Journal of Young Pharmacists, 2024; 16(3):439-446.
https://www.jyoungpharm.org

Review Article

Effect of ARNI (Sacubitril/Valsartan) and SGLT2 Inhibitors (Dapagliflozin) either alone or in Combination on Heart Failure: An Exploration of Novelty

Girish B. S*, Joel M. Johns, C. S Meghana, R. Srinivasan

Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences (Formerly PES College of Pharmacy), PES University, Electronic City Campus, Bangalore, Karnataka, INDIA.

ABSTRACT

Cardiovascular Diseases (CVD) have claimed millions of lives, despite the efforts of medical professionals. There are several treatment methods for blocking a few neurohormonal cascades; however, it is debatable because there are few hypotheses, which claim that in Heart Failure (HF), these systems tend to activate potential counter-regulatory mechanisms. Angiotensin Receptor Neprilysin Inhibitors (ARNI) are developed to modulate both Renin-Angiotensi n-Aldosterone-System and Natriuretic Peptide, regulating neurohormonal cascade in HF. LCZ696 (Sacubitril/Valsartan) is the first-in-class ARNI, approved for managing HF. Initially, ARNI was developed to manage Hypertension, later the FDA regulatory label was expanded for the management of HF. Dapagliflozin belongs to the class of SGLT2 inhibitors that have shown potentially beneficial effects in HF. Would the two medications, which have distinct mechanisms of action but a similar effect-a decrease in the risk of HF-show additive or synergistic effects when taken together? India, known as "The Chronic Heart Disease Capital of the World", is accounting sharp rise in sudden cardiac death with young adults being the worst sufferers. This review inference that, using ARNI and Dapagliflozin together may have a larger positive effect on HF patients' quality of life by lowering their need for hospitalization due to HF deterioration.

Keywords: ARNI, Sacubitril/Valsartan, SGLT2 Inhibitors, Dapagliflozin, Heart Failure.

Correspondence:
Mr. Girish B S
Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences (Formerly PES College of Pharmacy), PES University, Electronic City Campus, Bangalore-560100, Karnataka, INDIA.
Email: girishsharma70268@gmail.com
ORCID: 0000000318947852

Received: 17-02-2024;
Revised: 30-03-2024;
Accepted: 05-04-2024.

INTRODUCTION

Cardiovascular Diseases (CVD) have claimed millions of lives, despite the efforts of medical professionals. Worldwide, 19.05 million people died from CVD in 2020.[1] Patients with Heart Failure (HF) are at an elevated risk of mortality, poor health-related quality of life and worsening HF episodes.[2] Owing to fewer evidence-based therapy options available, the suffering of the afflicted population has grown.[3]

HF pathogenesis is significantly influenced by the neurohormonal cascade, which includes the Sympathetic Nervous System (SNS) and the Renin-Angiotensin-Aldosterone-System (RAAS).[4-7] There are several treatment methods for blocking them, however, it is debatable because a few hypotheses that claim that, these systems tend to activate potential counter-regulatory mechanisms.[8] It is believed that a variety of mediators, including Natriuretic Peptide (NP) have potential benefits in HF which are cleaved and inactivated by a membrane-bound endopeptidase, neprilysin.[9] Hence, the blockade of neprilysin is sought to be a boon in HF treatment. Thus, Angiotensin Receptor Neprilysin Inhibitors (ARNI) are developed to modulate both RAAS and NP, regulating the neurohormonal cascade in HF.[10]

On February 16, 2021, with data suggesting a fall in the risk of cardiovascular death and hospitalization for HF, the US Food and Drug Administration (FDA) broadened the labelling of Sacubitril/Valsartan, the first-in-class ARNI for its use in HF in adults with long-standing hypertension.[11] These modifications were made in response to the PARAGON-HF study,[12] which demonstrated a significant interaction between Left Ventricular Ejection Fraction (LVEF) and treatment efficacy, stating that patients with LVEFs at or below the median value of 57% seemed to experience greater clinical benefits.[13]

Heart failure frequently originates from inadequately managed Type 2 Diabetes Mellitus (T2DM),[14] resulting in less than a quarter of cases having unfavourable outcomes and a five-year survival rate of 25% or less.[15] This emphasizes the need of developing novel agents managing both hyperglycemia and reducing the risk of CVD, especially HF. Previous experiences have established the reliability of lowering blood glucose levels in T2DM and

DOI: 10.5530/jyp.2024.16.57

concomitantly improving microvascular events, but it is dubious regarding macrovascular impacts like CVD and stroke.[16] Thus more emphasis is to be laid on specificity and methods of glucose reduction.

Emphasizing the Asia-Pacific and Middle East, the prevalence of T2DM is alarmingly raising,[17,18] where CVD continues to be the predominant cause of mortality and morbidity. Prioritizing this, the Asia-Pacific Cohort Studies Collaboration compiled archival data from Asian regions and acknowledged that T2DM was associated with a doubled increase in the risk of CVD and a nearly 67% increase in the risk of All-Cause-Mortality (ACM), with a significantly higher hazard ratio in the younger population opposed to the older population.[19] Yet, control of adverse CVD is not well described.

The availability of several glucose-lowering medicines calls into doubt the guidance of cardiovascular events; to be precise, DPP4 Inhibitors studies revealed no increase or decrease in cardiovascular events.[20,21] However, numerous recent clinical trials have shown that newer classes of anti-diabetic medications, particularly Sodium-Glucose-cotransport-2 (SGLT2) inhibitors improve HF situations.[22] Dapagliflozin, an SGLT2 inhibitor (SGLT2i) is extremely selective and malleable to SGLT2 receptors found in the proximal tubule of the kidney, which reabsorbs the majority of the glucose typically filtered via glomeruli[23,24] leading to hypoglycaemic impact.

A meta-analysis of Phase 2 and Phase 3 studies of Dapagliflozin indicated cardiovascular benefits with a tendency towards reduction of composite cardiovascular events including cardiovascular death and hospitalization for HF and myocardial infarction with no effect on stroke.[25] Hence, in this review, the authors would like to put up the effects of ARNI and SGLT2i either alone or in combination on HF.

This review addresses the significance of ARNI and SGLT2i for the management of HF, both alone and in combination. A comprehensive literature search was conducted using the terms ARNI, Sacubitril/Valsartan, LCZ696, SGLT2i, Dapagliflozin and Heart Failure in databases including PubMed, Embase, Medline and Google Scholar that were published after 2012. Solely English-language literature was considered. In addition, references from archived papers were carefully examined for any additional conceivably relevant information. The literature was chosen based on high-quality data on the drugs of interest, ARNI and SGLT2i, which was studied for HF with preserved EF (HFpEF) and/or HF with reduced EF (HFrEF), regardless of the dosage strengths. Studies of drugs on other indications, animal studies and extensive reviews weren't taken into account. Data from the literature were manually retrieved, collated and reviewed for projected data.

ARNI in Heart Failure

Activation of the RAAS initially improves blood pressure and cardiac vagal tone, but eventually becomes paradoxical and deteriorates HF due to volume accumulation. HF treatment is cantered on comprehension of these pathways, whose backbone of its pharmacotherapy comprises diuretics, β blockers, Angiotensin-Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB). Throughout the last two decades, these medications have been the bedrock of HF therapy. Apart from RAAS, additional neurohormonal chemicals, including NP, are implicated in the pathogenesis of HF.

The NP is a group of related but molecularly different proteins encompassing Atrial, Brain-type and C-type NP (ANP, BNP, CNP respectively).[25] ANP and BNP enhance cytoplasmic GMP, which facilitates smooth muscle relaxation, antiproliferative effects and diuresis. They also influence RAAS, endothelin and vasopressin, as well as lipid mobilization, aiding in the treatment of HF.[26,27] One of the greatest strategies to augment these NPs are by hampering Neprilysin, an enzyme that destabilizes NPs.[28,29] Additional studies should be done in this domain to make this a therapeutic option for both Hypertension (HTN) and HF.

Neprilysin and ACE inhibitors

Omapatrilat, the primeval compound to be developed in this category is an orally available, protracting, selective and molecular inhibitor of neprilysin and ACE that has superlative hypotensive actions to that of ACE inhibitor, Enalapril. However, it is also linked to a higher risk of angioedema.[30] Since it skyrockets bradykinin by inhibiting its degraders, ACE and Aminopeptidase P (APP). Hence, it is advantageous to have a dual-acting ARB and NEP inhibitor (ARNI), which would not directly influence ACE or APP activity and may therefore be the safest method to block RAAS and supercharge natriuretic peptide. Table 1 summarizes the safety data of Omapatrilat vs Enalapril.

Neprilysin and ARB

The invention of ARNI, Sacubitril/Valsartan (LCZ696), addressed the main drawback of omapatrilat, the possibility of angioedema. LCZ696 constitutes molecular moieties of valsartan (ARB) and NEP inhibitor prodrug AHU377 (Sacubitril) in a 1:1 molar ratio. On proteolytic cleavage of its ethyl ester, it is biologically transformed into an active NEP inhibitor, LBQ657.[31,32]

Dose and availability

Sacubitril/valsartan is taken twice a day at a baseline dose of 49/51 mg (100 mg of combination) summing up to 97/103 mg (200 mg of combination) as the final dose. It comes in fixed doses of 24/26 mg, 49/51 mg and 97/103 mg film-coated tablets. It is recommended to adjust adult doses every 2 to 4 weeks and pediatric doses every 2 weeks to the intended maintenance dose, as tolerated by the patient. It is also advised to reduce the

routine starting dose by half for patients who are previously not on ARB or ACEi or who have severe renal and moderate hepatic impairment.[11]

Sacubitril/valsartan on HF with reduced EF

As aforementioned, evidence-based medicine increases survival rates, thereby reducing HF hospitalizations with a beneficial impact on the Quality of life of patients with Chronic HF. Woefully, not many evidence-based strategies in this domain accounting poor prognosis in chronic HF patients. According to the ESC classification of HF, individuals with normal LVEF (usually defined as 50%; HFpEF) and those with decreased LVEF (often defined as 40%; HFrEF) fall into two categories.[33] Due to the unique features and severity of this condition, the therapy differs depending on the kind of HF.

Solomon SD *et al*, compared ARNI with ACEi to ascertain the effect of EF on outcomes and the effectiveness of ARNI in HF with decreased EF where 8399 individuals with NYHA class II to IV were randomly assigned to receive 97/103 mg of sacubitril/valsartan and 10 mg of enalapril twice daily. Hospitalization for HF or cardiovascular mortality was the main study endpoint. Although sacubitril/valsartan was able to improve HF symptoms, the primary outcome was more prevalent in patients with low EF (17.5%) than those with high EF (> 32.5%). However, the overall results of this trial indicate LVEF was a substantial and independent predictor of all outcomes in HF patients and sacubitril/valsartan was efficacious throughout the whole range of LVEF in lowering cardiovascular mortality and HF hospitalization.[34]

The PARADIGM-HF experiment revolutionized the idea of using ARNI in HFrEF. The 2017 ACC/AHA/HFSA HF Focused Update recommends patients with chronic symptomatic HFrEF who can tolerate ACE inhibitor or an ARB be switched to ARNI, to further reduce morbidity and mortality. This study conceptualized the replacement of ACEI or ARB with Sacubitril/valsartan in the management of chronic HF.[35] In light of this, Sacubitril/Valsartan has been considered a potentially significant treatment option in HFrEF.

Sacubitril/Valsartan in HF with preserved EF

Contrary to recommendations and guidelines for using Sacubitril/Valsartan in patients with HFrEF, no therapies have demonstrated a definitive improvement in hospitalization or mortality in patients with HFpEF. This may be because the majority of hospitalizations and deaths are most likely to be non-cardio-related. As a result, the current practice encourages the control of risk factors and comorbidities while merely treating fluid overload patients symptomatically with diuretics.

NT-proBNP is a crucial peptide and can be utilized as a biomarker to track the development of HF. Strategizing this, PARLLAX randomized controlled study by Pieske B *et al*. examined the effectiveness of sacubitril/valsartan in patients with chronic HF and LVEF>40%. With an adjusted geometric mean ratio of 0.84 (p .001), patients in the sacubitril/valsartan arm had substantially lower NT-proBNP values than the comparison group following 12 weeks. They found the sacubitril/valsartan treatment led to a proportionately higher reduction in plasma NT-proBNP levels at 12 weeks in patients with HF and a left ventricular ejection factor of greater than 40%, thus suggesting the use in HFpEF.[36]

Given that the PARAGON-HF trial was a game-changer for broadening the regulatory labeling of sacubitril/valsartan,

Table 1: Summary of the safety of Omapatrilat vs Enalapril from OCTAVE study.[30]

Sample size		Any adverse events		Serious adverse events		Angioedema	
Omapatrilat	Enalapril	Omapatrilat	Enalapril	Omapatrilat	Enalapril	Omapatrilat	Enalapril
12609	12557	6426 (50.96%)	6327 (50.38)	441(3.49%)	470 (3.74%)	274 (2.17%)	86 (0.68%)

Table 2: Summary of incidences of a few adverse events from various clinical trials.

Studies	N in ARNI group/ arm	Symptomatic hypotension	Renal dysfunction/elevated serum creatinine	Hyperkalemia
Solomon SD *et al* 2012.[38]	149	28	3	12
McMurray JJ *et al* 2014.[39]	4187	588	139	674
Velazquez EJ 2019.[40]	440	66	60	51
Pieske B *et al* 2021.[36]	1280	180	149	149
Mann DL *et al* 2022.[41]	167	29	7	28
Total	6223	891	358	914

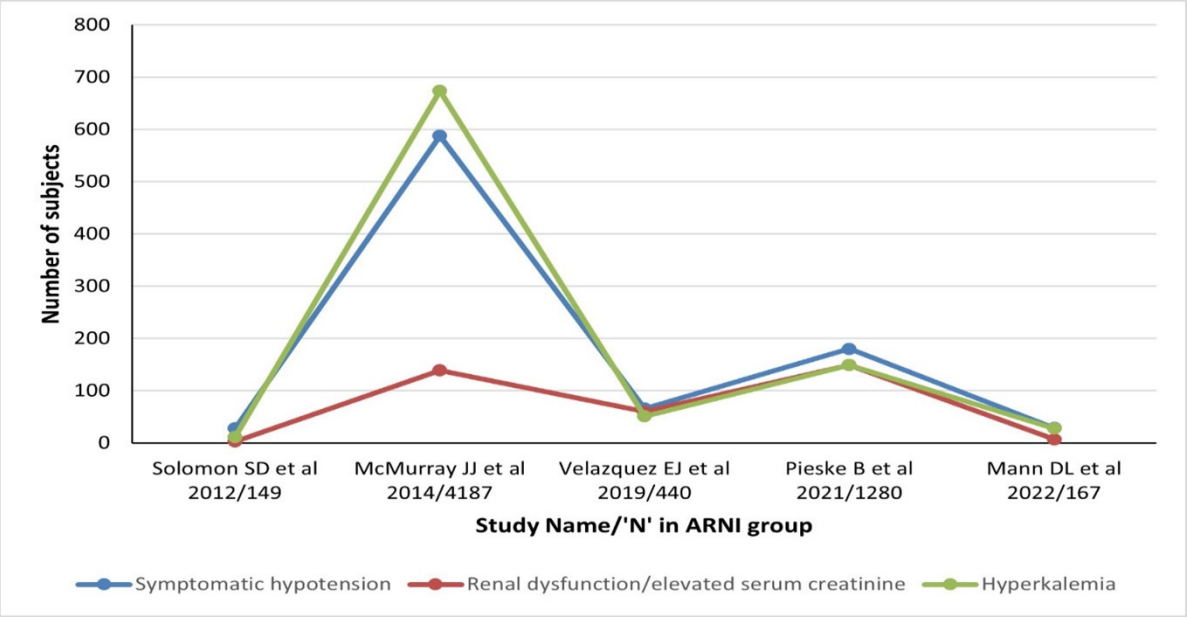


Figure 1: Summary of the safety of ARNI in different clinical trials.[36,38-41]

Solomon SD *et al*. similarly extended this research to deduce the effectiveness of this medication in patients with HF and maintained EF. Sacubitril-valsartan 97/103 BD or valsartan 160 mg BD was given to 4822 patients with New York Heart Association (NYHA) class II to IV HF, EF of 45% or higher, elevated level of NP and structural heart disease with the primary outcome as a composite of total hospitalizations for HF and death from cardiovascular causes. In the sacubitril-valsartan group, there were 894 primary events among 526 patients, compared to 1009 primary events among 557 patients in the valsartan group, indicating no statistically significant difference. (p=0.06).[37]

With various large-scale clinical data providing inconsistent claims concerning the use of Sacubitril/valsartan, more studies are required in patients with HFpEF.

Safety of ARNI

Many studies have focused on the safety of ARNI and compiling it provides a comprehensive understanding and is depicted in Figure 1 and Table 2.

Dapagliflozin in Heart Failure

In general, long-term use of anti-diabetic medications has been linked to a reduction in cardiovascular adverse events through several pathways, including a decrement in atherosclerosis, with either an enhanced or little effect on the incidence of HF.[42,43] Nevertheless, only one medication class, SGLT2i, has been shown to reduce the risk of cardiovascular adverse events, principally by slowing the course of HF.[42,44] Large T2DM clinical trials on dapagliflozin, have demonstrated a reduction in the likelihood of HF hospitalization.[42,45,46] This suggested the notion that the cardiovascular advantages of dapagliflozin were distinct from its hypoglycemia impact. Hereon, we emphasize dapagliflozin's impact on HF.

The most frequently cited theory of SGLT2i on HF is that these work as diuretics by inhibiting SGLT2 receptors in the proximal tubule of the nephron, which at different levels of granularity colocalizes and operationally interacts with Sodium Hydrogen Exchanger, which is primarily in charge of the large percentile of sodium reabsorption after filtration. NHE activity is well-known to be dramatically elevated in HF, which explains the resistance of some people to diuresis and endogenous NP. Hence, it is predicted that inhibiting SGLT2-associated NHE will both reduce heart damage and produce diuresis. It may result in lessened heart wall stress and lower intravascular volume, halting the advancement of HF.[47]

Dose and availability

Dapagliflozin is available in 5 and 10 mg, where 5mg, is the initial dose for the treatment of T2DM once daily and can be increased to a dose of 10mg once daily in patients tolerating 5 mg who require additional glycemic control. For the use in HF, 10 mg once daily is recommended to reduce the risk of hospitalization in adults with T2DM and established CVD or multiple cardiovascular risk factors.[48]

Dapagliflozin in HF with reduced and preserved EF

To evaluate the effectiveness of SGLT2i in adults with chronic HF and a decreased EF, regardless of the presence of T2DM, an experiment was carried out with 4744 patients, randomly assigned to receive either dapagliflozin 10mg OD or a placebo in addition to the advised course of treatment if they met the criteria for NYHA class II, III, or IV HF and had an EF of 40% or

less. 10.0% of the dapagliflozin group and 13.7% of the placebo group had worsening HF, with corresponding mortality rates from cardiovascular events of 9.6% and 11.5%. Thus, this trial found that among patients with HF and a reduced EF, the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than those who received a placebo.[49]

With a view to bolster the evidence for the usage of dapagliflozin in HFpEF, the DELIVER study was carried out in patients with a higher LVEF to evaluate dapagliflozin's effectiveness in individuals with a higher LVEF. In 6263 patients with HF with an EF of >40%, a time-to-event analysis of cardiovascular mortality and worsening HF was the primary outcome; these events occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and 610 of 3132 patients (19.5%) in the placebo group, resulting in a hazard ratio of 0.82 with statistical significance of $p<0.001$. As a result, the study concluded that Dapagliflozin decreased the risk of cardiovascular mortality or worsening HF in individuals with HF and a modestly reduced or preserved EF.[50]

Additionally, several systematic reviews and meta-analyses have examined the effectiveness of dapagliflozin in HFpEF and HFrEF, showing that dapagliflozin may be effective in slowing the course of HF in people with diabetes.[22,51]

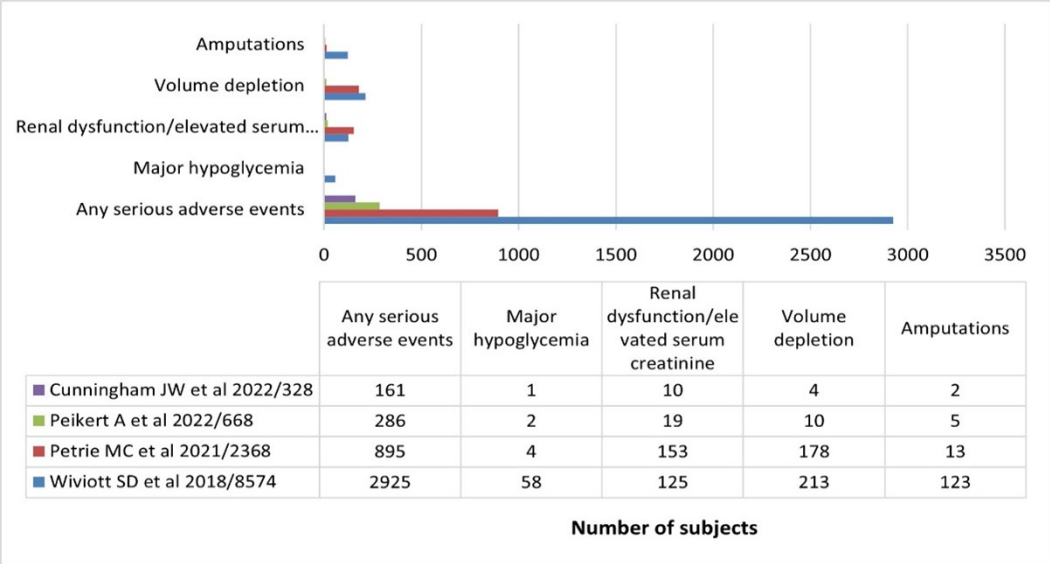
Safety of Dapagliflozin

Regardless that dapagliflozin is renowned for its higher effectiveness, safety issues are often brought up. A few safety issues noticed and researched throughout the clinical trials are shown in the accompanying figure. In addition to these, its usage is articulated by nasopharyngitis, urinary tract infections and female genital mycotic infections.[48] The major safety profile of Dapagliflozin has been summarized and displayed in Figure 2.

Combination of ARNI and Dapagliflozin

Regardless of the certainty, these medications were originally developed for distinct reasons, but subsequent research has shown their capability of ameliorating HF. Would the two medications with distinct mechanisms, but a similar effect-a decrease in the risk of HF - show additive or synergistic effects when taken together?

To answer this, Kim HM *et al.*[55] carried out research by retrospectively identifying T2DM individuals with HFrEF administered with ARNI and/or SGLT2i. Participants were separated into those who received treatment with both ARNI and SGLT2i (group 1), ARNI but not SGLT2i (group 2), SGLT2i but not ARNI (group 3) and those who received neither ARNI nor SGLT2i (group 4). Hospitalization for HF (HHF), cardiovascular mortality and changes in echocardiographic markers were examined after propensity score matching. According to this study, group 1 patients had a lower risk of HHF and cardiovascular deaths than patients in the other groups and also noted more significant improvements in LVEF and E/e' ratio than patients in groups 2, 3 and 4. Moreover, compared to the start of SGLT2i, these echocardiographic changes were more evident following the initiation of ARNI. This study conjectured combination of ARNI and SGT2i significantly improved cardiac function and prognosis in diabetic individuals with HFrEF. Concomitantly, the beneficial effects of the combined use of sacubitril/valsartan and dapagliflozin on long-term cardiac mortality in comparison to ARNI standalone therapy in patients with HFrEF was evaluated in a retrospective analysis by Karabulut U *et al.*[56] in 2021. Two groups of 244 patients were involved, with a median follow-up of 2.5 years. Long-term cardiac mortality rates were discovered to be significantly lower in the ARNI+Dapagliflozin group i.e., 7.4% compared to the ARNI alone group i.e., 19.5%, indicating$p=0.01$.



	Any serious adverse events	Major hypoglycemia	Renal dysfunction/elevated serum creatinine	Volume depletion	Amputations
Cunningham JW et al 2022/328	161	1	10	4	2
Peikert A et al 2022/668	286	2	19	10	5
Petrie MC et al 2021/2368	895	4	153	178	13
Wiviott SD et al 2018/8574	2925	58	125	213	123

Figure 2: Summary of the safety of dapagliflozin from different clinical trials.[46,52-54]

Mareev YV *et al.*[57] undertook a risk of death analysis per 100 patient-years to evaluate the overall impact of ARNI and SGLT2i treatment in Russian patients with both decompensated and stable HFrEF. The risk of mortality per 100 patients reduced from 12.2% to 8.9% in the individuals who were replaced with ARNI from conventional RAAS inhibitors with the addition of SGLT2i, representing a 27% overall risk reduction. The probabilistic risk of fatalities upon discharge for patients with decompensated HF who switched from conventional RAAS inhibitors to ARNI with augmentation of SGLT2i has been quoted as 26.9 deaths per 100 patient-years. It was exceptionally remarkable to observe that, based on this evidence, patients receiving ARNI and SGLT2i supplements had a fall in the death rate per 1000 patient-years from 36.8 to 19.9%. Thus, this study underlines the significance of prompt initiation of ARNI and SGLT2i in patients with both decompensated and stable HFrEF.

An extensive analysis was conducted to explore the benefits of the combined effects of ARNI and dapagliflozin by Huang Y *et al.*[58] where data from trials comparing the use of ARNI or SGLT2i alone or in combination with ARNI in patients with HFrEF were gathered from the Medline, Embase and Cochrane Library databases. When ARNI+SGLT2i combination was compared to ARNI monotherapy in patients with HFrEF, both hospitalization for HF and cardiovascular mortality decreased by 35%. Additionally, combination of ARNI and SGLT2i reduced cardiovascular mortality in patients with HFrEF by 36% compared to SGLT2i alone. In line with this study, ARNI and SGLT2i might be safe and effective in HFrEF patients.

A study by Yang M *et al.*[59] evaluated the effectiveness and safety of dapagliflozin when used in combination with preexisting ARNI therapy in patients with HFpEF/HF with mildly reduced EF. The favorable effects of dapagliflozin on cardiovascular mortality and/or worsening HF were similar in both those receiving ARNI and those not receiving an ARNI, with a Hazard Ratio of 0.74 in patients receiving an ARNI.

Using this comparison as a guide, the data suggests that using ARNI and Dapagliflozin together has increased quality of life while lowering the likelihood of hospitalization for HF in both preserved and reduced EF. Yet, much more research is needed to strengthen the evidence regarding the combined use of ARNI and Dapagliflozin. This review focuses mainly on clinical trials, carried out with consideration for many components of the medication and a particular population was chosen for the study. Hence, it is necessary to understand and monitor the effects of these medications on HF in a wider population, in the market and in actual clinical settings. A small number of clinical studies have been taken into consideration, namely in medication safety criteria, for a variety of reasons. The whole study discusses clinical trials while excluding marketing or observational data from the clinical context.

CONCLUSION

India, known as "The Chronic Heart Disease Capital of the World", is accounting sharp rise in sudden cardiac death with young adults being the worst sufferers. Advancements and newer technology in Cardiology are the pressing priority to tackle cardiac anomalies. HF, which accounts for the majority of fatalities, calls for special consideration. Regarding this, ARNI and Dapagliflozin though having different indications and mechanisms of action have shown beneficial effects in HF. This review inference that, using ARNI and Dapagliflozin together may have a larger positive effect on HF patients' quality of life by lowering their need for hospitalization due to HF deterioration.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ARNI: Angiotensin Receptor and Neprilysin Inhibitor; **SGLT2i:** Sodium-Glucose-Cotransporter-2 Inhibitor; **HF:** Heart Failure; **CVD:** Cardiovascular Disease; **EF:** Ejection Fraction; **RAAS:** Renin-Angiotensin-Aldosterone System; **NP:** Natriuretic Peptidase; **FDA:** Food and Drug Administration; **LVEF:** Left Ventricular Ejection Fraction; **T2DM:** Type 2 Diabetes Mellitus; **HFpEF:** Heart Failure with Preserved Ejection Fraction; **HFrEF:** Heart Failure with Reduced Ejection Fraction; **ACEi:** Angiotensin Converting Enzyme Inhibitors; **ARB:** Angiotensin Receptor Blockers; **ANP:** Atrial Natriuretic Peptide; **BNP:** Brain-type Natriuretic Peptide; **CNP:** C-type Natriuretic Peptide; **HTN:** Hypertension; **APP:** Aminopeptidase P; **NYHA:** New York Heart Association; **HHF:** Hospitalization for Heart Failure.

ETHICS APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analysed are included in this research article.

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Cite this article: Girish BS, Johns JM, Meghana CS, Srinivasan R. Effect of ARNI (Sacubitril/Valsartan) and SGLT2 Inhibitors (Dapagliflozin) either alone or in Combination on Heart Failure: An Exploration of Novelty. J Young Pharm. 2024;16(3):439-46.