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Dapagliflozin and Spironolactone Improved Clinical Symptoms and CV Outcomes in Patient with HF Preserved Ejection Fraction (HFpEF) in Hard-to-Reach Rural African Population: A Case Series

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Abstract

Objective: To observe the benefit of mineralocorticoid receptor antagonist and sodium-glucose co-transport 2 inhibitor (SGLT2 inhibitor) in heart failure preserved ejection (HFpEF) in rural Tanzania. ***Background and Result***: The use of spironolactone and dapagliflozin was shown to be effective in improving the clinical outcome and reducing CV hospitalization rate and CV mortality in patients with heart failure preserved left ventricular ejection fraction (HFpEF). This is the case presentation of one patient with HFpEF with diastolic dysfunction grade 3, obesity grade 3, Type 2 Diabetes, and Atrial Fibrillation (permanent). In the case of a 76-year-old female after previous ineffective treatment, the initiation of Spironolactone and Dapagliflozin led to a rapid and marked improvement in the clinical conditions. Diastolic dysfunction was improved from stage III to stage I. Moreover, the initiation of spironolactone and dapagliflozin therapy avoided a referral for surgical intervention and interrupted a long series of hospitalizations for acute HF and prevented CV death. ***Conclusion***: Based on our experience, we conclude that the treatment with spironolactone and dapagliflozin allows for better treatment optimization with a positive impact on the control of clinical outcomes and preventing CV death and CV hospitalization in HFpEF and related comorbidities in the African population, which is underrepresented in most of the trials.

Keywords

HFpEF, Spironolactone, Dapagliflozin, Africans Population

1. Introduction

Heart Failure (HF) is an inability to provide adequate cardiac output to the body at rest, or with exertion, or do so only in the setting of elevated filling pressure [1]. HF has recently been classified into three subtypes based on Left ventricular ejection fraction: HF with reduced left ventricular ejection fraction (HFrEF) with EF ≤40%; HF with preserved left ventricular ejection fraction (HFpEF) with EF >50%, elevated BNP levels, and presence of structural heart disease and LV diastolic dysfunction; and HF with mildly-reduced left ventricular ejection fraction (HFmrEF) with EF 41% - 49%, elevated BNP levels, and presence of structural heart disease and diastolic dysfunction [2]. HFpEF is a result of comorbidities the patient can have that will result in this disease; the comorbidities include advanced age, diabetes, arterial hypertension, and obesity. These results in systemic inflammation and multiorgan involvement that affect the lung, myocardium, skeletal muscle, and kidney are leading to diverse HFpEF phenotypes wfth variable involvement of pulmonary hypertension, myocardial remodeling, deficient skeletal muscle oxygen extraction during exercise, and renal Na+ retention [3]. During an Echocardiography examination, the patient may have any abnormalities such as left atrial dilatation, regional wall abnormality, diastolic dysfunction, left ventricular hypertrophy, or LVEF ≥50% [4]. The outcomes of HFpEF are a little better than HFrEF but the outcomes of hospitalized patients with HFpEF are similar to those with HFrEF [5] [6]. In some studies, the QOL may be bad and in some studies, the outcomes may be worse in HFpEF [7]. No guideline recommendations for specific HFpEF treatment but if a patient is congested, a diuretic should be used [8]. The ACC/AHA/HFSA guidelines (class IIb) now recommend the use of aldosterone receptor antagonists for consideration inappropriately for the selected patients to reduce hospitalization in patients with HFpEF if either elevated BNP or HF admission within 1 year or eGFR ≥30 mL/min/1.73m^2 or serum potassium <5.0 mEq/L and creatinine 2.5 mg/dL [8] [9]. The DAPA-HF, EMPEROR Reduced, EMPEROR Preserved and DELIVER Study both trials revealed benefits in clinical outcomes with SGLT2 inhibitors in patients with HFrEF within 1 month in the DAPA-HF trial, a reduction in the primary outcome of a composite of worsening HF or cardiovascular death with Dapagliflozin was rapidly apparent, with a sustained significant benefit at 28 days [10]. EMPEROR Preserved, Empagliflozin demonstrated a significant benefit compared with placebo at 18 days [11].

1.1. T2DM and Left Ventricular Diastolic Dysfunction

Type 2 Diabetes is associated with HFpEF presenting as left ventricular diastolic

dysfunction or possibly with HF with mildly-reduced ejection fraction HFmrEF [12]. LV diastolic dysfunction is considered the preclinical form of diabetes-related cardiac complication [13]. However, LV diastolic dysfunction is identified as an independent predictor of outcome even for patients with HFrEF [13].

1.2. Mechanism of Dapagliflozin on Cardiovascular Effect

The mechanism of dapagliflozin as other SGLT2 inhibitors in improving cardiovascular outcomes is by lowering blood pressure, weight loss, and reduction of HbA1c level; these changes have a positive effect on improving the function of Left ventricular diastolic function and prevent MACE [14] [15] [16]. Dapagliflozin has a natriuretic effect and resultant osmotic diuresis which have beneficial effects on HF [16]. Dapagliflozin decreases visceral fat area (VFA), subcutaneous fat area SFA, and total fat area (TFA) and significantly increases plasma adiponectin levels, and improves endothelial microvascular dysfunction [17]. This drug lower triglyceride levels and LDL-C without interfering with the HDL/LDL-c ratio [18]. All these effects are associated with lowering cardiovascular risk and improving left ventricular diastolic function, improving symptoms, physical function, and quality of life [19] [20] [21] [22].

In most of the trials mentioned, rural Africans are underrepresented making it difficult to draw conclusions on the benefits of these drugs in HFpEF in rural African countries. The costs of the drugs especially SGLT2 inhibitors make it difficult for rural Africans to afford this medication. We report 1 case with HFpEF who was successfully treated with Spironolactone and Dapagliflozin in our daily practice and breaking off a long series of hospitalization episodes.

2. Case Reports

Patient History

The patient was a 76-year-old female who had been a diabetic for 11 years until the month before coming to our attention. Following previous diabetes and hypertension, Metformin 1000 mg twice daily and Bendroflumethiazide 5 mg, and Amlodipine 10 mg once daily therapies were ongoing. In October 2021, the patient was admitted to the emergency room with dyspnea on moderate exertion, and a cough but she also had the same complaint one year ago prior and was treated at other hospitals. The patient was diagnosed with severe community-acquired pneumonia and was hospitalized for 5 days. After 2 weeks, the patient was hospitalized again, with the same complaints plus lower limb edema, and she reported having no improvement since the first admission. On general examination, she was dyspneic, SPO_2 75% but kept on 4 L/min nasal cannula and SPO_2 increased to 96%, obesity grade 1 (BMI 35.3 kg/m^2), BP 150/76 mmHg. On clinical examination she had lower limb pitting edema (grade 3), gallop rhythm and a heart rate of 125 bpm, irregular-irregular rhythm, and fine crackles on the anterior chest. The electrocardiogram (ECG) examination showed evidence of Left ventricular concentric hypertrophy and left ventricular overload

and atrial fibrillation. Echocardiography studies revealed the left ventricular end-diastolic dimension (LVEDD) was 61 mm (indicating dilation), with moderate wall thickness and minimal left ventricular wall dysfunction, and left ventricular ejection fraction (LVEF) was preserved at 58%. Minimal secondary mitral and tricuspid regurgitation was found, and the left atrium was normal. The inferior vena cava (IVC) diameter was 20 mm collapsing. She had elevated filling pressure with diastolic dysfunction grade III. Her diastology studies revealed E/A 2.7, E/e/16.2, LAVI 46 ml/m^2, DT (MS) 96, TAPSE (mm) 16, and estimated pulmonary arterial pressure was 43 mmHg. Chest radiography the cardiac silhouette was slightly enlarged, prevalently on the left ventricle, with cephalization and alveolar infiltrates suggestive of cardiogenic pulmonary edema. The values of blood examinations were (e.g., Hb1Ac 8.4% (4.0% - 6.0%), FBG 12.1 mmol/L (3.5 mmol/L - 5.5 mmol/L), K + 4.62 mEq/L (3.5 mEq/L - 5.1 mEq/L), creatinine 124.6 μmol/L (60 - 120 μmol/L), eGFR (CKD-EPI) 58.5 ml/min/1.73m^2 (>90 ml/min/1.73m^2), FBP normal, CRP 5 mg/L (0 - 5 mg/L), ALT 35.3 U/L (7 - 55 U/L), AST 19 U/L (8 - 33 U/L), LDL-C 7.2 mmol/L (<3.4 mmol/L, Triglyceride 2.32 mmol/L (<1.7 mmol/L), NT-proBNP not done, coronary angiography not done also. The diagnosis of new-onset HF with preserved LV ejection fraction, NYHA class II was confirmed (H2FPEF Score 9 points) and the patient was treated and discharged, after 1 week of hospitalization, with the following therapeutic plan (amiodarone was given for a short time rhythm control for Atrial fibrillation):

- Lisinopril 5 mg q.d, Amiodarone 800 mg b.d 2/52 then 400 mg b.d 2/52 Furosemide 40 mg po q.d, Metformin 1 gm b.d, Atorvastatin 40 mg q.d and Rivaroxaban 15 mg q.d

In November 2022, the patient presented for a follow-up visit in good condition, reporting some mild muscle pain after taking Atorvastatin. Dyspnea with moderate-intense exertion was present and easy fatigability and cough. The patient was clinically well compensated, with normal blood pressure and functional NYHA class II, normal FBG. ECG confirmed possible left ventricle hypertrophy and normal rhythm but the rate was not controlled; the therapeutic plan was updated as follows:

- Lisinopril 10 mg q.d, Metoprolol 50 mg q.d, Metformin 1 gm b.d, Atorvastatin 40 mg q.d, and Rivaroxaban 15 mg q.d

In December 2021, the patient presented at the programmed 1-month follow-up visit with improvement, albeit with asthenia and dyspnea with moderate exertion and moderate lower limb pitting edema. She reported frequent night coughs last two weeks and occasionally muscle pain. The patient was clinically compensated and maintained NYHA class II. Blood values were normal except for FBG. At ECG (sinus rhythm, heart rate 77 bpm), possible left ventricle hypertrophy with left ventricle overload was confirmed. Echocardiography examination showed an increase of concentric remodeling, LVEDD from 62.2 mm and LVEF was 55%, and regional wall moderate dysfunction, and her diastology

revealed E/A 4.90, E/e/15, DT (ms) 102.00, LAVI (ml/m^2) 86.00, TAPSE (mm) 22.00 and estimated pulmonary pressure (mmHg) 40.00, mild mitral regurgitation (EROA) 13.00 mm^2. These ECHO parameters qualified to be in stage 3 diastolic dysfunction. A dynamic ECG Holter examination was performed, showing an average heart rate of 89 bpm (min-max: 66 - 114 bpm), no ventricular couplet, no isolated ventricular ectopic (VE), and atrial fibrillation. The average arterial pressure was 140/80 mmHg with hypotensive peaks. Following these results, the diagnosis of HFpEF was still there and ameliorated by initiating Spironolactone and Dapagliflozin, by modifying the therapeutic plan as follows:

- Spironolactone 25 mg q.d;
- Dapagliflozin 10 mg q.d;
- Lisinopril 10 mg q.d;
- Metoprolol 50 mg q.d;
- Atorvastatin 40 mg q.d;
- Rivaroxaban 15 mg q.d.

A titration was planned for Lisinopril and spironolactone for two weeks. After the second step-up (from 20 mg to 40 mg) a lipothymia episode (as transient global cerebral hypoperfusion characterized by rapid onset, short duration, and complete spontaneous recovery) was reported, with arterial pressure of 70/51 mmHg; therefore the dosage of Lisinopril was reduced to 10 mg q.d, spironolactone was up titrated 50 mg q.d and potassium was monitored every after two weeks and all results were maintained at an average 4.32 mEq/L (min-max 3.72 - 4.9 mEq/L). There was no significant side effect reported after one-month follow-up but only mild recurrent urinary tract infection and some muscle pain due to statin.

In May 2022, the patient presented asymptomatic at the follow-up visit, with minimal dyspnea on intense exertion, and was ranked NYHA I. At the medical evaluation, the patient lost weight (10 kg), had an arterial pressure of 128/80 mmHg, and had good clinical compensation. HbA1c 6.2% and other Blood values were normal, LDL-C 3.8 mmol/L, Triglyceride 1.8 mmol/L. The ECG revealed sinus rhythm and heart rate at 86 bpm. At echocardiography, LVEF 60%, and normal morphological/functional parameters of both heart sides, diastolic dysfunction grade I. Treatment was modified by maintaining at Metoprolol 50 mg q.d. and reducing the dose of atorvastatin to 20 mg q.d, continuing with Rivaroxaban 15 mg for stroke prevention.

3. Discussion

This patient presented with elevated filling pressure E/e/ and increased LAVI, increased LV remodeling, high BMI, hypertension, pulmonary hypertension, atrial fibrillation, and advanced age; all of these are reported to be diagnostic criteria for HFpEF in most of the studies [1] [2] [3]. Most HFpEF patients have comorbidities that induce systemic inflammation that affect the lung, myocardium, skeletal muscle, and kidney dysfunction leading to diverse HFpEF pheno-

types with pulmonary hypertension, myocardial remodeling, and renal sodium retention [4]. This patient presented with elevated filling pressure and pulmonary hypertension as a result of the effect occurring in the lung, and myocardium in HFpEF [5]. Although this patient has good outcomes after being treated with MRA and SGLT2 inhibitor in general, the outcomes in HFpEF are a little better when not hospitalized than outcomes in HFrEF but the outcomes in hospitalization patients are similar for patients with HFpEF and patient for patients with HFrEF [6]. The overall burden of HFpEF is heavy and in some studies, QOL was impaired in HFpEF, and in some studies, QOL may be even worse in HFpEF [7]. This patient had many comorbidities that could lead to death and in most studies, the proportion of death due to Non-CV causes is higher in HFpEF than in HFrEF, and although both have functional capacity are significantly reduced, so we speculate the use of MRA (spironolactone) and SGLT2I (dapagliflozin) prevented death in this patient [8] [9] [10]. This patient presented with congestion and responded well to diuretics, which contributed to the good outcome of this patient, and in most of the studies, and they have recommended the use of diuretics in patients with HFpEF with congestion [9] [10]. All the comorbidities in this patient have managed accordingly, which could have contributed to the good outcome; the pressure was aggressively managed although a number of studies including I-PRESERVE, PEP-CHF, and TOPCAT showed that lowering BP did not necessarily improve HF outcomes [11] [12] [13]. Cross-sectionally more than 40% with HFpEF have Atrial Fibrillation (AF) and above 67% will have AF in the future; the presence of AF is associated with worsening outcomes [14]. In this patient, there was paroxysmal atrial fibrillation, the rhythm was controlled and stroke prevention which improved the outcome, although the impact of rhythm in HFpEF has not been adequately studied [14] [15]. The heart rate in this patient was maintained above 60 bpm because the patient with HFpEF frequently has chronotropic incompetence, where stroke volume or diastolic volume reserves may not be presented; high heart rate may be beneficial in this patient that resulted in a good outcome [6]. When compared with placebo both in EMPEROR Preserved and DELIVERY trials, the SGLT2i the Empagliflozin, and Dapagliflozin both reduced death and worsening heart failure in HFpEF [12]. This is the reason why our patient had a good treatment outcome. The decrease in HF severity, the patient's clinical condition, and the dose reduction of other drugs for the polytherapy optimization, echocardiographic parameters, and the break of a long series of hospitalizations were achieved in only 6 months.

4. Conclusion

In conclusion, the real-life case series reported here demonstrates that Dapagliflozin and spironolactone therapy were beneficial for improved outcomes in hard-to-reach rural African population patients with HFpEF. The MRA and SGLT2 inhibitors given together to HFpEF patients in the African population

play a crucial role in optimizing treatment and in reducing the need for surgical interventions or international referrals, preventing CV death and hospitalization events in HFpEF patients with different characteristics and comorbidities similar to other race in the real world. A big observational study is recommended in Africa to determine the benefit of SGL2 inhibitors (Dapagliflozin) and MRA (Spironolactone) in HFpEF patients.

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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].

Authors Contributions

First authors: DMR contributed to conceptualization, data curation, formal analysis, writing original draft, investigation, visualization, and writing a review, supervision, BK investigation, writing a review, and editing, EM, writing review and editing, ABM visualization, review, and editing. All authors read and approved the final manuscript.

Declaration of Interest

The authors declare no conflict of interest to declare.

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