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The use of LCZ-696(Sacubitril/Valsartan) and SGLT2inhibitors: A Real World Experience in a Rural African Patient with Heart Failure with Reduced Ejection Fraction (HFrEF). A Case Series

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Background: Angiotensin Receptor-Neprilysin inhibitor (ARNI) is preferred over angiotensin-converting enzymes inhibitor or an angiotensin II receptor blocker as foundation therapy for patients with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death, Heart failure hospitalization, and Heart failure symptoms. SGLT2 inhibitor (Dapagliflozin and Empagliflozin) is among the four foundation drugs in managing HFrEF.

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Method: A case series of 3 patients with HFrEF. Here we report a case series of three patients with HFrEF associated with Hypertension (cases #1, 2), and one postpartum dilated cardiomyopathy (case #3). The first case was a 49-year-old male, and the second was a 61-year-old male, third was a 34-year-old female. After previous ineffective treatment, the administration of ARNI and SGLTI led to a rapid and marked improvement of the clinical conditions in all three cases. All cases underwent a baseline ECHO, and 6–month follow-up time, very few patients were reported in this case report series due to economic reasons. Most of the patients cannot afford the costs of these drugs.

Results: In case number 1(case#1) the was an increase of (Left ventricular ejection fraction (LVEF) by 33.3% at –months. There was a reduction of (Left ventricular end-diastolic diameter (LVEDD) by 20% at six months, and the clinical symptoms were improved. All patients had function class I NYHA at a time of follow-up. There was one episode of Heart failure hospitalization, but there was no CV death. In case number 2(case #2), we observed a significant increase in LVEF by 75%, and a reduction of LVEDD by 14.3% at the 6-month follow-up. In the case number 3 (case#3) a patient with postpartum dilated cardiomyopathy, we observed a significant increase in LVEF from 15% to 45% at 6-month, and a reduction of LVEDD by 31.25%. The patient had a significant improvement in diastolic dysfunction from grade III to grade II. All patients showed improvement in LV wall dysfunction, and decreasing in valve regurgitation severity from severe regurgitation to mild regurgitation.

Conclusion: These data demonstrate the efficacy and safety of combining ARNI and SGLT2 inhibitors as among the four foundation drugs in HFrEF in improving morphofunctional remodeling parameters, clinical symptoms, preventing cardiovascular death, and Heart failure hospitalization in rural African patients with HFrEF.

Keywords: HFrEF; sacubitril/valsartan; SGLT2i; Rural Africa Population.

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I. Introduction

Heart failure is a highly prevalent condition, over 600 million people have heart failure; this, is more than 5x the number of cancer patients globally, which means a 1 in 5-lifetime risk of developing Heart failure for people at 40 years old [1]. Heart failure is associated with a high rate of morbidity and mortality; 50%, of HFrEF patients will die within five years of diagnosis [2]. The most recent publication in rural Africa in Tanzania, involving 812 participants, revealed a high prevalence of Hypertension 66%, Left ventricular hypertrophy 42%, severe systolic Heart failure 22%, Hypertensive Heart disease (41%), Valvular heart disease (18%), Coronary heart disease (18%), Peripartum cardiomyopathy (7%), other non-hypertensive dilated cardiomyopathies (6%) in adults, and congenital heart disease (34%) in children [3]. Symptoms and signs of heart failure are attributed to the inability of the heart to produce sufficient cardiac output

[4]. The classification of Heart failure based on Left ventricular ejection fraction resulted in four subtypes, and among of subtypes is Heart failure with reduced left ventricular ejection fraction (HFrEF) with ejection fraction (EF) of ≤40%; [5-6].

A large, Phase III randomized clinical trial, PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), showed massive improvements in the outcome with Sacubitril/Valsartan, changes in clinical symptoms (NYHA), LVEF, reduction of NT-proBNP, Heart failure hospitalization and CV death [7]. The DAPA-HF, EMPEROR Reduced, and DELIVER study both trials revealed benefits in clinical outcomes with Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors and ARNI in patients with HFrEF when added as one of the foundation drugs in the HFrEF. Within one month in the DAPA-HF trial, a reduction in the primary outcome of a composite of worsening Heart failure or cardiovascular death with Dapagliflozin was rapidly apparent, with a sustained significant benefit at 28 days [8]. SGLT2 inhibitor either Empagliflozin or Dapagliflozin is recommended to be used in patients with HFrEF, with or without accompanying Type 2 Diabetes (T2DM), to improve HF symptoms and quality of life and to reduce the risk of HF hospitalization and, or CV death [9]. Despite advancements in medical equipment, procedures, and treatments, Heart failure management is complex and remains a challenge to Healthcare providers. The cost of the drugs for four foundation therapies (ARNI+MRA+SGL2i+BB) of heart failure management, especially ARNI and SGL2i, makes it difficult for rural Africans to afford these medications.

a) *Pathophysiology of Heart failure and consequences of reduced Ejection F*

Reducing in left ventricular ejection fraction activates a cascade of adaptive mechanisms to maintain adequate cardiac output [10]. The RAAS and adrenergic system are activated; the activated RAAS results in increases sodium and water retention, while activated adrenergic system which leads to increased left ventricular contractility and vasoconstriction [10-11]. Neuroendocrine is started to meet cardiac output demand, but continuous activation results in poor adaptation and cardiac remodeling; these, affects Left ventricular function ability to meet metabolizing tissue demands [12]. The free circulating levels of angiotensin-II have been shown to increase in heart failure patients, which impacts cell function, impair intrinsic myocardial contractility, increase ventricular stiffness, and impair diastolic function [13]. Sympathetic activation causes eccentric hypertrophy of the left ventricular, remodeling, and worsening heart failure [14].

b) *Mechanism of LCZ-696(Sacubitril/valsartan)*

Sacubitril/valsartan (LCZ-696) is a combined Neprilysin inhibitor and angiotensin AT1 receptor blocker [15]. Sacubitril is a prodrug, and the therapeutic effect of Sacubitril/Valsartan is partly achieved via the action of the active metabolite of Sacubitril, which inhibits Neprilysin. At the same time, blockade of the Angiotensin II type 1 (AT1) receptor is provided by the action of valsartan [16-17].

c) *Mechanism of SGLT2 Inhibitors on cardiovascular effect*

The mechanism of SGLT2 inhibitors in Heart failure works by constriction of renal afferent arteriolar that results in a reduction of intraglomerular pressure hence causing diuresis, glycosuria, natriuresis, and proteinuria; thus results in a decrease of preload, reduction in Left ventricular wall stress, decrease in afterload, reduction of HbA1c level (due to glycosuria), reduce blood pressure, and increase cardiac output (Ejection fraction) [18-20]. SGLT2 inhibitors decrease visceral fat area, subcutaneous fat area, total fat area, lower triglyceride level and LDL-C without interfering with HDL/LDL ratio, significantly increase plasma adiponectin levels, and improve endothelial microvascular dysfunction [21-23].

Despite awareness concerning Sacubitril/ valsartan and SGLT inhibitors and their efficacy when used for the managing of HFrEF, there are no published studies on efficacy, safety, and outcomes of Sacubitril/Valsartan with SGLT2I in the real-world African rural population. Therefore, this case series aim to show how the rural African population, which was underrepresented in most trials globally, responds to the novel drug ARNI and SGLTI together on the clinical symptoms, echocardiographic parameters, and cardiovascular outcomes (CV death and HF hospitalization) in HFrEF patients.

We report 3 cases with HFrEF who could afford these drugs and were successfully treated with four foundation drugs of HFrEF (ARNI+MRA+SGL2i+BB) regime in our daily practice and breaking off a long series of hospitalization episodes and prevented CV morbidities and mortality.

Case Reports #1

Patient history

Patient #1 was a 49-year-old male known case of Hypertension and type 2 diabetes on irregular medication, none smoker, and none alcohol drinker. He presented to the emergency department because of progressive dyspnea, palpitation, fatigability, and lower limb edema. He was admitted and started on 3L of oxygen via nasal cannula, spironolactone 12.5mg orally daily and intravenous (IV) furosemide to relieve congestion. On examination he was obese grade 2, with high Blood Pressure 170/92mmHg, Pulse Rate 110bpm

(60-102), lower limb edema grade 3, elevated jugular venous pressure (JVP 7cm), Apex beat on the 5-intercostal space lateral to the midclavicular line, S3-Gallops sound, bilateral basal coarse crepitation, and anterior crackles. His Laboratory workup reveals elevated FBG 150.3mg/dl (65-95mg/dl), Hb1AC 7.7 % (<5.7%), LDL-C 160mg/dl (62-130mg/dl), Total cholesterol 230mg/dl(0-200mg/dl), HDL-C 21mg/dl(<40-0mg/dl), Hemoglobin(Hb) 15.4g/dl(13.3-16.2), white blood cell (WBC) 5.0 X1000/mcL (3.54-9.06), serum Creatinine 1.3mg/dl(0.5-1.5mg/dl), BUN 15mg/dl(7-20), Potassium 4.0mmol/L(3.5-5.0), Sodium 139mmol/L, ALT(SGPT) 15U/L(7-41), AST(SGOT) 24U/L(12-38). (NT-proBNP, hsTnT, and Troponin T were not tested). The electrocardiogram (ECG) examination showed features of Left ventricular hypertrophy with sinus tachycardia Heart rate 110bpm. Echocardiography studies revealed severe concentric left ventricular hypertrophy with severe heart failure, Ejection fraction 36%, Left ventricular end-diastolic dimension (LVEDD) was 54mm, E/A 2.2, E/e/ 15), LAVI 46/mm2, DT(ms) 106(>200ms), TAPSE 14mm secondary mitral regurgitation moderate–severe, normal leaflets, mild tricuspid regurgitation, Global hypokinesia, inferior vena cave was dilated, and none-collapsing and estimated pulmonary arterial pressure was 33 mmHg, and there was no sign of thrombus. Chest x-ray revealed pulmonary edema, bilateral mild pleural effusion, and Left ventricular enlargement.

The patient was diagnosed with Heart Failure, reduced Ejection Fraction [HFrEF] NYHA Class III with Diastolic failure grade III, T2DM, and dyslipidemia. He was kept on IV Furosemide 80mg 6hrly, and then he had a weight loss of more than 1.5kg, and urine output was 5L/day. Furosemide was switched to orally route 40mg three times daily, Spironolactone 12.5mg, Lisinopril was added 2.5mg once daily then adjusted on the third day to 5mg once daily, and before discharge Carvedilol 3.125mg twice daily was added, Clopidogrel 75mg once daily, Atorvastatin 40mg (high-intensity management) once daily, Metformin 1g twice daily. He was discharged on the 5th day after being admitted. He was instructed to come for a clinic visit and doses titration after two weeks and potassium and creatinine monitoring after two weeks.

Seven days post-discharge, he started experiencing paroxysmal nocturnal dyspnea, orthopnea, nocturnal cough, and an increase in lower limb edema, and he had functional class III NYHA. The patient was hospitalized again, on examination he was dyspneic grade 3, desaturation on room air with SPO_2 90%, Blood Pressure 156/97mmHg, Pulse rate 109bpm (60-100 bpm) regular-regular, pitting edema grade 3, gallops sound on the cardiac exam and bilateral fine and coarse crackles anterior chest and posterior. The plan of management was changed as follows: kept on oxygen with nasal cannula 4L/min, Lisinopril was stopped for three days before starting ARNI, and Metformin was stopped to Dapagliflozin 10mg once daily, carvedilol was adjusted to 6.25mg twice daily, spironolactone was adjusted to 25mg once daily, IV Furosemide was given stating dose of 120mg then reduced to 80mg IV three times daily plus Metolazone 5mg once daily. On the fourth-day post admission, ARNI was initiated at a dose of 25mg twice daily. So the patient was kept on the evidence-based treatment guidelines with ARNI+MRA+SGLT2i+BB+DIURETIC and was discharged on the 7th day.

Two weeks later, the patient came back for a follow-up; he, was stable, had no severe Heart failure symptoms, only minimal fatigability on exercise, functional class I NYHA, serum potassium (K+) was 3.7mmol/L (3.5-5.0), and serum creatinine was 1.2mg/dl (0.5-1.5mg/dl. The doses were titrated as follows: Adjusted ARNI 50mg twice daily, Spironolactone 25mg once daily, dapagliflozin 10mg once daily, Atorvastatin 40mg (high intensity), Furosemide 40 mg three times daily, Metolazone 5mg once daily, and carvedilol 12.5mg twice daily.

After one month (4 weeks follow-up), he came for a follow-up, he reported tremendous improvement, and he had no symptoms and signs of heart failure to disclose. Blood Pressure was 134/87mmHg, Pulse Rate 69bpm (Target <70-60), serum potassium (K+) 3.7mmol/L (3.5-5.0), FBG 75.3mg/dl (65-95mg/dl). He was planned to continue with a similar therapeutic plan, but still Metolazone was stopped, Furosemide was changed to 40mg twice daily, and ARNI was adjusted to 100mg twice daily, but other medications remained the same. The patients continued throughout all the clinic visits without up-titrating the doses of medicine because of hypotension and economic challenge. So he was maintained on the following therapeutic plan: ARNI 100mg twice daily, Spironolactone 25mg once daily, Dapagliflozin 10mg once daily, Carvedilol 12.5mg twice daily, Furosemide 40mg twice daily, Atorvastatin 40mg once daily, Clopidogrel 75mg once orally daily.

At six months (24 weeks follow up), the baseline investigations were performed. Blood Pressure 125/78mmHg, Pulse rate 69bpm, FBG 68.1mg/dl (65-95mg/dl), Hb1AC 4.9 % (<5.7%) LDL-C 65mg/dl (62-130mg/dl), and Total cholesterol 163.2mg/dl(0-200mg/dl), HDL-C 32mg/dl(<40-0mg/dl), Hemoglobin(Hb) 14.4g/dl(13.3-16.2), white blood cell (WBC) 5.3 X1000/mcL (3.54-9.06), serum Creatinine 0.9mg/dl(0.5-1.5mg/dl), BUN 12mg/dl(7-20), Potassium 4.4mmol/L(3.5-5.0), Sodium 136mmol/L, ALT(SGPT) 21U/L(7-41), AST(SGOT) 26U/L(12-38)), at echocardiography, Left ventricular end-diastolic dimension (LVEDD) was 45mm, indicating hypertrophy, with minimal wall thickness and left ventricular ejection fraction (LVEF) was increased to 48%. No mitral insufficiency was found, all valves were standard, and the left atrium was slightly enlarged. The inferior vena cava (IVC) was normal. The estimated pulmonary arterial

pressure was 30 mmHg. So he was maintained on the following therapeutic plan: ARNI 100mg twice daily, Spironolactone 25mg once, Dapagliflozin 10mg once daily, Carvedilol 12.5mg twice daily, Torsemide 10mg once daily, Atorvastatin 40mg once daily, and Clopidogrel 75mg once daily.

Case Reports #2

Patient history

Patient #2 was a 61-years-old male known case of Hypertension, CKD stage3B, T2DM, old cerebral infarction, and lateral myocardial infarction, and not on regular medication for three months, a smoker and none alcohol drinker. He presented as the emergency department because of progressive dyspnea, palpitation, nocturnal cough, fatigability, and lower limb edema but no chest pain and no night sweat. He was admitted and started on 4L/min of oxygen via nasal cannula. Still, his SPO_2 rose from 78% to 86%, and then was changed to a simple face mask 10L/min, which rose SPO2 from 86% to 97% as well as Eplerenone 25mg orally daily and intravenous (IV) furosemide 120mg to relieve congestion. On examination, he was confused, restless, obese grade 3, with high Blood Pressure 230/127mmHg, Pulse rate 117bpm (60-102), ascites, lower limb pitting edema grade3, elevated jugular venous pressure (JVP 10cm pulsating and easily occluded by finger), apex beat on the 6-intercostal space lateral to the midclavicular line, S1 and S2 heard with regurgitation murmur at the mitral and tricuspid, bilateral basal coarse crepitation and reduced air entry on lower lobes bilaterally. His Laboratory workup reveals elevated FBG 205.8mg/dl (65-95mg/dl), Hb1AC 9.5 %(<5.7%) LDL-C 196mg/dl (62-130mg/dl), and Total cholesterol 253mg/dl(0-200mg/dl), HDL-C 19mg/dl(<40-0mg/dl), Hemoglobin(Hb) 12.4g/dl(13.3-16.2), Mean Corpuscular Volume (MCV) 81.8fL(79-93.3), Ferritin 200(0-300) Platelet count 339 x1000/mcL(165-415), white blood cell (WBC) 4.3.0 X1000/mcL (3.54-9.06), serum Creatinine 2.3mg/dl(0.5-1.5mg/dl), BUN 35mg/dl(7-20), Potassium 4.6mmol/L(3.5-5.0), Sodium 136mmol/L(136-146), ALT(SGPT) 19U/L(7-41), AST(SGOT) 31U/L(12-38), Albumin 4.2g/dl(4.0-5.0), C-RP 15(0-5), hSTnT, TnT and NT-proBNP were not done. The electrocardiogram (ECG) examination showed features of Left ventricular hypertrophy with sinus tachycardia (Heart rate 122bpm), ST Elevation on Lead 1, aVL, and V5-V6. Echocardiography studies revealed concentric left ventricular hypertrophy with severe heart failure, LVEF 20%, left ventricular end-diastolic dimension (LVEDD) was 54mm, IVSd (10.4mm), PWd (8.7mm), LVIDs (53mm), LVOT (21.36mm), RA (71ml), LA (41mm), LA (68mL), LAVI (43.00ml/m2), TAPSE 10.00, Sa (7.6cm/s), E/A 0.33), E/e/ 5.88, DT(ms) (130.00), secondary mild mitral regurgitation (EROA 11.00mm2), Vmax (423cm/s), VTI (95.60cm), normal anterior leaflet, lateral wall dysfunction, inferior vena cave was dilated and none-collapsing, and not estimated pulmonary pressure. Chest x-ray revealed pulmonary edema, bilateral mild pleural effusion, and enlarged both right ventricle and left ventricle.

The patient was diagnosed with Heart Failure, reduced Ejection Fraction [HFrEF] NYHA Class III, CKD stage 3B, T2DM and Dyslipidemia, old cerebral infarct (ischemic stroke), and lateral myocardial infarction. He was kept on IV Furosemide 80mg 6hrly, and then he had a weight loss of more than 2.5kg, and urine output was 4.5L. Furosemide was reduced to 40mg IV TDS, Eplerenone 25mg, Enalapril was added to 2.5mg twice daily then adjusted on the third day to 5mg twice daily for two weeks, and before discharge Bisoprolol, 5mg once daily was added, DAPT (Aspirin 75mg and Clopidogrel 75mg once orally daily), Atorvastatin 80mg (high-intensity management), Emplagliflozin 10mg once daily. He was discharged on the 8th day after being admitted. He was instructed to come for clinic follow-up and dose titration after two weeks, plus monitoring of serum potassium and creatinine.

Two weeks later, he came back for clinic follow up; he reported to have minimal improvements, although for the past seven days since discharged he had been experiencing progressive dyspnea at night, nocturnal cough, lower limb edema, and fatigability despite using all the medications as instructed by the discharging doctor. On assessment, he had functional class III NYHA. The patient was hospitalized again, on examination he dyspneic grade 2, desaturation on room air with SPO_2 93breath/min, Blood Pressure 187/107mmHg, Pulse rate 102bpm (target <70-60) regular-regular, pitting edema grade 2, regurgitation murmur at mitral and tricuspid valves on the cardiac exam and on Respiratory system he had bilateral fine crackles. The plan of management was changed as follows: kept on oxygen with nasal cannula 4L/min, Enalapril was adjusted to 10mg twice daily, Bisoprolol was adjusted to 10mg once daily, Eplerenone remained the same 25mg once daily, IV Furosemide was given stating dose of 120mg then 80mg three times daily plus Metolazone 10mg once daily. On the fourth-day after discharge, he reported that he had been experiencing easy fatigability, dry cough, and shortness of breath. On examination, the Blood Pressure was 170/97mmHg. He was hospitalized and Enalapril was stopped for one week before initiating ARNI. One week later, ARNI was initiated at a dose of 25mg twice daily and continued with DAPT (Aspirin 75mg and Clopidogrel 75mg once orally daily both).There is no Catheter lab in our setting, and referral to the tertiary hospital was not possible due to unstable clinical condition and financial problem)). So the patient was kept on the evidence-based treatment guidelines with ARNI+MRA+SGLT2i+BB+DIURETIC and continued with other drugs for other comorbidities and was discharged on the 12thday post admission.

Two weeks later, the patient came back for a follow-up. He was stable, had no severe Heart failure symptoms, functional class II NYHA, lower limb edema grade 2, Blood Pressure 167/102mmHg, Pulse rate 98bpm(target <70-60), serum potassium (K+) was 4.8mmol/L (3.5-5.0), and serum creatinine was 1.1mg/dl (0.5-1.5mg/dl. The doses were up-titrated, ARNI 50mg twice daily, Eplerenone 25mg once daily, Dapagliflozin 10mg once daily, Atorvastatin 80mg (high intensity) once daily, Furosemide 40 mg twice daily, stopped Metolazone 5mg, Bisoprolol 10mg once daily. The ESC 2021 HFrEF management guideline recommends the addition of Isosorbide dinitrate +Hydralazine to Africans with heart failure whose blood pressure is not controlled, so Isosorbide Dinitrate 20mg three times daily and Hydralazine 37.5mg three times daily was added. After one month (4 weeks follow-up) follow-up, he reported tremendous improvement. Blood Pressure was 131/80mmHg, Pulse rate 70bpm (target <70-60), serum potassium (K+) 4.7mmol/L (3.5-5.0), FBG 85.5mg/dl (65-95mg/dl). So he was maintained on the following therapeutic plan: ARNI 100mg twice daily, Eplerenone 25mg once daily, Dapagliflozin 10mg once daily, Bisoprolol10mg once daily, Furosemide 40mg twice daily, Atorvastatin 80mg once daily, Clopidogrel 75mg once daily, Aspirin 75mg once daily, Isosorbide Dinitrate+Hydralazine 20/37.5mg three times daily.

At six months (24weeks follow up) the baseline was performed; Blood Pressure 135/98mmHg, Pulse rate 69bpm, FBG 78.1mg/dl (65-95mg/dl), Hb1AC 5.2 % (<5.7%), LDL-C 85mg/dl (62-130mg/dl), and Total cholesterol 190mg/dl(0-200mg/dl), HDL-C 37mg/dl(<40-0mg/dl), Hemoglobin(Hb) 13.4g/dl(13.3-16.2), Mean Corpuscular Volume (MCV) 86.4fL(79-93.3), Ferritin 150(0-300) white blood cell (WBC) 4.8 X1000/mcL (3.54-9.06), serum Creatinine 1.4mg/dl(0.5-1.5mg/dl), BUN 10mg/dl(7-20), Potassium 4.9mmol/L(3.5-5.0), Sodium 140mmol/L(136-146), ALT(SGPT) 21U/L(7-41), AST(SGOT) 22U/L(12-38)), at echocardiography, left ventricular end-diastolic dimension (LVEDD) was 46mm, lateral wall akinesia, and left ventricular ejection fraction (LVEF) was increased to 35%, TAPSE 18, mild mitral insufficiency was found, mild tricuspid insufficiency, and the left atrium was mild enlarged, LAVI 38.0ml/m^2. The inferior vena cava (IVC) was normal. No Estimated pulmonary arterial pressure. So the doses were adjusted as follows: ARNI 100mg twice daily, Eplerenone 50mg once daily, Dapagliflozin 10mg once daily, Bisoprolol 10mg once daily, Furosemide 40mg twice daily, Isosorbide Dinitrate +Hydralazine 20/37.5mg three times daily, Atorvastatin 80mg once daily, Aspirin 75mg once daily, and Clopidogrel 75mg once daily. The target LDL-C recommended in a very high-risk ASCVD patient is <1.4mmol/L[<55mg/dl], so this patient did not achieve his target LDL-C which is why Ezetimibe 10mg once daily was added on high intensity statin. He was advised to have salt reduction due to his recurrent dyspnea, and also to have minimal physical activities and continue with monthly clinical follow-up.

Case Reports #3

Patient history

Patient #3 was a 34-year-old female unknown case of Hypertension and none alcohol drinker; she, presented to the emergency department because of asthenia, dyspnea with moderate exertion, fatigability, lower limb edema, paroxysmal nocturnal dyspnea, nocturnal cough. She was three (3 months) post spontaneous vertex delivery of a twin pregnancy. On examination, she was dyspnea grade 3, SPO_2 93% on room air .Still, she was kept on oxygen therapy 2L/min with a nasal cannula, with high Blood Pressure 127/92mmHg, Pulse rate 130bpm (60-102) irregular-irregular, lower limb edema grade 3, elevated jugular venous pressure (JVP 9cm), Apex Beat on the 6-intercostal space lateral to the midclavicular line, mitral regurgitation murmur, bilateral basal coarse crepitation. Her Laboratory workup reveals, Hemoglobin(Hb) 15.4g/dl(13.3-16.2), white blood cell (WBC) 5.0 X1000/mcL (3.54-9.06), serum Creatinine 1.2mg/dl(0.5-1.5mg/dl), BUN 8mg/dl(7-20), Potassium 4.5mmol/L(3.5-5.0), Sodium 135mmol/L(136-146), ALT(SGPT) 19U/L(7-41), AST(SGOT) 28U/L(12-38). NT-proBNP was not done. The electrocardiogram (ECG) examination showed features of Left ventricular hypertrophy and atrial fibrillation (HR 132bpm). Chest x-ray revealed pulmonary edema, bilateral mild pleural effusion, and globular heart. Echocardiography studies revealed severe eccentric left ventricular hypertrophy with severe Heart failure, LVEF 15%, ventricular end-diastolic dimension (LVEDD) was 63mm, IVSd (7.00mm), PWd (10.00mm), LVIDs (64mm), LVOT (20.00mm), RA (61ml), LA (42mm), LA (64mL), LAVI (43.00ml/m2), D-sign on the regional wall, Mild pericardial effusion, TAPSE 15.00, Sa (11.00cm/s), FAC (31), MPI (1.33), E/A 2.16, E/e/ 21, DT(ms) 72, mild secondary mitral regurgitation, normal anterior and posterior leaflet, Vmax(430cm/s), VTI (94.00cm), mild tricuspid regurgitation, inferior vena cave was dilated, and none-collapsing and an estimated pulmonary arterial pressure were (39.00mmHg), and there was no sign of thrombus.

The patient was diagnosed with Postpartum dilated cardiomyopathy with severe Heart Failure reduced Ejection Fraction [HFrEF] NYHA Class III, Diastolic dysfunction Grade III, and Paroxysmal atrial fibrillation (Afib). She was kept on IV Furosemide until she had a weight loss of 1.5kg and urine output was 5L. IV Furosemide was switched to orally route 40mg three times daily. The patient was discharged after one week of hospitalization, with the following therapeutic plan: Spironolactone 12.5mg once daily, ARNI 25mg twice daily, Dapagliflozin 10mg once daily, Rivaroxaban 15mg

once daily, Amiodarone 800mg twice daily for two weeks then 400mg twice daily for two weeks, Metoprolol 50mg once daily. She was instructed to come after two weeks for the follow-up clinic for dose titration and to monitor serum potassium and serum creatinine. Bromocriptine was not initiated because she could not afford an alternative feeding for her twin babies.

Two weeks later, the patient came back for a follow-up. She was stable, Heart failure symptoms functional class II NYHA, Blood Pressure 110/70mmHg, Pulse rate 100bpm irregular-irregular, serum potassium (K+) was 3.9mmol/L (3.5-5.0), and serum creatinine was 1.4mg/dl (0.5-1.5mg/dl, eGFR 50.6ml/min/1.73m2, CrCl 47ml/min, and resting ECG showed similar findings. The doses were up-titrated as follows: Adjusted ARNI 50mg twice daily, Spironolactone 25mg once daily, Furosemide 40mg twice daily, Dapagliflozin 10mg once daily, Rivaroxaban 15mg once daily (not adjusted because the CrCl was <50ml/min), Amiodarone 400mg twice daily, Metoprolol 100mg once daily.

After one month (4 weeks follow-up), she came for a follow-up. She reported much improvement, she had Heart failure symptoms class I NYHA, BP was 108/77mmHg, Pulse rate 96bpm (Target <70-60) irregular-irregular, serum potassium (K+) 4.7mmol/L (3.5-5.0), serum creatinine was 1.2mg/dl (0.5-1.5mg/dl, eGFR 60.9ml/min/1.73m2, CrCl 55ml/min. A dynamic ECG Holter examination showed an average heart rate of 102 bpm, atrial fibrillation, no ventricular couplet, and no isolated ventricular ectopic (VE). The doses were up-titrated as follows: Adjusted ARNI 100mg twice daily, Spironolactone 25mg once daily, dapagliflozin 10mg once daily, Rivaroxaban 15mg once, Amiodarone 400mg twice daily (was continued for long-term rhythm control), Metoprolol 100mg once daily, Ivadradine was added 2.5mg twice daily (because the HR was still >70bpm) on the maximum dose of Metoprolol, and Furosemide was reduced to 40mg once daily.

At six months (24 weeks follow up), the baselines were performed; Blood Pressure 105/78mmHg, Pulse rate 80bpm regular-regular rhythm, Hemoglobin(Hb) 14.0g/dl(13.3-16.2), white blood cell (WBC) 5.9 X1000/mcL (3.54-9.06), serum Creatinine 1.2mg/dl(0.5-1.5mg/dl), BUN 11.2mg/dl(7-20), Potassium 4.6mmol/L(3.5-5.0), Sodium 140mmol/L(136-146), ALT(SGPT) 29U/L(7-41), AST(SGOT) 18U/L(12-38), Resting ECG examination showed features of Left ventricular hypertrophy and presences of P-wave, regular-regular rhythm, no feature of atrial fibrillation. The Echocardiography studies showed normal inferior vena cava, revealed moderate eccentric left ventricular hypertrophy with mildly reduced ejection, EF 45%, ventricular end-diastolic dimension (LVEDD) was 44.00mm, IVSd (10.00mm), PWd (6.00mm), LVIDs (37mm), LVOT (20.00mm), RA (23ml), LA (37mm), LA (35mL), LAVI (19.00ml/m2), hypo-kinesia on the regional wall motion, no pericardial effusion, TAPSE (25.00mm), Sa (18.00cm/s), FAC (33), MPI (1.23), E/A (1.50), E/e/ 26, DT(ms) 185.00(>200ms), mild secondary mitral regurgitation, EROA (7.00mm2), normal anterior leaflet, VTI (202.00cm), Vmax (616.00cm/s), no tricuspid regurgitation, and pulmonary arterial pressure was not estimated(no tricuspid regurgitation). So the doses were adjusted as follows: ARNI 100mg twice daily, Spironolactone 50mg once daily, Dapagliflozin 10mg once daily, Metoprolol 100mg once daily, Furosemide 40mg once daily, Ivabradine 5mg twice daily, Rivaroxaban 15mg once daily, and stopped Amiodarone. She was advised to have sodium reduction (advised on table spoon salt strategy), to avoid pregnant until she has completely recovered, good drugs adherence, and regular cardiac clinic follow-up.

II. Discussion

Heart failure occurs after decrease in cardiac output which triggers over-activation of different compensatory mechanisms in the body that include: increased sympathetic nerves activation, increased activation of RAAS, and increased vasoconstriction due to conversion of angiotensin I to angiotensin II. The continuous activation of these compensatory mechanisms leads to hypertrophy and ventricular remodeling that result in a decrease of cardiac output [24]. All our patients showed better outcomes when they were initiated on four foundation therapies of HFrEF (ARNI+MRA+BB+SGLT2I) that we blocked Sympathetic nervous system activation (Norepinephrine) with Beta-blockers, we blocked Renin-Angiotensin-Aldosterone System (RAAS) with ARNI, and blocked the Angiotensin pathway with mineral ocorticoid receptor antagonists[25,26]. The current recommended evidence-based SGLT2 inhibitors with good cardiovascular outcomes in Heart failure patient with or without type 2 diabetes (T2DM) are either Dapagliflozin which is mainly used in HFrEF and HFpEF, Empagliflozin, mainly used in Heart failure regardless of Ejection Fraction spectrum, and Sotagliflozin, which is used primarily in worsening Heart Failure[27,28]. The addition of either of SGLT2 inhibitors to our patients resulted in a tremendous improvement in clinical symptoms especially on the edema, blood pressure, sugar(HbA1c), left ventricular wall stress, decreasing afterload, decreasing preload and increasing LV ejection fraction (EF%)[29].

In a patient with acute heart failure features the use of diuretics is recommend to start with, in our cases all patients presented with acute decompensation heart failure with the symptoms of congestion that included lower limb edema, pulmonary edema, elevated jugular venous pressure, hepatomegaly, and ascites, that's why diuretics were initiated first [30]. The initiation of diuretics to our patients helped to improve their clinical

symptoms, the use of loop diuretics (furosemide) and mineralocorticoid receptor antagonists, and SGLT2 inhibitors showed a significant impact in reducing congestion and decreasing preload [31,32].

Additional treatment strategies are needed to further decrease the risk for patients with acute Heart failure and for those with worsening Heart failure from getting poor Cardiovascular outcomes [32]. The European Society of Cardiology recommended the addition of Metolazone to loop diuretic if decongestion in patient with acute Heart failure is not achieved [33]. In case number 2 of this report we managed to achieve decongestion and good diuresis after adding Metolazone as a thiazide diuretic to loop diuretic without any mortality [34, 35].

The addition of Isosorbide Dinitrate and Hydralazine to ARNI in case number 1(case#1) helped to reduce the resistance Hypertension and improved Cardiovascular outcomes as it was shown to other studies. The use of ISDN/Hydralazine is indicated in African American or African patients with Heart failure who have uncontrolled Arterial Blood pressure on maximum tolerable of ACEI/ARB/ARNI or who are intolerance to ANRI/ACEI/ARB [36-38].

Dilated cardiomyopathy is associated with a high prevalence of different types of atrial fibrillation, as seen in our patient case number 3(case#3), who presented with paroxysmal atrial fibrillation [26]. The presence of Atrial fibrillation (AFib) in HFrEF makes the Heart failure outcomes even worse [39]. We controlled the rhythm of our patient with Amiodarone which is only indicated in Afib patients with structural heart disease [40]. For our case, the rhythm at the time of follow-up (at six months) was restored into a normal sinus rhythm which contributed to improved cardiovascular outcomes in this patient [41, 42]. None-vitamin K Oral Anti-Coagulant (Rivaroxaban) was used to prevent stroke in our case; although, this patient needed a long-term follow-up but at the six-month follow-up, there was no incidence of stroke or transient ischemic attack reported, the use of anti-coagulant in AFib is indicated to prevent cardio-embolic stroke if the patient has mitral regurgitation and aortic stenosis or regurgitation [43]

The Cardiovascular (CV) outcomes in our cases were improved when ARNI and SGLT2 inhibitors were initiated, but after initiation of ARNI, there was no HF hospitalization [44]. CV Death was not reported during follow-up time.All patients achieved good CV outcomes, and the combination of ARNI and SGLT2I did not harm the patients but reduced morbidity and mortality [45, 46].The patients in this case reported were either attended at St. Francis Referral Hospital (SFRH) or Good Samaritan Cancer Hospital (GSCH). Sacubitril/Valsartan is available at GSCH pharmacy only in our local setting. One tablet of ANRI costs USD 4.3 and needs to be taken twice daily, making it even harder for ordinary rural dwellers to afford this medicine, and the cost of Dapagliflozin/Empagliflozin is USD 1.5. Most rural African patients diagnosed with HFrEF qualify to use ARNI and SGLT2inhibitor, but few of them afford, and sometimes the patient can afford the drug for one month only.

III. Conclusion

This case report broke the gap in the uncensored data and shows that using of both ARNI and SGLT2 inhibitors in the rural African population with heart failure-reduced ejection fraction (HFrEF) was efficacious and safe. This suggests that using of both agents together could further lower morbidity and mortality in patients with HFrEF in the rural African population. Using of ARNI and SGLT2I in preventing cardiovascular death and Heart failure hospitalization events in rural African population with HFrEF patients with different characteristics and comorbidities was similar to other races who were involved in different real-world trials and studies. A large observational study or randomized trial is recommended for rural African populations with long-term follow-up on using of both ARNI and SGLT2I in HFrEF patients.

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Declaration of interest

The authors declare no conflict of interest to declare.

Ethical statement

Since it was a case report, ethical clearance was waived, and the data were all fully anonymized before being accessed. The study followed the principles of the Declaration of Helsinki [WHO, 2001].Informed consent to all patients were obtained and agreed to use their data in this case report.

Author's contributions

First authors: DMR contributed to conceptualization, data curation, writing original draft, investigation, visualization, and writing a review, supervision, GM investigation, writing a review, and editing, RM writing review and data collection, AHM review, and editing, BK investigation, and editing. All authors read and approved the final manuscript.

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