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Combined Effects of ARNI & SGLT2 2 Inhibitors in Diabetic Patients with Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Objective: To compare the efficacy of SGLT2i+ARNI and SGLT2i+ARB combination therapy in reducing heart failure hospitalization rates among diabetic patients with heart failure with reduced ejection fraction. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** The study was conducted from May 2024 to November 2024 at the Medicine Department of CMH Multan. **Methodology:** 610 diabetic patients with heart failure with reduced ejection fraction (LVEF ≤40%) were randomly divided into two groups of 305 each. Group A received empagliflozin + sacubitril/valsartan while Group B received empagliflozin + valsartan. Patients were followed for six months with monthly clinical assessments. The primary outcome was heart failure hospitalization. **Results:** The SGLT2i+ARNI group showed significantly lower HF hospitalization rates (17%) compared to the SGLT2i+ARB group (23.9%, p=0.035). Subgroup analysis revealed particular benefits in patients aged 61-80 years (p=0.031), males (p=0.033), and NYHA class II patients. Logistic regression identified age (OR=0.973, p=0.034) and NYHA class (p<0.001) as significant predictors of hospitalization. **Conclusion:** The combination of SGLT2i and ARNI demonstrates superior efficacy in reducing heart failure hospitalization compared to SGLT2i and ARB in diabetic patients with HFrEF, particularly among older adults and males.

INTRODUCTION

Diabetic patients with heart failure, and with reduced ejection fraction (HFrEF), have a complex and challenging picture.[1] Diabetes mellitus is an established cardiovascular disease risk factor for heart failure development, and when both occur together, a synergistic cardiovascular disease burden is generated.[2] Patients with HFrEF and with diabetes mellitus have a poor prognosis with regard to both single disease processes, with increased hospitalization, morbidity, and mortality.[3] There is a complex pathophysiological substrate for such a combination, with insulin resistance, ongoing inflammation, oxidative stress, and neurohormonal activation, with all contributing to impairment in myocardial function and remodeling.[4] In addition, a concomitant presence of diabetes mellitus will complicate heart failure therapy through shared disturbances in both metabolites and hemodynamics.[5]

The management of HFrEF in diabetic subjects entails a multi-modal therapy in terms of both glycemic control and cardiovascular stability.[6] Traditional interventions include interventions in lifestyle, blood pressure and lipid profile optimizations, and guideline-directed medical therapies for heart failure.[7] Optimum success in such a population, however, continues to elude, with numerous antidiabetic medications having been associated with cardiovascular adverse consequences, and with poor efficacy in heart failure improvement.[8] As a result, newer advances in drugs in terms of pharmacotherapy included drugs with not only glycemic control but with cardiovascular protective actions, and such development saw new classes of drugs, such as angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose cotransporter 2 (SGLT2) inhibitors, emerging with potential in both controlling diabetes mellitus and heart failure.[9] ARNIs and SGLT2 inhibitors are two such breakthroughs in heart failure and diabetes mellitus therapy.[9] ARNIs, including sacubitril/valsartan,

combine inhibition of neprilysin, with augmentation of beneficial activity of natriuretic peptides, with antagonism of angiotensin, countervailing deleterious activity of the renin-angiotensin-aldosterone axis.[10] ARNIs have consistently been proven in trials, including PARADIGM-HF, to have a significant role in cardiovascular mortality and heart failure-related hospitalization in HFrEF subjects.[11] SGLT2 inhibitors, including dapagliflozin and empagliflozin, induce blood sugar lowering through increased loss of sugar in the urine but have cardioprotective activity in addition to this.[12] Breakthrough trials including DAPA-HF and EMPEROR-Reduced have underpinned improvement in heart failure in with and without diabetes mellitus.[13] All such drugs have become cornerstones in HFrEF therapy, with additional value in concomitant cases of diabetes mellitus. Therapy with ARNIs and SGLT2 inhibitors together in diabetic HFrEF subjects is particularly powerful, with complementary actions through complementary pathways to maximize cardiovascular and metabolic wellness.[14] ARNIs correct neurohormonal disturbances and stimulate restoration of myocardium, and SGLT2 inhibitors maximize diuresis, lessen cardiac work, and stimulate systemic metabolism.[15] Together, such drugs have additive, even synergistic, beneficial actions, with reduced heart failure-related events and in improvements in quality of life. SGLT2 inhibitors have, in addition, been proven to reverse many of the renal complications of diabetes mellitus, providing even additional value in such a high-risk group.

This study is crucial as it explores the combined effects of Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) and Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in diabetic patients suffering from heart failure with reduced ejection fraction (HFrEF). Both conditions significantly impact patient morbidity and mortality, and existing therapies may not fully address the complex interplay between diabetes and heart failure. By examining how these two classes of drugs work together, the study aims to uncover potential synergies that could improve outcomes for this high-risk patient population, offering insights into more effective treatment strategies.

METHODOLOGY

This randomized controlled trial was conducted between May 2024 and November 2024 at the Medicine Department of CMH Multan. The study included 610 diabetic patients diagnosed with heart failure with reduced ejection fraction (HFrEF), confirmed through echocardiographic assessment (LVEF ≤40%) and clinical evaluation. Participants were randomly divided into two groups of 305 each, following predefined inclusion and exclusion criteria. The sample size was determined using sample size calculator, with an 80% power of test and a 5% significance level, based on assumed HF hospitalization rates of 37.7% versus 27.1%, as referenced from previous real-world data.[14]

Inclusion criteria comprised individuals aged 40 to 80 years, of both genders, diagnosed with HFrEF and type 2 diabetes mellitus (T2DM), and receiving stable guideline-directed medical therapy for at least three months before enrollment. Exclusion criteria included patients with end-stage renal disease (eGFR <30 mL/min/1.73m²), recent hospitalization for acute decompensated heart failure (HF) within the past one month, history of intolerance to study medications, or use of both ARNI and SGLT2i prior to the study period. After obtaining institutional ethical approval and informed consent, participants were randomly allocated into two treatment groups using the lottery method. Group A received SGLT2i (empagliflozin 10 mg daily) in combination with ARNI (sacubitril/valsartan 97/103 mg twice daily), while Group B received SGLT2i (empagliflozin 10 mg daily) alongside ARB (valsartan 160 mg twice daily, respectively).

Patients were followed for six months, with clinical assessments conducted every four weeks. The primary outcome was HF hospitalization, defined as an admission requiring intravenous diuretics, inotropes, or other acute HF management strategies. Renal function, blood pressure, and potential adverse effects (e.g., hyperkalemia, acute kidney injury) were monitored throughout the study.

Data were collected by trained fellows under the supervision of senior physicians. Demographic details, clinical history, echocardiographic parameters, and treatment outcomes were recorded in a structured proforma. Statistical analysis was performed using SPSS version 26. Continuous variables, such as age and LVEF, were expressed as mean ± standard deviation, while categorical variables, including gender and HF hospitalization, were presented as frequencies and percentages. The chi-square test was used to compare HF hospitalization rates between the two groups, with a p-value ≤ 0.05 considered statistically significant. Stratification was conducted for age, gender and HF severity (NYHA Class (I–IV)) to control for potential confounders, followed by post-stratification chi-square analysis.

RESULTS

From Table 1, both treatment groups had comparable demographics: mean age was 58.947±10.67 years in the SGLT2i+ARNI group and 59.062±12.47 years in the SGLT2i+ARB group. BMI measurements were similar between groups (SGLT2i+ARNI: 25.639±2.54 kg/m², SGLT2i+ARB: 25.695±3.61 kg/m²). Both groups showed reduced ejection fraction with mean LVEF values of 29.042±7.45% in the SGLT2i+ARNI group and 27.655±7.36% in the SGLT2i+ARB group. Gender distribution showed a male predominance in both groups (SGLT2i+ARNI: 232 males [76.1%], 73 females

[23.9%]; SGLT2i+ARB: 238 males [78%], 67 females [22%]). Regarding NYHA functional classification, Class II was most prevalent in the SGLT2i+ARNI group (43.3%, n=132), followed by Class III (37%, n=113), Class IV (13.8%, n=42), and Class I (5.9%, n=18). In the SGLT2i+ARB group, Class III was most common (42.6%, n=130), followed by Class II (31.8%, n=97), Class IV (17.7%, n=54), and Class I (7.9%, n=24).

Table 1

Demographics of the Patients

Demographics		Group A n=305 Mean ± SD	Group B n=305 Mean ± SD
Age (years)		58.947±10.67	59.062±12.47
BMI (Kg/m^2)		25.639±2.54	25.695±3.61
LVEF (%)		29.042±7.45	27.655±7.36
Gender	Male n(%)	232 (76.1%)	238 (78%)
	Female n(%)	73 (23.9%)	67 (22%)
NYHA Class	I n(%)	18 (5.9%)	24 (7.9%)
	II n(%)	132 (43.3%)	97 (31.8%)
	III n(%)	113 (37%)	130 (42.6%)
	IV n(%)	42 (13.8%)	54 (17.7%)

Table 2 revealed significantly lower HF hospitalization rates in the SGLT2i+ARNI group (17%, n=52) compared to the SGLT2i+ARB group (23.9%, n=73) with p=0.035.

Table 2

Comparison of HF Hospitalization Between the Two Groups. n=610

HF Hospitalization	Group A n=305 n (%)	Group B n=305 n (%)	P value
Yes	52 (17%)	73 (23.9%)	
No	253 (83%)	232 (76.1%)	0.035
Total	305 (100%)	305 (100%)	

Table 3

Stratification of HF Hospitalization Based on Demographic Variables Across Groups

Demographics variables		Group	HF Hospitalization Yes (n, %)	HF Hospitalization No (n, %)	P-value
Age (years)	40-60	A	28 (17.9%)	128 (82.1%)	0.411
		B	34 (21.7%)	123 (78.3%)	
	61-80	A	24 (16.1%)	125 (83.9%)	0.031
		B	39 (26.4%)	109 (73.6%)	
Gender	Male	A	39 (16.8%)	193 (83.2%)	0.033
		B	59 (24.8%)	179 (75.2%)	
	Female	A	13 (17.8%)	60 (82.2%)	0.644
		B	14 (20.9%)	53 (79.1%)	
BMI (Kg/m^2)	≤25	A	34 (15.8%)	181 (84.2%)	0.209
		B	39 (20.6%)	150 (79.4%)	
	>25	A	18 (20%)	72 (80%)	0.127
		B	34 (29.3%)	82 (70.7%)	
NYHA Class	I	A	0 (0%)	18 (100%)	1.000*
		B	0 (0%)	24 (100%)	
	II	A	0 (0%)	132 (100%)	0.031*
		B	4 (4.1%)	93 (95.9%)	
	III	A	16 (14.2%)	97 (85.8%)	0.367
		B	24 (18.5%)	106 (81.5%)	
	IV	A	36 (85.7%)	6 (14.3%)	0.750
		B	45 (83.3%)	9 (16.7%)	

*Fischer Exact Test

According to Table 3's stratified analyses, significant differences in HF hospitalization rates were observed between treatment groups for patients aged 61-80 years (SGLT2i+ARNI: 16.1% vs SGLT2i+ARB: 26.4%, p=0.031) and male patients (SGLT2i+ARNI: 16.8% vs SGLT2i+ARB: 24.8%, p=0.033). NYHA class II patients also showed significant between-group differences (SGLT2i+ARNI: 0% vs SGLT2i+ARB: 4.1%, p=0.031).

Logistic Regression Analysis model demonstrated strong predictive capability with Nagelkerke $R^2 = 0.582$ and achieved 90.3% overall classification accuracy (sensitivity = 64.8%, specificity = 96.9%). The Hosmer-Lemeshow test yielded χ^2=18.488 (df=8, p=0.018). Age emerged as a significant predictor (B=-0.027, SE=0.013, OR=0.973, 95% CI [0.949-0.998], p=0.034). NYHA functional class was also a significant predictor (p<0.001), though individual class comparisons showed computational limitations due to separation in the data (Class II vs I: B=-16.982, SE=6149.534, p=0.998; Class III vs I: B=-19.245, SE=6149.534, p=0.998; Class IV vs I: B=-22.590, SE=6149.534, p=0.997). Other variables including gender (B=0.044, SE=0.339, OR=1.045, 95% CI [0.538-2.030], p=0.897), BMI (B=0.049, SE=0.049, OR=1.050, 95% CI [0.953-1.157], p=0.324), and LVEF (B=0.012, SE=0.055, OR=1.012, 95% CI [0.909-1.126], p=0.832) did not significantly predict heart failure hospitalization as shown in Table 4

Table 4

Logistic Regression Analysis for Heart Failure Hospitalization

Variable	B Coefficient	S.E.	Odds Ratio (95% CI)	P-value
Age	-0.027	0.013	0.973 (0.949-0.998)	0.034
Gender (Male vs Female)	0.044	0.339	1.045 (0.538-2.030)	0.897
BMI	0.049	0.049	1.050 (0.953-1.157)	0.324
LVEF	0.012	0.055	1.012 (0.909-1.126)	0.832
NYHA class overall	-	-	-	<0.001
Class II vs I	-16.982	6149.534	0	0.998
Class III vs I	-19.245	6149.534	0	0.998
Class IV vs I	-22.59	6149.534	0	0.997

DISCUSSION

Our findings revealed SGLT2i+ARNI group having a significant reduced HF hospitalization (17%) compared with SGLT2i+ARB (23.9%, p=0.035). There can be a range of mechanism for such an increased performance with SGLT2i+ARNI combination. First, ARNI exhibits dual actions with inhibition of Neprilysin (augmenting beneficial peptides like natriuretic peptides) and antagonism of angiotensin receptors, but ARB exhibits only the latter one. With increased natriuretic peptide system with ARNI, one reaps increased hemodynamics,

reduced cardiac remodeling, and balanced neurohormonal state. Besides, when added with SGLT2i, whose cardiac preload reduction and cardiac energetics improvement occur in an additive manner, ARNI combination seems to have synergistic actions. That is, most evident in our subgroup analysis, with most benefit in older (61-80 years) and male subjects, possibly through increased baseline cardiovascular risk in them. That significant difference in NYHA class II subjects in our analysis could mean SGLT2i+ARNI combination started at an early stage could possibly prevent disease progression and following hospitalization with a better efficacy compared with SGLT2i+ARB. That observation conforms with current evidence that ARNI outperforms conventional RAAS blockade in heart failure morbidity and mortality improvement.

Our findings agree with Kim et al. [15] who have proven that HFrEF with diabetes, when both SGLT2i and ARNI were taken together, exhibited less HF admission and cardiovascular deaths when compared with both drugs together and neither of them alone, respectively. Hsiao et al. [16] have, in a real-life HFrEF with T2DM, proven that SGLT2i and ARNI combination therapy exhibited less HF admission and composite events (HF admission and all-cause deaths) respectively. In both studies, additive efficacy with combination therapy was emphasized, and our observation of less HF admission in SGLT2i+ARNI group re-emphasizes the same.

Furthermore, subgroup analysis in our study revealed significant HF admission rate discrepancies between specific groups of patients, such as 61–80 years (SGLT2i+ARNI: 16.1%, SGLT2i+ARB: 26.4%, p=0.031) and male (SGLT2i+ARNI: 16.8%, SGLT2i+ARB: 24.8%, p=0.033) groups. All these observations concur with studies in the past that have postulated SGLT2i therapy will have a larger beneficial impact in terms of positive cardiovascular and kidney consequences in subjects with fewer comorbidities and preserved kidney function and in male and younger subjects.[16] In addition, reduced HF admissions in NYHA Class II subjects in SGLT2i+ARNI (0%, 4.1%, p=0.031) contrast with Hsiao et al., who have stated that subjects with mild HF symptoms respond positively with combination therapy.[16]

Despite the overall concurrence with studies in the past, a few discrepancies must be taken into consideration. For instance, logistic regression analysis in our work revealed age to be an independent predictor for HF admission (B=-0.027, SE=0.013, OR=0.973, 95% CI [0.949–0.998], p=0.034), but not factors of age, gender, and LVEF. In contrast, LVEF and improvements in mitral E/e′ have been observed in significant events in a study conducted by Kim et al. [15] Variability in study population, follow-up duration, and study design could have possibly been responsible for such a discordance. In our work, a relatively younger cohort (mean age ~59 years) with similar baseline LVEF values in groups (SGLT2i+ARNI: 29.042±7.45%, SGLT2i+ARB: 27.655±7.36%) could have possibly diminished LVEF's predictive role.

Another notable variation is no considerable relation between HF admission and BMI in our analysis (B=0.049, SE=0.049, OR=1.050, 95% CI [0.953–1.157], p=0.324). In contrast, SGLT2i's efficacy in lowering body weight and visceral fat have been stressed in early studies as a mechanism for its therapeutic actions.[17] Differences in baseline metabolic profiles between study groups, or in sample size and statistical power, could underlay such discrepancies.

The observed beneficial actions of SGLT2i+ARNI combination therapy can best be understood through complementary actions of SGLT2i and ARNI. SGLT2i induces its cardioprotective actions through its actions of natriuresis, osmotic diuresis, reorientation of myocardial fuel energetics towards ketone bodies, and anti-oxidative and anti-inflammatory actions.[18] ARNI, in contrast, potentiates the natriuretic peptide system, with vasodilation, natriuresis, and inhibition of myocardial remodeling actions.[19] Complementarity between such actions most probably underlies additive beneficial actions in the SGLT2i+ARNI group

Notably, our subgroup analysis brings a spotlight onto individualized therapy in relation to individual factors in a patient. For example, improvement in older adults (61–80 years) and in males brings a spotlight onto these groups in terms of benefiting most with early initiation of combination therapy. Besides, no HF admissions in NYHA Class II SGLT2i+ARNI brings a spotlight onto its efficacy in disease inhibition in less severe HF stages.

In summary, our observations serve to further confirm the added value of combining SGLT2i with ARNI in HFrEF in type 2 diabetes mellitus patients. Added value in, most particularly, heart failure admission and ventricle function, re-affirms value in such a combination therapy in managing complex patient groups. As pleasing as observations, at first glance, initially appear, future studies with larger, multi-centre trials will become important in firmly confirming long-term value and in assessing for value in secondary events, such as renal function and survival in general.

There are a few limitations in this study that have to be kept in mind. First, it was a single-center study, and its generalizability in larger populations could therefore be limited. Otherwise, renal outcomes in detail have not been analyzed in this study, and both ARNI and SGLT2i therapy have a significant role in them. In future, studies have to include such limitations and assess long-term consequences of combination therapy in a larger group of subjects.

CONCLUSION

Our study concluded that a combination of Sodium-

Glucose Cotransporter 2 Inhibitors (SGLT2i) and Angiotensin Receptor-Neprilysin Inhibitors (ARNI) is of therapeutic benefit for heart failure with reduced ejection fraction and for type 2 diabetes subjects. In terms of heart failure-related outcomes and overall patient care, such a combination therapy can promote, according to the findings.

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