Section A -Research paper

Effect of Newly Approved Medications Sacubitril/Valsartan, Empagliflozin and Dapagliflozin on the Quality of Life in Patients with Heart Failure with Reduced Ejection Fraction

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Article History: Received: 10.10.2022 **Revised:** 12.11.2022 **Accepted:** 10.12.2022

ABSTRACT

Background: Per the guidelines established by the European Society of Cardiology (ESC) guidelines for diagnosing and managing chronic and acute heart failure, Sacubitril/Valsartan, Empagliflozin, and Dapagliflozin are suggested to replace an angiotensin-converting enzyme (ACE) inhibitor to significantly minimize the heart failure (HF) associated risks including hospitalization and possible death of HF ambulatory patients with reduced ejection fraction that remain symptomatic. **Objective:** This work aimed to evaluate the health-related quality of life (HRQOL) changes in HFrEF patients throughout treatment with newly approved medications sacubitril/valsartan, Dapagliflozin, and empagliflozin using Minnesota living with heart failure questionnaire (MLHFQ) and Kansas City Cardiomyopathy Questionnaire (KCCQ) -12 at baseline, 3 months, and 6 months of treatment [1-4]. **Methods:** This prospective study was conducted on 500 patients with chronic HF with 35% or less LVEF, New York Heart Association class III or IV symptoms who visited Minia university cardiothorasic hospital ,cardiology outpatient clinic from period of March 2022 to October 2022. Patients were treated using maximum tolerated doses of guideline-directed medical therapy; angiotensin-converting enzyme inhibitors (ACEIs), ß-blocker (BB), mineralocorticoid receptor antagonist (MRA), and systolic blood pressure greater than 105 mmHg. A total of 3 visits were done (baseline visit, months 3 and 6). At the baseline visit, patients were on ACEIs, BB, MRA, and diuretics, and quality of life (QOL) was assessed for this regimen by MLHFQ and KCCQ.12 Then dapagliflozin or empagliflozin was added to the previous regimen, and a reevaluation of patients' QOL was done at 3 months. The ACEI or ARBs was replaced by sacubitril/valsartan, and the reevaluation of QOL was evaluated at 6 months. **Results:** Systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), E/e' ratio, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were remarkably decreased at 6 months compared to baseline (P value <0.001), at 6 months compared to 3 months (P value <0.001), and at 3 months compared to baseline (P value <0.001). Left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), and potassium were significantly increased at 6 months compared to baseline (P value <0.001), at 6 months compared to 3 months (P value <0.001), and at 3 months compared to baseline (P value <0.001). MLHFQ and KCCQ-23 scores were significantly improved at 6 months compared to baseline (P value <0.001), compared to 3 months (P value <0.001), and at 3 months compared to baseline (P value <0.001). 28 (5.6%) patients had stopped the medications due to adverse events (AEs). **Conclusions:** Treatment of HFrEF patients with sodium-glucose Co-transporter-2 inhibitors (SGLT2i) and/or sacubitril/valsartan is associated with rapid and significant improvement in patients' QOL according to both KCCQ and MLHFQ scores.

Keywords: Heart failure with reduced ejection fraction, Sacubitril/Valsartan, Dapagliflozin, Empagliflozin, Quality of Life

DOI: 10.53555/ecb/2022.11.11.137

INTRODUCTION

The heart failure pathophysiology comprises a maladaptive response activating the renin-angiotensin-aldosterone system (RAAS). Activation of RAAS may increase

sympathetic tone, vasoconstriction, hypertension, elevated aldosterone levels, and cardiac remodeling, which contribute negatively to the disease's progression. By blocking these maladaptive elements, angiotensin receptor blockers (ARBs), or angiotensin-converting enzyme inhibitors (ACEIs), HF morbidity and mortality can be reduced significantly [1, 2]. Concurrently, higher B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) are observed in HF exacerbations due to activating the natriuretic peptide system. This compensatory mechanism may result in vasodilation, natriuresis, diuresis, sympathetic tone, reduced blood pressure, and aldosterone levels.

The natriuretic peptide system opposes RAAS and benefits heart failure's pathogenesis. Natriuretic peptides are metabolized by an enzyme known as neprilysin, and blocking of its actions by a neprilysin inhibitor prevents the natriuretic peptides, leading to extended positive effects of peptides [3]. Sacubitril/valsartan (LCZ696) is the first known medication containing an angiotensin II (Ang-II) receptor blocker (valsartan) and a neprilysin inhibitor (sacubitril). Blocking neprilysin leads to the accumulation of angiotensin II since neprilysin is responsible for breaking it down.

So, a neprilysin inhibitor should be combined with an ARB to block the excess angiotensin II effect [4]. In addition, bradykinin is broken down by neprilysin, and the inhibition of neprilysin will result in the bradykinin buildup. Consequently, due to the elevated risk of angioedema when angiotensin receptor-neprilysin inhibitor (ARNI) and ACEI are used in close association, sacubitril is not recommended with ACEI. To minimize the risk of angioedema, patients need to undergo a 36-hour washout period when transitioning between ACEI and sacubitril/valsartan [5]. According to the European Society of Cardiology guidelines (ESC) published in 2020 for diagnosing and treating HF, a beta-blocker and a mineralocorticoid receptor antagonist (MRA) are suggested to replace ACE-I to minimize HF hospitalization and death risk in ambulatory patients diagnosed with HFrEF[6].

Patients with HFrEF are characterized by an impaired right ventricular (RV) function, indicating heart failure (HF) progression and additional detrimental predictive value. In contrast, the enhanced outcome is associated with RV recovery [7]. Also, a direct relationship is evident between amplified carotid intimal-medial thickness (cIMT), diastolic function, and lower left ventricular (LV) systolic were evaluated using asymptomatic individuals with myocardial strain without former clinical cardiovascular disease [8, 9].

AIM OF THE WORK

This work aimed to assess health-related quality of life (HRQOL) variances in HFrEF patients throughout treatment with newly approved medications sacubitril/valsartan, Dapagliflozin, and empagliflozin using KCCQ-12 and MLHFQ at baseline, 3 months, and 6 months after starting the medical trials.

PATIENTS AND METHODS

This study was carried out over a group of 500 patients with chronic HF with LVEF of 35% or less, New York Heart Association class III or IV symptoms who visited Minia university cardiothorasic hospital ,cardiology outpatient clinic from period of March 2022 to October 2022, the treatment with maximum tolerated dosages of guideline-directed medical therapy (ACE inhibitor, BB, MRA), and systolic blood pressure greater than 105 mmHg [7-9]. The patient or their relatives provided informed written consent. The study was carried out after approval from the Ethical Committee, Minia University Hospitals.

Exclusion criteria were patients who refused to give their written informed consent, current or prior treatment with Sacubitril-

valsartan, hepatic impairment, a heart transplant or ventricular assistance device, intention to or intent to use ventricular assistance device or transplant, use of cardiac resynchronization therapy devices implanted within six months of the screening visit, and pregnancy. Hepatic impairment is a critical situation that arises in individuals without any existing liver conditions. It is marked by liver damage (abnormal liver function tests), coagulation dysfunction (international normalized ratio [INR] >1.5), and hepatic encephalopathy [10].

A total of 3 visits were arranged for each patient (baseline visit, months 3 and 6). At the baseline visit, patients were on ACEI, BB, MRA, and diuretics; and QOL was assessed for this regimen by MLHFQ and KCCQ-12. Then SGLT2i ,Dapagliflozin or empagliflozin was added (Dapagliflozin 10 mg/day Empagliflozin 10 mg/day) to the previous regimen, and a reevaluation of patients' QOL was done after 3 months. The ACE was replaced by sacubitril/valsartan, and the reevaluation of QOL was evaluated after 6 months. Those taking an ACE inhibitor underwent a 36-hour washout, then started - sacubitril/valsartan, the drug, with a preliminary dose of 24/26 mg twice daily, followed by up-titration every 2-4 weeks, to reach the maximally tolerated dose.

All patients were subjected to history taking, serial 12-lead ECG, resting echocardiographic examination, and 2D echocardiography, by employing the echocardiography system (Acuson SC2000 PRIME ultrasound system, Siemens, Germany). Conventional echocardiographic measurements were obtained following the established guidelines of the European Association of Cardiovascular Imaging/ American Society of Echocardiography. Subsequently, speckle-tracking echocardiography (STE) analyses were conducted. This analysis focused on assessing LV,To assess left ventricular function and structures, left ventricular end-diastolic and systolic volume (LVEDV, LVESV), LVEF, and E/e' ratio, which was assessed by transmitral pulsed-wave Doppler using A4C view, specifically the global longitudinal strain (GLS), which was depicted using color coding. The GLS value was calculated as the average peak longitudinal strain of the 16 LV segments and was extracted as an absolute value [11, 12].laboratory measurements as venous blood samples were drawn from patients for measuring pro-BNP, renal function test, and potassium. The NT-proBNP blood samples were gathered within EDTA-containing vials. Collected specimens were tested with the NT-proBNP assay (proBNP II; Roche Diagnostics) and Diagnostics BNP assay (Siemens).

MLHFQ

The MLHFQ comprises 21 self-completed questions with a scale of 6-point response (0–5). The scores may vary between 0 to 105. The greater score indicates poorer QoL. The MLHFQ requires a two-dimensional score considering physical and emotional aspects, and the number of questions was divided as follows: 8 items (range 0–40) for physical characteristics and 5 items (range 0–25) for emotional aspects [11-13].

KCCQ

The KCCQ -12 provides a great tool to evaluate the HRQOL within patients suffering from HF. The KCCQ measures 7 domains that might be affected by HF, including physical limitations, symptom stability, self-efficacy, symptom burden, quality of life, symptom frequency, and social limitation. The scores obtained through KCCQ can be briefed as follows, (i) the total symptom score (TSS) considering the domains of the symptom frequency and burden; (ii) the clinical summary score (CSS) considering TSS and physical limitation; and (iii) the overall summary score (OSS) containing physical limitation, quality of life, TSS, and social limitation The KCCQ-12 final score may vary from 0 to 100, with 100 is the best probable HRQOL score [12].

The key outcome was to determine the impact of newly approved medications

sacubitril/valsartan, Dapagliflozin, and empagliflozin on QOL in patients with HFrEF at baseline, 3 months, and 6 months of treatment using MLHFQ and KCCQ. The secondary outcomes were to assess the safety and tolerability of sacubitril/valsartan, Dapagliflozin, and empagliflozin after 6 months of therapy (severity, number, type, adverse events (AEs) frequency, serious AEs, and clinically significant alterations in laboratory test results were within the reference ranges established by the laboratory), patient overall survival and complication-free survival at 6 months and to evaluate treatment compliance while on Dapagliflozin and empagliflozin by finding the medication non compliance frequency and the underlying reasons. Our team will determine non compliance based on an evaluation of the prescription pattern.

Statistical analysis

SPSS v27 (IBM©, Armonk, NY, USA) software was employed for the statistical analysis of data. The results were examined using the Shapiro-Wilks test and histograms to estimate the data normality distribution. The mean and standard deviation (SD) were used to present quantitative parametric data, which were then analyzed using ANOVA (F) test with a post hoc test. The median and interquartile range (IQR) displayed the quantitative non-parametric data. To compare groups, the quantitative non-parametric data were explored using the Kruskal-Wallis and Mann-Whitney tests. The qualitative variables were evaluated as frequency and percentage (%) and investigated using the Chi-square test. The statistically significant limit was set using the two-tailed P value of ≤ 0.05.

RESULTS

Table 1 provides the studied patients' baseline characteristics, with 500 individuals included in the analysis. The table comprises various parameters and their corresponding values. Overall, this table provides a snapshot of the baseline characteristics of the patients under study, which can help understand their demographic and physiological profiles.

Table 1: Characteristics of the selected group

Sample size		**n = 500**
Age (years)		48.95 ± 9.27
Gender	**Male**	195 (39%)
	Female	305 (61%)
BMI (kg/m^2)		26.58 ± 2.76
BSA (m^2)		2.02 ± 0.12
Pulse (beats/min)		80.19 ± 10.12
RR (cycle/min)		15.11 ± 2.09

Information is shown as mean ± SD or frequency (%), BMI: body mass index, BSA: body surface area, RR: respiratory rate.

Table 2 displays the changes in the QOL measurements of the patients at baseline, 3 months, and 6 months. Figures 1 (A) and (B) show changes in MLHFQ and KCCQ, respectively, at the measurement time. Figure 1 displays the MLHFQ (A) and KCCQ (B) scores of the patients under study. These measures are likely indicators of patients' health and quality of life, with (A) representing the MLHFQ and (B) representing KCCQ. The figure shows how these scores vary among the studied patients, providing insights into their overall well-being and heart failure-related quality of life at baseline, 3 months, and 6 months.

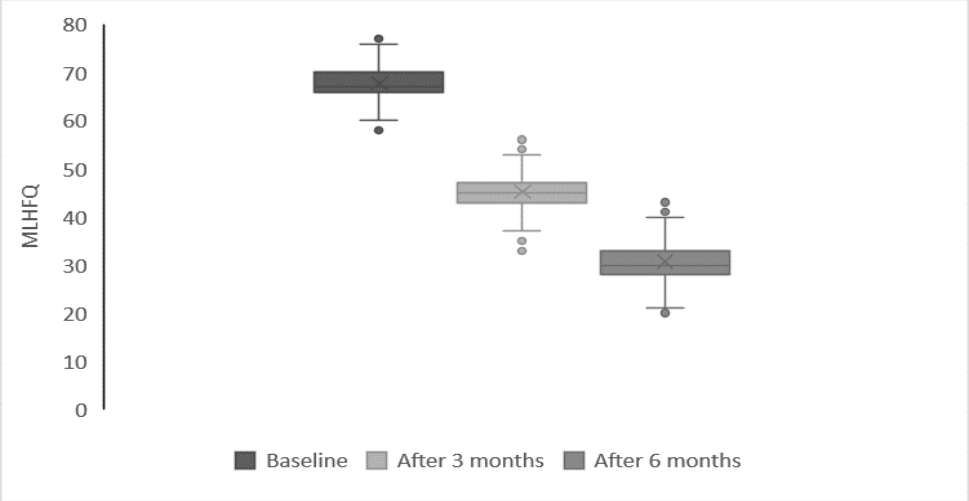
SBP, DBP, LVEDV, LVESV, E/e' ratio, GLS, and NT-proBNP were significantly decreased at 6 months compared to baseline (P value <0.001), at 6 months compared to 3 months (P value <0.001), and at 3 months compared to baseline (P value <0.001). LVEF, GLS, and potassium were increased considerably at 6 months compared to baseline (P value <0.001), at 6 months compared to 3 months (P value <0.001, and <0.025), and at 3 months compared to baseline (p-value <0.001). MLHFQ and KCCQ scores were significantly improved at

6 months compared to baseline (P value <0.001), compared to 3 months (P value <0.001), and at 3 months compared to baseline (p-value <0.001). Creatinine and BUN were insignificantly different between time measurements, as shown in Table 2.

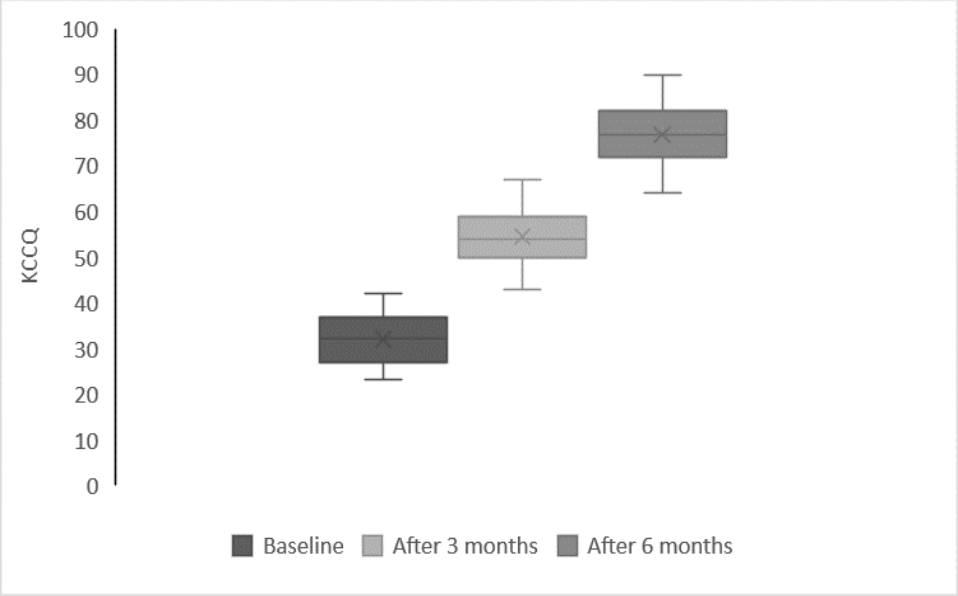
Table 2: Changes in repeated measurements of the studied patients

	Baseline	3 months	6 months	P value	
SBP (mmHg)	137.76 ± 6.15	132.76 ± 6.28	126.79 ± 6.47	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
DBP (mmHg)	83.3 ± 4.71	78.24 ± 4.85	72.39 ± 5	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
LVEDV (mL)	139.04 ± 6.98	134.03 ± 7.03	131.42 ± 7.2	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
LVESV (mL)	89.83 ± 4.73	84.81 ± 4.83	82.17 ± 5.07	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
LVEF (%)	34.82 ± 2.86	40.27 ± 3.05	44.22 ± 6.81	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
E/e' ratio	11.11 ± 3.15	10.64 ± 3.18	9.41 ± 2.73	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
GLS (%)	-15.4 (-18.1, -12.9)	-16.9 (-19.63, -14.38)	-17.9 (-20.6, -15.4)	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
NT-proBNP (pg/ml)	2446.5 (1589 - 3450.75)	2018.5 (1144.5 - 2997)	1558.5 (698.5 - 2547.75)	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
NT-proBNP difference from baseline to 6 months (pg/ml)				-892 (-924, -861)	
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.2	0.995	
Creatinine difference from baseline to 6 months (mg/dL)				0 ± 0.11	
BUN (mmol/L)	7.85 ± 2.56	8.85 ± 3.56	8.85 ± 4.56	0.596	
BUN difference from baseline to 6 months (mmol/L)				0.08 ± 2.09	
Potassium (mmol/L)	3.99 ± 0.32	4.12 ± 0.42	4.19 ± 0.32	<0.001*	P1 <1E-3* P2 <1E-3* P3 =2.5E-2*
Potassium difference from baseline to 6 months (mmol/L)				0.2 ± 0.03	
MLHFQ	67 (66 - 70)	45 (43 - 47)	30 (28 - 33)	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*
KCCQ-12	32 (27 - 36.25)	54 (50 - 59)	77 (72 - 82)	<0.001*	P1 <1E-3* P2 <1E-3* P3 <1E-3*

*: significant as P value ≤ 0.05, P1: P value for baseline compared to 3 months, P2: P value for baseline compared to 6 months, P3: P value for 3 and 6 months comparison.



(A)



(B)

Figure 1: MLHFQ (A) and KCCQ (B) of the studied patients

Table 3 presents complications observed in a group of 500 examined patients. The adverse events (AEs) that led to treatment discontinuation were reported in 5.6% of cases. Other complications included volume depletion in 11% of cases, renal adverse events in 10%, and a rare instance of amputation(0.4%)major hypoglycemia (0.2%).

Table 3: Complications of the examined patients

	n = 500
AEs necessitating discontinuation	28 (5.6%)
Volume depletion	55 (11%)
Renal AE	50 (10%)
Amputation	2(0.4%)
Major hypoglycemia	1 (0.2%)

Data are presented as frequency (%), AE: adverse event.

Table 4 displays the overall survival and complication-free survival rates over 6 months. The incidence of mortality was 7.6%, affecting 38 individuals, while complications were observed in 27.2% of cases (136 individuals). The 95% confidence intervals for the mean were 5.76 to 5.88 months for mortality and 4.9 to 5.18 months for complications.

Table 4: Overall survival and complication-free survival at 6 months

	Mortality	**Complications**
Incidence	38 (7.6%)	136 (27.2%)
Mean survival time (months)*	5.82	5.04
95% CI for the mean	5.76 – 5.88	4.9 – 5.18

CI: confidence interval, *: time from start medication to incidence of mortality or complications

DISCUSSION

Despite the abundance of evidence-based therapies available for managing HFrEF, morbidity, and mortality remain high [13]. In the last few decades, only one new pharmacological therapy, sacubitril/valsartan, has been approved to reduce morbidity and mortality in HFrEF. This therapy significantly reduced cardiovascular HF hospitalization and death compared to enalapril in the PARADIGM-HF trial. Consequently, it has obtained a Class I indication in international guidelines commonly. This makes sacubitril/valsartan the sole approved treatment introduced in the past 10 years for effectively addressing HFrEF-related outcomes [14].

Dapagliflozin significantly reduced cardiovascular death and HF decline composite in HFrEF patients in the Dapagliflozin and inhibition of Adverse Outcomes in Heart Failure (DAPA-HF) trial [15]. We aimed to assess changes in HRQOL in patients with HFrEF throughout treatment with newly approved medications Sacubitril /valsartan, Dapagliflozin, and empagliflozin.

We found that SBP, DBP, LVEDV, LVESV, E/e' ratio, GLS, and NT-proBNP were significantly decreased at 6 months compared to baseline (P value <0.001), at 6 months compared to 3 months (P value <0.001), and at 3 months compared to baseline (p-value <0.001). LVEF, GLS, and potassium were significantly increased at 6 months compared to baseline (P value <0.001), at 6 months compared to 3 months (P value <0.001, and <0.025), and at 3 months compared to baseline (p-value <0.001). MLHFQ and KCCQ scores were greatly improved at 6 months compared to baseline (p-value <0.001), compared to 3 months (p-value <0.001), and at 3 months compared to baseline (p-value <0.001). Creatinine and BUN were insignificantly different between time measurements.

In line with our findings, Jiang et al.[16] performed a study containing 136 patients. Sacubitril/valsartan and Dapagliflozin were used to treat 72 patients (Group A), and sacubitril/valsartan monotherapy was given 64 patients (Group B). For group A), remarkable cardiac function improvements were observed after using sacubitril/valsartan plus Dapagliflozin for 189 days. A significant reduction of the median N-terminal pro-B-type natriuretic peptide (NT-proBNP) was detected (P<0.001). Regarding safety, there were significant decreases in diastolic blood pressure (P=0.002) and systolic blood pressure (P=0.002).

Similarly, in a recent study, the patients were divided into two groups treated with sacubitril/valsartan plus dapagliflozin and sacubitril/valsartan. The percentage of patients with comorbid diabetes mellitus within the sacubitril/valsartan group was substantially lower compared to the sacubitril/valsartan plus Dapagliflozin group (51.9% vs. 74.1%, P = 0.001). The results indicate that sacubitril/valsartan plus Dapagliflozin is more effective for treating HFrEF and concomitant diabetes mellitus patients [17].

Another study involving diabetic HFrEF patients demonstrated that ARNI and SGLT2 inhibitors combination led to a more favorable clinical course of HFrEF compared to ARNI monotherapy [18]. Treatment using ARNI and SGLT2 inhibitors reduced the HF Patients' hospitalization and mortality (P = 0.04) compared to treatment with ARNI only. Furthermore, higher LVEF was observed in patients treated with ARNI and SGLT2 inhibitors compared to patients treated with ARNI only. Nevertheless, these differences were insignificant, potentially diminishing the additional benefit of the treatment using ARNI plus SGLT2 inhibitors combination on echocardiographic parameters linked to ARNI alone [18].

Conspicuously, Hwang et al. [19] reported that HF patients exhibited a considerable drop in LVEDD (P < 0.001) and enhancement in LVEF (P < 0.001) when treated with SGLT2 inhibitors. Hence, it is necessary further to investigate the effective mechanism and role of SGLT2 inhibitors when combined with ARNI treatment regimens [19].

Solomon et al. [20] performed a study on HFrEF patients by conducting a randomized, double-blind, placebo-controlled study related to 10 mg dapagliflozin in combination with placebo. 508 patients (10.7%) took sacubitril/valsartan at baseline, and the other 4236 patients not taking Sacubitril/Valsartan. The advantage of using Dapagliflozin as the primary and key secondary endpoints appeared to be consistent in patients, despite if sacubitril/valsartan was employed at the beginning of the study. KCCQ–TSS, Creatinine, and potassium were identical in both groups, although patients treated with sacubitril/valsartan exhibited remarkably lower blood pressure. They concluded that morbidity and mortality in HFrEF patients could be decreased by sacubitril/valsartan and Dapagliflozin without safety compromise. The authors concluded that sacubitril/valsartan and Dapagliflozin treatment showed significantly better clinical advantages than sacubitril/ valsartan monotherapy [20, 21].

In 2012, the PARAMOUNT trial investigated the sacubitril/valsartan effect on HFpEF. Within the PARAMOUNT trial, the study subjects were randomized into two groups treated twice daily with 200 mg sacubitril/valsartan or 160 mg valsartan. A remarkable decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP) was monitored after 12 weeks with the group treated with the sacubitril/valsartan [22]. In the PARADIGM HF trial, sacubitril/valsartan demonstrated greater efficacy than enalapril concerning heart failure hospitalizations (HHF), cardiovascular-related mortality, and all-cause mortality in HFrEF [23]. A significant positive impact was also observed on health-related quality of life (HRQOL) by demonstrating sacubitril/valsartan [24].

Several studies have demonstrated that in HF treatment, SGLT-2 inhibitors, like Dapagliflozin and the angiotensin receptor bloker, have noticeably positive outcomes. Further study is necessary to explore the unknown mechanism by which SGLT-2 inhibitors demonstrate the observed cardiovascular positive outcome. This leads to a drop in sodium and glucose reabsorption in the kidneys' proximal tubule. However, It has been hypothesized that the diuretic properties and valuable modifications changes in cardiac

metabolism, achieved by altering cardiac substrate utilization, could be potential mechanisms by which SGLT-2 inhibitors demonstrate such effect [25].

Sacubitril/valsartan works by concurrently blocking the renin-angiotensin system through angiotensin type 1 receptor blockade, enhancing endogenous vasoactive peptide systems. This effect is achieved by inhibiting the breakdown of biologically active natriuretic peptides [26]. Even though Sacubitril/valsartan may minimize the pre-load and afterload and provide a possibility of natriuretic properties, if the drug's acting mechanism overlapped considerably, Solomon et al. [20] assessed the potential extent of the effect of attenuation treatment in patients who were on sacubitril/valsartan at the study onset.

Compared to the enalapril group, the sacubitril/valsartan group showed a lower occurrence of renal impairment, hyperkalemia, and cough but a higher incidence of hypotension and mild to moderate angioedema [23]. Patients in the EMPEROR-Reduced study were randomized to receive either a placebo or 10 mg of empagliflozin once daily. As part of the DAPAHF trial, patients with HFrEF were given Dapagliflozin (10 mg) or a placebo once daily. The SGLT2i group had a lower incidence of HF hospitalization and cardiovascular-related death [27, 28].

In the DECLARE-TIMI 58 trial, type 2 diabetes patients were randomly assigned to receive 10 mg dapagliflozin or a placebo. Among these patients, a subgroup had HFrEF. The HFrEF patients administrated Dapagliflozin exhibited a lower HHF incidence and reduced deaths due to cardiovascular diseases. The numerical effect was reported on both heart failure (RR: 0.64 [95% CI: 0.43-0.95]) and cardiovascular mortality (RR: 0.55 [95% CI: 0.34-0.90])

Additionally, the dapagliflozin group mortality rate decreased (RR: 0.59 [95% CI: 0.40–0.88]) [28]. In the DAPA-HF trial, Dapagliflozin demonstrated no significant increase in adverse events (AEs) related to renal dysfunction, volume depletion, and hypoglycemia compared to the placebo groups [27].

By comparing the outcome between the Dapagliflozin and the placebo groups during the DECLARE-TIMI 58 trial, patients who discontinued the assigned regime were lower in the Dapagliflozin group (8.1% vs. 6.9%). The placebo groups patients showed a higher rate of severe AEs (36.2% vs. 34.1%), acute kidney injury (2% vs. 1.5%), hypoglycemia (1% vs. 0.7%), or bladder cancer (0.5 vs. 0.3%) compared to the dapagliflozin group. At the same time, the dapagliflozin group showed a higher diabetic ketoacidosis rate of (0.3 vs. 0.1%). The assigned regime was discontinued for male and female patients within the dapagliflozin group, and serious AEs were observed due to genital infections [29].

Yang et al. [30] showed Dapagliflozin discontinuation was similar to the placebo group in general and for patients with background MRA or ARNI therapy. There were no notable differences in any of the examined adverse events between Dapagliflozin and placebo, both overall and when considering background mineralocorticoid receptor antagonist (MRA) or angiotensin receptor-neprilysin inhibitor (ARNI) therapy.

LIMITATIONS

Our study had some limitations since it is a single-center-based study with a comparatively small sample size, and a placebo group was not included. Congestion indicators involving central venous and pulmonary capillary wedge pressure were not evaluated during the study. The sacubitril/valsartan optimal dosage must be

investigated in a future study. It is imperative to implement scheduled drug-escalation programs to assist patients with HFrEF in reaching optimal daily doses of sacubitril/valsartan, which can benefit their treatment.

CONCLUSIONS

We may conclude that in patients with HFrEF, the use of SGLT2i and/or sacubitril/valsartan may be associated with rapid and significant improvement in the patient's quality of life (QOL) according to both KCCQ as well as MLHFQ scores with lower incidence of mortality and complications. In the future, the sample size must be increased significantly, and the study must be conducted in several centers to investigate the impact of former hospitalization for Heart Failure (HF) on the efficacy of medical therapy needs to be examined and emphasize these conclusions. Understanding this relationship is crucial for determining how medical treatments can benefit patients with a history of HF-related hospitalizations.

Authors contributions : AS and HA designed the study and wrote the manuscript. HF,AR & AT re-evaluate and analyzed the data. AS & HF reviewed and revised the manuscript. All authors contributed to the article, approved the submitted version, and accepted to be held responsible for all aspects of the work

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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