



COMPARATIVE EFFICACY OF SGLT2 INHIBITOR (DAPAGLIFLOZIN) & ARNI VS COMBINATION THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Cardiology

Sharma M. K.	Sr. Professor And Hod Department Of Cardiology, Rnt Medical College, Udaipur
Ameta D.	Assistant Professor Department Of Cardiology, Rnt Medical College, Udaipur
Ranawat Y. S.*	Senior Resident Department Of Cardiology, Rnt Medical College, Udaipur *Corresponding Author
Singh A	Senior Resident Department Of Cardiology, Rnt Medical College, Udaipur

ABSTRACT

Objective: To compare the effects of sodium-glucose cotransporter-2 inhibitor (SGLT2i) with angiotensin receptor neprilysin inhibitor (ARNI) in heart failure with reduced ejection fraction (HFrEF) and to assess whether combination of SGLT2i and ARNI is better than monotherapy. **Methods:** In this study, patients with HFrEF who received treatment at department of Cardiology, RNT Medical College were identified and classified into four subgroups according to the treatment received as follows: 1) No SGLT2i and no ARNI 2) ARNI and no SGLT2i 3) SGLT2i and no ARNI 4) ARNI and SGLT2i. We compared the events of worsening heart failure and cardiovascular mortality among all subgroups during follow-up of 6 months. Statistical analysis was done using Student's independent t-test for comparing continuous variables and Chi-square test for categorical variables. **Results:** A total of 525 patients were included in the study, among them 341 patients in the no SGLT2i no ARNI subgroup, 85 patients in the ARNI and no SGLT2i subgroup, 63 patients in the SGLT2i and no ARNI subgroup and 36 patients in the SGLT2i and ARNI subgroup. The comparison at 6 months follow-up showed similar rates of heart failure hospitalization and cardiovascular mortality in SGLT2i and ARNI monotherapy subgroup and combination of SGLT2i and ARNI achieved lowest rates of heart failure hospitalization and cardiovascular mortality while subgroup 1 (no SGLT2i no ARNI) had the highest event rates. The improvement in distance covered in 6 minutes walk test and improvement in KCCQ summary score was significantly higher in combination therapy subgroup as compared to other subgroups. (p value <0.05). **Conclusion:** SGLT2i and ARNI showed similar effects, while combination of both resulted in a better outcome in terms of cardiovascular mortality, heart failure hospitalizations and improvement in the quality of life in patients with HFrEF.

KEYWORDS

INTRODUCTION:

The prevalence of heart failure is rapidly increasing and currently affects more than 26 million people worldwide, out of them approximately 50% have heart failure with reduced ejection fraction.¹

The morbidity and mortality is significantly high despite of multiple available evidence based therapies and patients have greatly compromised quality of life.

Numerous studies have shown that sodium- glucose co-transporter-2 (SGLT-2) inhibitors like dapagliflozin and angiotensin receptor-neprilysin inhibitor (ARNI) – sacubitril/ valsartan have a beneficial role on reducing cardiovascular mortality and hospitalization for heart failure.²⁻⁶

In the DAPA-HF trial dapagliflozin reduced the incidence of worsening heart failure events and cardiovascular mortality in HFrEF patients irrespective of their diabetic status.⁶ In addition PARADIGM-HF trial showed reduced incidence of clinical events in patients of HFrEF treated with angiotensin receptor –neprilysin inhibitors (ARNI) as compared to those treated with enalapril.²

However there have been very few studies comparing ARNI vs SGLT2i and whether combination usage of these two drugs would achieve better results than a monotherapy is also not clear. Therefore the aim of this study was to compare the efficacy of monotherapy of ARNI and SGLT2i as well as combined therapy in patients with HFrEF at 6 month follow up.

MATERIAL AND METHODS:

The study included patients with HFrEF who received treatment at department of Cardiology, RNT Medical College, Udaipur and were followed up for 6 months.

Patients diagnosed with HFrEF (defined as left ventricular ejection fraction <40 % by echocardiography), who were treated with either an ARNI, angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) were included. Patients with end stage renal disease, those receiving renal replacement therapy were excluded.

The included patients were classified into four subgroups according to

the use of ARNI and/or SGLT2i as following- 1) No SGLT2i and no ARNI 2) ARNI and no SGLT2i 3) SGLT2i and no ARNI 4) ARNI and SGLT2i

We collected their data which included their demography, symptoms using NYHA functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ), vital parameters, baseline echocardiography and routine investigations.

The clinical outcome of interest included worsening of heart failure (defined as either an unplanned hospitalization or an urgent visit that required intravenous diuretics) and cardiovascular mortality over a period of 6 months. The secondary endpoints were 6 minute walk test, change in the Kansas City Cardiomyopathy Questionnaire Clinical Total Symptom Score (KCCQ-TSS) and Each patient was followed for up to 6 months.

Statistical Analysis: The baseline characteristics, laboratory data, functional class among the study groups were compared using the chi-square test for categorical variables and for continuous variables independent student's t test was used. A p value of < 0.05 was considered to be statistically significant. All the analysis were conducted in SPSS version 20 (SPSS Inc, Chicago, IL, USA).

RESULTS:

A total of 525 patients were eligible for analysis, including 341 patients in the no SGLT2i no ARNI subgroup, 85 patients in the ARNI and no SGLT2i subgroup, 63 patients in the SGLT2i and no ARNI subgroup and 36 patients in the SGLT2i and ARNI subgroup.

The baseline characteristics of the study population is demonstrated in Table no. 1 >0.05 (NS); <0.05 (S); <0.001 (HS)

Variables	No SGLT2i No ARNI (n=341)	ARNI (n=85)	SGLT2i (n= 63)	ARNI and SGLT2i (n=36)	P value
Age, years	67.2±10.9	63.1±9.8	60.8±8.6	59.6±7.2	<0.001
Male, no. (%)	236(69.2)	63(74.1)	45(71.4)	25(69.4)	0.84
Smoker, no. (%)	136(39.8)	30(35.3)	24(38.0)	13(36.1)	0.87

Hypertension, no. (%)	238(69.8)	52(61.1)	38(60.3)	23(63.9)	0.27
Diabetes Mellitus, no. (%)	121(35.4)	28(32.9)	23(36.5)	20(55.5)	0.10
Dyslipidemia, no. (%)	268(78.6)	63(74.1)	47(74.6)	27(75.0)	0.76
Coronary artery disease, no. (%)	214(62.7)	55(64.7)	40(63.4)	22(61.1)	0.18
Stroke, no. (%)	16(4.7)	3(3.5)	1(1.5)	0	0.39
BUN mg/dL	30.4±19.6	30.1±17.4	26.8±16.3	24.7±14.2	<0.001
Creatinine mg/dL	1.4±1.2	1.4±1.1	1.1±0.8	1.1±0.6	0.302
Potassium, mmol/L	4.2±0.6	4.1±0.5	4.1±0.6	4.1±0.5	0.521
Beta blocker, no. (%)	306(89.7)	72(84.7)	55(87.3)	31(86.1)	0.58
Diuretics, no. (%)	326(95.6)	80(94.1)	60(95.2)	34(94.4)	0.94
Digoxin, no. (%)	56(16.4)	11(12.9)	9(14.2)	4(11.1)	0.74
Mineralocorticoid receptor antagonist (MRAs), no. (%)	246(72.1)	60(70.5)	46(73.0)	26(72.2)	0.99
Antiplatelets, no. (%)	238(69.8)	59(69.4)	45(71.4)	25(69.4)	0.99
NYHA class, no. (%)					
1	0	0	0	0	
2	151(44.3%)	45(52.9%)	36(57.1%)	21(58.3%)	0.10
3	113(33.1%)	27(31.8%)	18(28.6%)	10(27.8%)	0.84
4	77(22.6%)	13(15.3%)	9(14.3%)	5(13.9%)	0.19

As depicted in table no. 1, the patients who were treated with combination therapy (SGLT2i + ARNI) were younger (mean age 59.6±7.2) as compared to patients in other subgroups. There was male predominance in all subgroups. Hypertension, Smoking and dyslipidemia were major risk factors in all subgroups. It was observed that majority of patients were taking beta blockers and diuretics in all subgroups.

The heart failure severity distribution of each subgroup was mainly in the range of moderate severity [New York Heart Association class (NYHA) 2/3]

Table 2 : Comparison of various parameters at baseline and at 6-month follow-up >0.05 (NS); <0.05 (S); <0.001 (HS)

Parameters	NO SGLT2i NO ARNI (n=341)		ARNI (n=85)		SGLT2i (n=63)		ARNI and SGLT2i (n=36)		P VALUE
	Base line	at 6 month	Base line	at 6 month	Base line	at 6 month	Base line	at 6 month	
Heart failure hospitalization	-	118 (34.6%)	-	20 (23.5%)	-	14 (22.2%)	-	6 (16.7%)	0.02
Cardiovascular death	-	31 (9.1%)	-	4 (4.7%)	-	3 (4.8%)	-	1 (2.8%)	0.25

As depicted in Table no 2, the patients treated with combination therapy (ARNI + SGLT2i) had the lowest rates for heart failure hospitalization (n=6, 16.7%) while the patients in the No ARNI No SGLT2i group had the highest rate for heart failure hospitalization (n=118, 34.6%) and was found statistically significant also (p value= 0.02) there was no major difference in the rates for heart failure hospitalization in the ARNI and SGLT 2i subgroup (n=20, 23.5% & n=14, 22.2% respectively).

The death events related to heart failure were maximum in the No SGLT2i No ARNI subgroup (n=31, 9.1%), while lowest in combination therapy subgroup (n= 1, 2.8%). There was no major difference in cardiovascular mortality between ARNI and SGLT2i subgroup (n=4, 4.7% & n=3, 4.8% respectively).

Table 3: Comparison of 6 Minute Walk Test and KCCQ Summary Score at baseline and at 6-month follow-up

	NO SGLT2i, NO ARNI (n =341)		ARNI(n=85)		SGLT2i (n=63)		ARNI and SGLT2i (n=36)		P value
	Basel ine	at 6 month h	Basel ine	at 6 month h	Basel ine	at 6 month h	Basel ine	at 6 month h	
6 minute walk test	174.6 +71.2	200+ 90.2	220.8 +82.9	305. 3+92 .4	216+ 83.1	310 +94. 3	218. 8+8 3.4	320. 6+9 5.4	<0.0 001 01
P value	<0.001		<0.001		<0.001		<0.001		
KCCQ summary score	53.6±3.7		71.8±2.8		54.9±3.6		77.8±4.9		55.6±3.1
P value	<0.001		<0.001		<0.001		<0.001		

Distance covered in 6 minute walk test was improved in all subgroups at 6 month follow-up but the improvement in the combination therapy subgroup (ARNI +SGLT2i) was significantly higher than the other subgroups (p<0.001)(Table 3)

The improvement in KCCQ summary score was significantly higher in the combination therapy subgroup as compared to other subgroups. (p<0.001).

DISCUSSION :

The effects of SGLT2i and ARNI on cardiovascular protection has been postulated in many studies. The EMPA-REGOUTCOME, the DECLARE-TIMI 58 trial and the CANVAS study demonstrated a significantly lower risk of hospitalization for heart failure in patients treated with SGLT2i^{8,9} Out of these three trials the EMPA-REGOUTCOME trial showed a significant reduction in cardiovascular death while the CANVAS and DECLARE-TIMI trial showed no significant difference in cardiovascular mortality. The DAPA-HF and EMPEROR-HF trials showed lower rate of cardiovascular death and heart failure hospitalization in patients with HFrEF regardless of diabetes status.^{6,10}

In our study also it was observed that the patients in SGLT2i subgroup had significantly lower rate of heart failure hospitalization (p value= 0.02) as well as improved quality of life as indicated by KCCQ summary score and 6 minute walk test (p value <0.001) as compared to patients in No SGLT2i No ARNI subgroup which can be considered as conventional treatment group as they received renin angiotensin system blocker only. There was decrease rate of cardiovascular death in SGLT2i subgroup as compared to conventional group (no SGLT2i no ARNI) but it was not significant statistically (p value =0.25).

The another heart failure therapy emerged in recent years, ARNI has been proven to be superior to ACEI in reducing hospitalization for heart failure and cardiovascular death in PARADIGM-HF.² We also observed the significant reduction in heart failure hospitalization and functional improvement in ARNI subgroup as compared to conventional treatment group. (p value <0.05)

Both SGLT2i and ARNI show excellent cardiovascular protection through different mechanisms and it is intriguing to determine which therapy is better. In our study we compared SGLT2i and ARNI monotherapy and it was observed that both the subgroups (ARNI and SGLT2i monotherapy) had almost similar rates of heart failure hospitalization and similar functional improvement so it indicates that SGLT2i and ARNI may serve as a substitute for each other in reducing heart failure hospitalization. Similar results were obtained in meta-analysis by Yuling et al¹¹ and a multi-institutional study conducted by Fu-Chih Hsiao et al.¹²

The post hoc analysis from the DAPA-HF and EMPEROR- Reduced trial showed evidence that SGLT2i and ARNI therapy should work in independent and additive ways but there are no published studies which has reported the use of SGLT2i and ARNI combination therapy. In our study it was observed that the patients in combination therapy subgroup had lowest rate of heart failure hospitalization as compared to SGLT2i and ARNI monotherapy. (p value =0.02) and significant improvement in 6 minute walk test and quality of life as indicated by KCCQ score improvement. (p value <0.05). The cardiovascular death was also least in the combination therapy subgroup but it was not

significant statistically (p value =0.25).

In summary, in our study it was found that combination of a SGLT2i and ARNI is significantly better than ARNI monotherapy and has favorable outcome in patients with HFrEF.

Limitations:

In our study Limited sample size and shorter follow up period might result in internal heterogeneity.

CONCLUSION :

In patients with HFrEF, the SGLT2i and ARNI combination therapy group showed better efficacy outcomes at the end of 6 month follow-up in terms of readmission rate due to heart failure, cardiovascular death, 6 minute walk test and improvement in KCCQ score as compared to ARNI or SGLT2i monotherapy.

REFERENCES:

1. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev.* 2017; 3:7
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin inhibition vs. enalapril in heart failure. *N Engl J Med.* (2014) 371:993–1004. doi: 10.1056/NEJMoa1409077
3. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin–Neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* (2019) 380:539–48. doi: 10.1056/NEJMoa1812851
4. Tsutsui H, Momomura SI, Saito Y, Ito H, Yamamoto K, Sakata Y, et al. Efficacy and safety of sacubitril/valsartan in Japanese patients with chronic heart failure and reduced ejection fraction—results from the PARALLEL-HF study. *Circ J.* (2021) 85:584–94. doi: 10.1253/circj.CJ-20-0854
5. Piepoli MF, Hussain RI, Comin-Colet J, Dosantos R, Ferber P, Jaarsma T, et al. OUTSTEP-HF: Randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. *Eur J Heart Fail.* (2021) 23:127–35. doi: 10.1002/ehf.2076
6. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* (2019) 381:1995–2008. doi: 10.1056/NEJMoa1911303
7. Spertus JA, Jones PG. Development and validation of a short version of the Kansas city Cardiomyopathy Questionnaire. *Circulation: Cardiovasc Qual Outcome.* 2015; 8:469e476.
8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S. Cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373:2117–2128.
9. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erond N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377:644–657.
10. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383:1413–1424.
11. Yuling Yan, Bin Liu, Jun Du, Jing Wang, Xiaodong Jing, Yajie Liu. SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta analysis. *ESC Heart Failure* 2021; 8: 2210–2219 Published online 21 March 2021 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.13313
12. Fu-Chih Hsiao, Chia-Pin Lin, Ying-Chang Tung, Po-Cheng Chang, John J.V. McMurray, Pao-Hsien Chu. Combining sodium-glucose cotransporter 2 inhibitors and angiotensin receptor-neprilysin inhibitors in heart failure patients with reduced ejection fraction and diabetes mellitus: A multi-institutional study. *International Journal of Cardiology* 330 (2021) 91–97.