Therapy NT pro BNP (pg/ml)	1806.6 ± 2265.3
Change in BNP (pg/ml)	1305 ± 5069
Percentage decrease in NT-pro BNP	41.9%

Figure 1.Ejection Fraction at Baseline and after Quadruple therapy (n=120)



(t=10.194, df=81, p=.001, 95% CI 13.238 to 8.914)

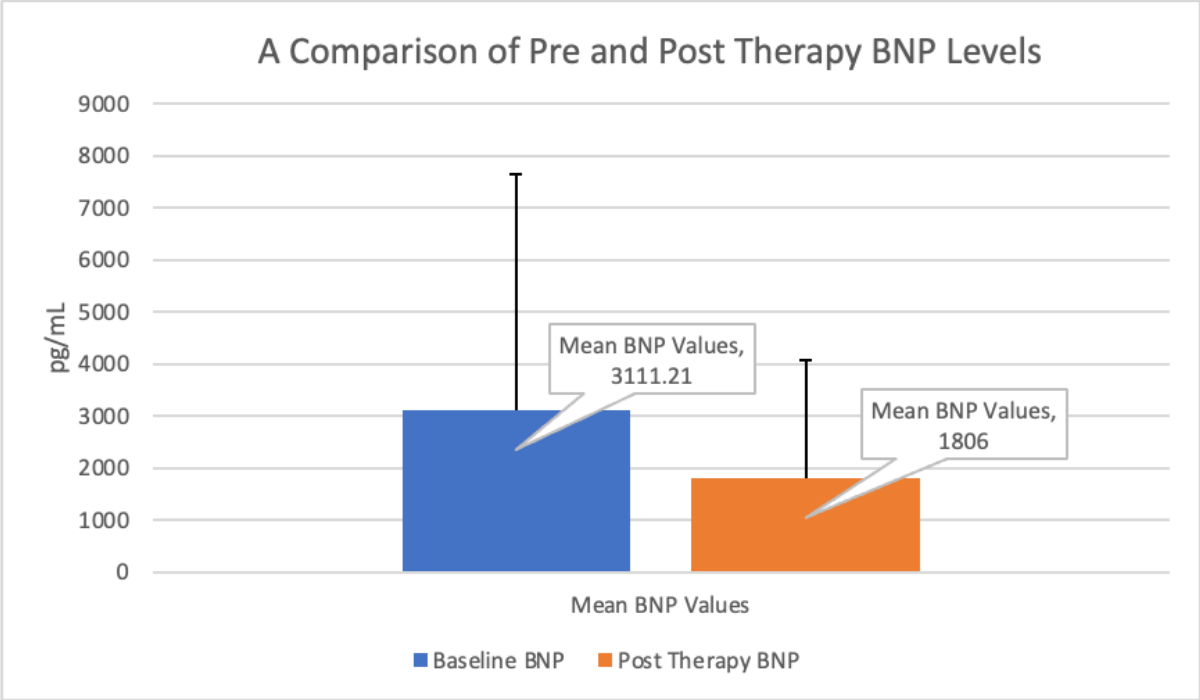
Figure 2. Proportion of responders according with rate of LVEF improving (n=120) within three to six months of quadruple therapy



N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE

Changes in NT- proBNP can be seen in the Table 2 and the Figure 3. The mean change in NT- proBNP level was 1305±5069 pg/ml consistent wit a statistically significant decrease of 41.9% in NT- proBNP levels following the quadruple therapy (t = 3.124, df = 64, p = 0.003).

Figure 3. NT-proBNP levels at Baseline and after Quadruple therapy (n=120)



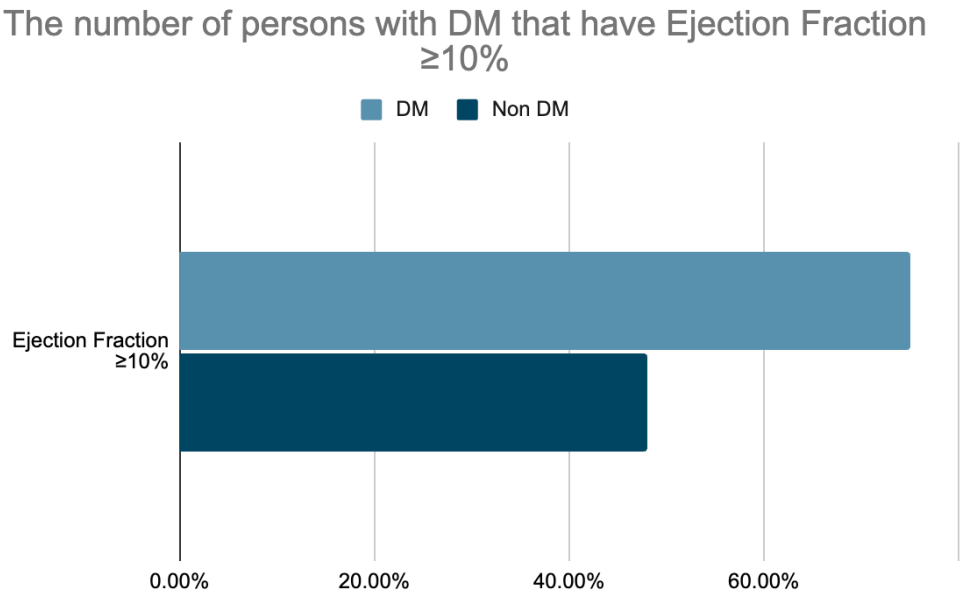
(t = 44.129, df=64, p= .001 95% CI 6.70 to 7.34)

SUB ANALYSIS IN RELATION WITH DIABETES MELLITUS STATUS

The subgroup of diabetic patients (mean age: 65.05±11.98 years old) with HFrEF constituted 31.7% of the total patients enrolled in this study. Female sex was more prevalent (55.2%). The majority of diabetic patients (73.7%) had a history of hypertension and elevated Body Mass Index (32.14±6.6 Kg/m2). Additionally, atrial fibrillation (15.3%), left bundle branch block (20.5%) , and a history of a previous myocardial infarction (23%) were more common among diabetic patients. Likewise, this subgroup had more compromised renal function (mean eGFR = 57.6±12.3 mL/min/1.73m2). As seen in the figure 4, a statistically significant difference in the increase of the Ejection Fraction was noted in the Diabetic subgroup (t=2.213, df=80, p=0.030), moreover, within the individuals with DM, 75% showed an EF increase of ≥10% in contrast with non-diabetic subgroup which showed an EF increase ≥10% in 48.1% ($X^2(1) = 4.392, 0.036$), suggesting a possible association between improvement in the EF ≥ 10% and the DM status after the quadruple therapy . However, there were not significant (t=-.987, df = 64, p=.326) differences in the reduction of NT pro-BNP levels between this two subgroups.

Variable	Diabetic subgroup	Non Diabetic subgroup	P value
Baseline Ejection Fraction(%)	35.4 % ± 8.2	32.5% ± 7.6	
Post therapy Ejection Fraction (%)	43.4% ± 8.5	40.0 ± 9.0	
Average increase in EF (%)	26.5	21.7	P=0.030

Figure 4. Comparison of persons with Ejection Fraction ≥ 10% by diagnosis of Diabetes Mellitus



Discussion

Our study represents the first report on the use of the combined quadruple therapy in an Afro-Caribbean Jamaican population with heart failure with reduced ejection fraction (HFrEF). The four drugs: a β blocker, a mineralocorticoid receptor antagonist (MRA), an angiotensin receptor–neprilysin inhibitor (ARNI), and a sodium/glucose cotransporter 2 (SGLT2) inhibitor were simultaneously initiated, starting all, rather than introducing each class in a stepwise fashion over the days or weeks, following for a tailored, personalized approach, and adjusted to the baseline patient profile. Our study provides new real-world data demonstrating the significant additive benefit of the Four Pillars therapy. Specifically, it has been demonstrated in this investigation an increase of 32.93 % in the left ventricle ejection fraction and a reduction of 41.9 % in the NT- Pro BNP levels after a average time of three months of therapy. Among patients with heart failure (HF) with reduced ejection fraction (EF), improvements in left ventricular EF (LVEF) are associated with better outcomes and remain an important treatment goal. Notably, 41.4 % of all patients treated with the quadruple therapy increased their ejection fraction by more than 10%. Some baseline patient characteristics like predominantly non ischemic cardiomyopathy, and no coronary disease, have been associated with better improvements in LVEF over time[17]. In our cohort we observed that among individuals with a rate of improvement in EF of 10% or higher, 44.7% had a diagnosis of Diabetes mellitus suggestive of a possible association between an improving in the EF ≥ 10% and DM status after the Quadruple however this data must be confirmed in a future analysis.

UNDERSTANDING THE COMPLEXITY OF OUR STUDY STUDY POPULATION

The majority of our patients were hypertensive, non ischemic etiology, with elevated Body Mass Index, and 31.7 % were Diabetic. Traditional and unique determinants of heart failure (HF) risk have been noted in

black population[18]. These can be summarized as follows: 1- Hypertension is the strongest modifiable risk factor for HF 2- Higher body mass index, possibly due to important cultural differences in ideal body image 3-Impaired endothelium-dependent and–independent vasodilation compared with whites 4- Greater arterial afterload in compared with whites, measured as higher systemic vascular resistance and reduced arterial compliance 5- Increased prevalence of left ventricle hypertrophy (LVH) with abnormal levels of cardiac troponin and N-terminal pro-B-type natriuretic peptide 6- Higher prevalence of rare genetic variants associated with cardiomyopathies and incident HF, for instance, the hereditary form of TTR (transthyretin)-related cardiac amyloidosis that disproportionately affects Blacks, as the valine-to-isoleucine substitution at position 122 on chromosome 18 is carried by 3% to 5% of black americans 7- Relative deficiency of natriuretic peptides in blacks 8- Blacks have a high prevalence of salt sensitivity that Is known to contribute to adverse cardiovascular outcomes.[18.] Moreover, other features are important such as the incident heart failure before 50 years of age, the high prevalence of Hypertension, and obesity[34,35]. Compared with whites, African Americans have almost a 3-fold increased risk for developing Dilated Cardiomyopathies38. Also, African Americans HF is more strongly associated with a non ischemic etiology of left ventricular dysfunction, with the main culprit being hypertension and in African Americans, and hypertension pathophysiology is associated with increased sodium sensitivity, relatively low renin activity, and possibly reduced nitric oxide production 42. In the same way, in a previous study, we have demonstrated that 39 % of the Afro-Caribbean Jamaican patients with Heart Failure are younger than 60 years old and they are mainly hypertensive with or without concomitant diabetes and most of them have non-ischemic HF. We also have documented that HFrEF is associated with dilated hypertensive heart Disease- (DHHD) in 30.3 %, a definite history of myocardial infarction in only 16.6 %, a combined hypertensive and ischemic heart disease in 33 % and dilated cardiomyopathy-(DCM) in 19.6 %[11]. This data is in accordance with the study of Afro-Caribbean patients with Heart Failure living in United Kingdom that reports that these patients were significantly younger, hypertension was significantly more prevalent, LV wall thickness was significantly higher and ischemic cardiomyopathy (ICM) was much less common in Afro-Caribbean than white patients. In addition, and worthy to note, cardiac amyloidosis was present in 11.4%[9].

GUIDELINE-DIRECTED MEDICAL THERAPY FOR HEART FAILURE IN OUR AFRICAN DESCENT POPULATION

All four guidelines directed medications – ARNIs, SGLT2is, BBs, and MRAs – were started simultaneously in our patients with HFrEF. The treatment was associated with improved cardiac function, and resulted in reductions in the NT-proBNP levels. These findings would expand the combined use of sacubitril/valsartan and dapagliflozin as a daily routine in clinical practice if supported by more high-quality, large-sample, multicenter studies in the future. There was an important need to identify optimal HF therapies in this high-risk population as genetic and other traits related to African ancestry, including heightened salt sensitivity and lower activity

of the renin-angiotensin-aldosterone system, may contribute to the possibly reduced response to angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta blockers in Black patients[36,37,42].

We have demonstrated in this study that 41.4 % of patients treated with the quadruple therapy achieved an increase in the Ejection Fraction > 10% and 58.5% <10%. A pre-specified subgroup analysis of the PIONEER-HF trial (assessing sacubitril /valsartan) and a post hoc subgroup analysis of DAPA-HF (assessing dapaglifozin) have reported similar response of Black vs. white population in reducing the risk of worsening HF and cardiovascular death, and it improved symptoms, without an increase in adverse events[24.44].

Although sex differences in Afro-Caribbean patients with Heart Failure prescribed Sodium -Glucose Transport Protein-2 inhibitor therapy has been described[45], we have reported here the first experience with the use of SGLT2i as a part of the combined quadruple therapy for HFrEF in this special population.

IMPLEMENTING THE QUADRUPLE THERAPY (THE FOUR PILLARS OR FANTASTIC FOUR) FOR HFREF

We have followed the newest recommendation for our patients with heart failure, which is to start the HF therapy with all four drug classes at the same time and rapidly and aggressively titrate to maximum tolerated dose[29]. We have followed a tailored personalized approach[31]. Both the 2021 ESC and 2022 ACCF/AHA /HFSA guidelines have firmly established that the four pillars of ARNI, evidence-based β-blockers, MRA, and SGLT2i form the foundational standard of medical therapy for patients with HFrEF[19,24]. Although current guidelines define the goal of quadruple therapy in HFrEF they have left open the question of how to initiate and sequence therapies in the individual patient. Numerous strategies have been suggested by experts[23.26.30]. However none of the proposed sequencing methods have been tested in prospective trials but the totality of evidence now suggests that patients with HFrEF should be treated early with a combination of the four drugs: an ARNI, beta-blocker, MRA, and SGLT2 inhibitor in order to benefit from substantial and sustained reductions of mortality, heart failure hospitalizations, and symptoms[19,20,22,23,24]. Data on the improvements in the cardiac function (ejection fraction improvement and NT-pro BNP reduction) with the utilization of the combined quadruple therapy in patient with HFrEF is scarce and it has been previously reported in others but not in African descendant special population[14.15]. Despite guideline recommendations and available evidence, implementation of treatment in heart failure is still poor. The Heart Failure Association of the ESC has suggested a patient profiling approach, tailoring therapeutic selection to patient characteristics such as heart rate and rhythm, blood pressure, renal function, and potassium level and this personalized approach, adjusting guideline-directed medical therapy to patient profile, may allow to achieve a better and more comprehensive therapy for each individual patient than the more traditional, forced titration of each drug class before initiating treatment with the next, accordingly, this has been the approach considered in our study[31].

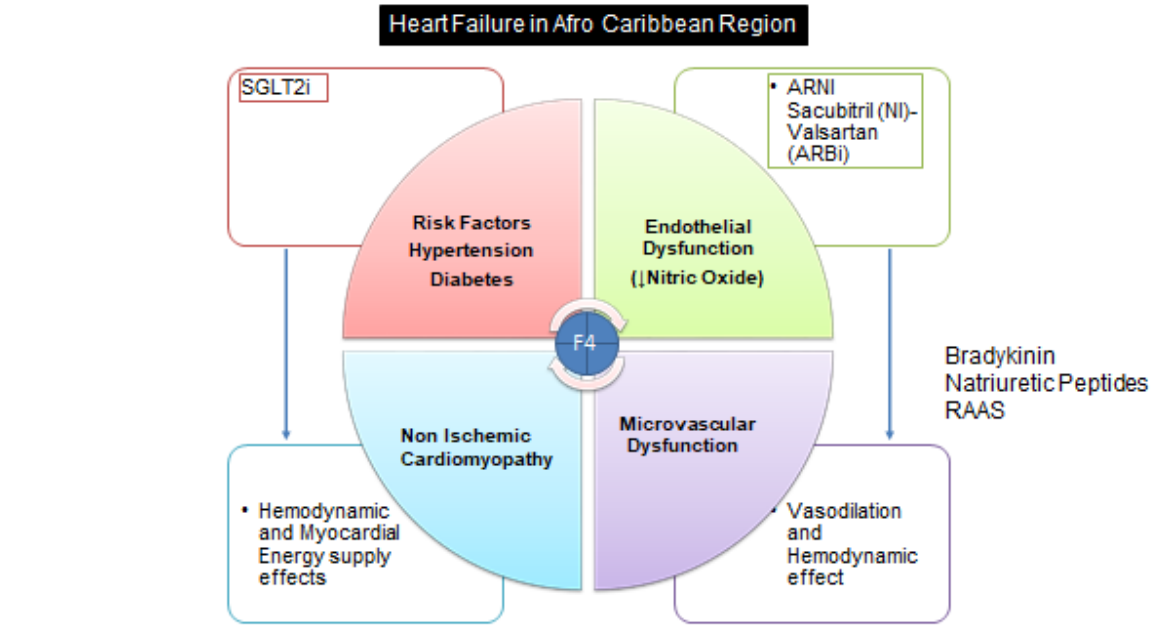
ARNI AND SGLT2 INHIBITOR THERAPY BENEFICIAL EFFECTS ON CARDIAC FUNCTION

Our study have demonstrated an improve in cardiac function after quadruple therapy that

included the use of combined ARNI and SGLT2i simultaneously initiated in a Jamaican Afro Caribbean population. In regards of ARNI therapy, the PROVE-HF, an open-label study demonstrated significant 37% reduction in NT-proBNP level and an average LVEF increase of 9.4% with decreased left ventricular (LV) and left atrial volumes, and improvement in diastolic function measured by the E/e' ratio after initiation of ARNI therapy[32]. Moreover, a sub analysis of the PIONEER-HF (Angiotensin-on Neprilysin Inhibition in Black Americans) suggests that the safety and efficacy of sacubitril/valsartan does not differ between Black and White patients and supports the in-hospital initiation of sacubitril/valsartan in hospitalized patients with acute decompensated heart failure following hemodynamic stabilization irrespective of race[33]. These results are consistent with our previous study about real-world Evidence for the Tolerance and Effectiveness of ARNI therapy in Afro-Caribbean Patients with HFrEF. In this study, we reported a post-treatment average increase of of 14.6% in EF, from 28.92% to 43.81% ($p<0.001$) over a median of 5.59 months of ARNI therapy[16].

In the other hand, not much is known about the effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on echocardiographic parameters of left ventricular systolic function in patients with heart failure and reduced ejection fraction (HFrEF) however left ventricular systolic function improvement after 3 Months of SGLT2 Inhibitor Therapy in HFrEF has been reported[15]. Moreover, pooled data from meta- analysis studies have shown that, based on the random-effects model, LVEF significantly increased with SGLT2i therapy compared with controls[30]. Reversed cardiac remodeling may partially explain the favorable effects of SGLT2i on HF as the potential effect of SGLT2 inhibitors on LV structure and function is thought to be multifactorial, and mediated predominantly by systemic hemodynamic and metabolic effects[40]. In our study 31.7 % were Diabetic and within this sub group of individuals the improvement in the EF looked more pronounced. In diabetic patients with HFrEF, combination of ARNI and SGT2i have showed significant improvement in cardiac function and prognosis. ARNI-SGLT2i combination therapy may improve the clinical course of HFrEF in diabetic patients. This has been extensively reviewed and potential mechanisms, like cardiac remodeling improving, have been suggested.[46] In summary, since ARNI and SGLT2i have different mechanisms of cardioprotective action, a combination of these drugs may exhibit synergistic effects which could explain the benefits of quadruple therapy in Jamaican Afro-Caribbean diabetic patients with heart failure. However, further studies will be required to confirm this result.

Figure 5. An Integrative proposal of the effects of quadruple therapy in Jamaican Afro-Caribbean heart failure.



Based on our previous and current experience with Afro-Caribbean patients affected with HFrEF, living in Jamaica, we propose that this population develops HF mostly as a result of hypertensive heart disease (HHD) which over time evolves to dilated hypertensive heart disease (DHHD). Despite the fact that patients from this region maintain a high cardiac and atherosclerotic risk (Hypertension, Diabetes, Obesity) profile, few patients show angiographically proven obstructive coronary artery disease (OCAD). Ischemic etiology (history of previous myocardial infarction) for HF is not common. Our observations are consistent with studies conducted in the African American population noted above, however they differ from the most frequent heart failure etiology reported for the American continent according to the recently published AMERICCAASS registry[47]. We believe that microvascular dysfunction, a type of non-obstructive coronary artery disease associated with endothelial dysfunction is a significant factor in the pathogenesis of heart failure in patients from this Jamaican Caribbean region. The real world evidence of cardiac function improving associated with the use of the quadruple therapy (Fantastic Four) reported in our study are consistent with synergic effects of the combination of ARNI and SGLT2i drugs in diabetic and non-diabetic patients affected with HFrEF. We hypothesize (Figure 5) that the combined Neprilysin and Renin-Angiotensin System Inhibition, the Sympathetic nervous system activation control and the cardio renal protective effects of SGLT2i, all four mechanisms, play a role in this final positive result in Jamaican Afro Caribbean heart Failure. Accordingly, we propose that targeting simultaneously the modulation of angiotensin II, norepinephrine, aldosterone, neprilysin, and sodium glucose cotransporter-2 by using the four drugs should be the goal.

Considering the high risk of patients with HFrEF, it stands to reason that the sooner all pathways are modulated, the better[48].

Conclusion

Guidelines Directed Medical Therapy (an angiotensin-receptor neprilysin inhibitor [ARNI], a beta-blocker, a mineralocorticoid receptor antagonist [MRA], and a Sodium-glucose cotransporter-2 inhibitor[SGLT2i]), simultaneously initiated led to significant improvement in Ejection fraction and reductions in NT-proBNP levels . The implementation of the Quadruple therapy in a non-stepped approach was demonstrated to be feasible, well tolerated and associated with significant functional improvement among Jamaican Afro-Caribbean patients with HFrEF.

Limitations

Tis study had several limitations.

1- We recognize that our non-stepped, simultaneous approach have not yet been tested in prospective trials

2- We recognizes that factors like tolerability, availability, costs, patient preference, patient compliance and other considerations specially treatment cost affordability may have affected the choices, the doses, and sequences of therapies and that not everyone will be prescribed everything based in his/her baseline characteristics.

3- This study included a relatively small number of patients and observations; thus, the results of the present study should be interpreted with caution.

4- Data on the baseline symptomatic status, such as NYHA functional class, and improvement of symptoms due to drug therapy could not be registered in all patients due to the nature of the study.

This study has not been focused on diabetic patients with HFrEF, hence our findings in this subgroup cannot be generalized. Further studies to investigate diabetic patients with HFrEF are warranted.

Declarations Competing interests:

The authors declare no competing interests.

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Consent for publication

All authors have read and approved the manuscript.

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