Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2023**; 28(4): 81
https://doi.org/10.31083/j.fbl2804081

Original Research

Sodium-Glucose Cotransporter 2 Inhibitors First Strategy Improve Decongestion in Patients with Symptomatic Heart Failure and Reduced Ejection Fraction When Compared to Angiotensin Receptor Neprilysin Inhibitor First Strategy

Wei-Chieh Lee[1,2,3,*], Wei-Ting Chang[1,2], Chon-Seng Hong[2], Chia-Te Liao[2], Po-Sen Huang[2], Shen-Chung Huang[2], Chih-Hsien Lin[2], Chun-Yen Chiang[2], Zhih-Cherng Chen[2,3], Jhih-Yuan Shih[2,3,*]

[1]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, 70101 Tainan, Taiwan
[2]Division of Cardiology, Department of Internal Medicine, Chi Mei Medical Center, 71004 Tainan, Taiwan
[3]School of Medicine, College of Medicine, National Sun Yat-sen University, 80424 Kaohsiung, Taiwan
*Correspondence: leeweichieh@yahoo.com.tw (Wei-Chieh Lee); s841027@gmail.com (Jhih-Yuan Shih)
Academic Editor: Riccardo Nevola
Submitted: 14 February 2023 Revised: 14 April 2023 Accepted: 19 April 2023 Published: 27 April 2023

Abstract

Background: Angiotensin receptor neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) are emerging medical treatments for decompensated heart failure (HF) with reduced ejection fraction. In clinical practice, the combination of ARNI and SGLT2i cannot be administered owing to the poor hemodynamic status in patients with HF with reduced ejection fraction (HFrEF). This study aimed to compare different strategies of HF management for ARNI first or SGLT2i first in such a population. **Methods**: From January 2016 to December 2021, 165 patients were diagnosed with HFrEF and New York Heart Association functional class $\geq$II and already received optimal medical treatment. Ninety-five patients received the ARNI-first strategy, and 70 patients received the SGLT2i-first strategy according to the physician's choice. Age, sex, hemodynamic condition, etiologies of HF, comorbidities, serum creatinine, N-terminal pro-B-type natriuretic peptide (NT-ProBNP), echocardiographic parameters, and clinical outcomes were compared between the ARNI and SGLT2i-first strategy groups. **Results**: In the SGLT2i-first group, the median interval between the addition of the second medication was longer (ARNI-first vs. SGLT2i-first; 74 [49–100] days vs. 112 [86–138] days; $p = 0.044$). Improvement in left ventricular ejection fraction (LVEF), change in left atrial dimension, and change in left ventricular end-diastolic and end-systolic volume (LVESV) did not differ between the two groups. The incidence of HF hospitalization, cardiovascular mortality, and all-cause mortality did not differ between the two groups. A non-significant trend of lower NT-proBNP levels (ARNI-first vs. SGLT2i-first; 1383 [319–2507] pg/mL vs. 570 [206–1314] pg/mL; $p = 0.055$) and significantly higher discontinuation rate of diuretic agents (ARNI-first vs. SGLT2i- first; 6.8% vs. 17.5%; $p = 0.039$) were noted in the SGLT2i-first group. When early combination ($\leq$14D) compared to late combination ($>$14D), better positive remodeling of LVESV presented significantly in early combination subgroups. **Conclusions**: In patients with symptomatic HFrEF, SGLT2i-first strategy may provide a higher possibility of discontinuing diuretic agents than the ARNI-first strategy. Changes in LV performance, progression of renal function, and clinical outcomes did not differ between the two groups. Early combination ($\leq$14D) provided better LV remodeling.

Keywords: heart failure with reduced ejection fraction; angiotensin receptor neprilysin inhibitor; sacubitril/valsartan; sodium-glucose cotransporter 2 inhibitors; decongestion; early combination

1. Background

The prevalence of heart failure (HF) in East Asian countries ranges from 1.3 to 6.7% and increases due to an aging society [1]. Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists (MRAs) have been important treatment options for patients with symptomatic HF for a long time, and their combination could significantly decrease mortality [2]. Significant improvements have been made in the management of HF, based on strong evidence from landmark trials of angiotensin receptor neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) [3–5]. In the PARADIGM-HF study, ARNI reduced the risk of death and hospitalization for HF in patients with symptomatic HF and reduced ejection fraction (HFrEF) compared with enalapril [3]. SGLT2i work by blocking glucose reabsorption in the kidneys and lead to increased glucose excretion in the urine [6]. In addition to improving glycemic control, SGLT2i has been shown to have several cardiovascular benefits, especially improving HF outcomes [7]. In patients with HFrEF, the risk of worsening HF or death from cardiovascular causes was lower in those who received dapagliflozin or empagliflozin than in those who received a placebo, re-

Table 1. Baseline characteristics.

Variable	Group 1	Group 2	*p* value
	ARNI first	SGLT2i first	
Number	95	70	
The duration of adding another medication (Sacubitril/valsartan or SGLT2i) (Days)	74 (49–100)	112 (86–138)	0.044
Combination with one month	57 (60.0)	23 (32.9)	<0.001
General demographics			
Age (years)	60 ± 14.7	60 ± 11.6	0.992
Male sex (%)	71 (74.7)	47 (67.1)	0.300
Hemodynamic condition			
SBP (mmHg)	126.2 ± 24.0	126.7 ± 22.8	0.894
<100 mmHg	15 (15.8)	9 (12.9)	0.660
HR (beat/min)	88.5 ± 18.0	89.0 ± 15.9	0.860
Etiology of HF			0.700
Ischemic cardiomyopathy (%)	90 (94.7)	68 (97.1)	
Non-ischemic cardiomyopathy (%)	5 (5.3)	2 (2.9)	
Comorbidities			
Diabetes mellitus (%)	82 (86.3)	63 (90.0)	0.630
Hypertension (%)	70 (73.7)	48 (68.6)	0.490
Atrial fibrillation (%)	9 (9.5)	7 (10.0)	0.910
PAOD (%)	0 (0)	1 (1.4)	0.424
COPD (%)	5 (5.3)	3 (4.3)	0.773
CKD, stage ≥3 (%)	13 (13.7)	7 (10.0)	0.630
Valvular heart disease (%)	20 (21.1)	8 (11.4)	0.142
ICD (%)	7 (7.4)	3 (4.3)	0.520
CRT (%)	5 (5.3)	2 (2.9)	0.700
Laboratory data			
Creatinine (mg/dL)	1.22 ± 0.57	1.17 ± 0.49	0.586
eGFR (mL/min/1.73 m^2)	68.15 ± 26.86	67.76 ± 24.54	0.924
NT-proBNP (pg/mL)	3132 (2270–4289)	3530 (1510–5452)	0.997
Medication			
Mean dose of ARNI (mg)	199.5 ± 125.6	147.5 ± 102.7	0.005
≥200 mg/day (%)	60 (63.2)	37 (52.9)	0.203
SGLT2i			0.319
Empagliflozin (%)	46 (48.4)	36 (51.4)	
Dapagliflozin (%)	46 (48.4)	34 (48.6)	
Canagliflozin (%)	3 (3.2)	0 (0)	
β-blocker (%)	88 (92.6)	68 (97.1)	0.304
Ivabradine (%)	57 (60.0)	40 (57.1)	0.750
Spironolactone (%)	82 (86.3)	55 (78.6)	0.212

Data are expressed as mean ± standard deviation or median and interquartile range (if data were not normally distributed) or numbers (percentages). Student's *t*-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables.

Abbreviation: ARNI, angiotensin receptor neprilysin inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SBP, systolic blood pressure; HR, heart rate; HF, heart failure; PAOD, peripheral arterial occlusive disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

gardless of the presence or absence of diabetes [4,5]. Although great results were observed for the HFrEF of Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trials, the combination of ARNI and SGLT2i was approximately 11% and 20% in the DAPA-HF, and EMPEROR-Reduced trials, respectively [4,5]. Therefore, data and experience of the combination of ARNI and SGLT2i were limited in randomized

control trials. Owing to the advancement of HF management, novel four pillar-directed medical therapies including β-blockers, MRAs, ARNI, and SGLT2i, achieved treatment with all four foundational treatments within 4 weeks [8]. If we follow a deliberate slow titration traditional approach, many patients with HFrEF will experience disease progression and HF hospitalization and mortality. In clinical practice, patients with symptomatic HFrEF who present with poor hemodynamic conditions and borderline-to-low systolic blood pressure can be challenging to manage with medication as they are at risk for worsening their hemodynamic status. The combination of the four foundational treatments for patients with symptomatic HFrEF may be difficult to perform in the initial phase of clinical practice. Sequencing of ARNI or SGLT2i may need greater emphasis.

Accordingly, we conducted a retrospective study to compare the sequencing effects of ARNI and SGLT2i on the clinical outcomes over a 12-month follow-up period in patients with symptomatic HFrEF.

2. Methods

2.1 Patient Population

Between January 2016 and December 2021, the HF registry of Chi Mei Medical Center enrolled 165 patients who had symptomatic HFrEF and New York Heart Association (NYHA) functional class $\geq$II, and were receiving a sequential combination of ARNI and SGLT2i for HF management. Participants who lacked baseline and follow-up laboratory data, follow-up echocardiographic parameters, regular follow-up, or used ARNI or SGLT2i for less than one month were excluded from the study. Ninety-five and 70 patients received the ARNI-first and SGLT2i-first strategies, respectively, by physician's choice. Data on general demographics, baseline hemodynamic condition, etiologies of HF, comorbidities, baseline and follow-up serum creatinine, follow-up N-terminal pro-B-type natriuretic peptide (NT-ProBNP), echocardiographic parameters, and clinical outcomes were compared between the ARNI and SGLT2i-first strategy groups. Echocardiographic examination was recommended every 3–6 months for patients with HFrEF. Baseline serum creatinine levels were based on data obtained within 1 month before using ARNI or SGLT2i.

2.2 Echocardiography

Echocardiographic parameters, including left ventricular ejection fraction (LVEF), left atrial dimension (LAD), and left ventricular end-systolic and end-diastolic volume (LVESV and LVEDV), were measured using GE Vivid 9 (GE Healthcare Chicago, IL, USA), or Philips IE33, or Philips EPIQ 7 (Philips Healthcare, Amsterdam, Netherlands). LVEF, LAD, LVESV, and LVEDV were quantified using the M mode and corrected using the two-dimensional guided biplane Simpson's method of disc measurements by using echocardiography. Echocardiographic examination was recommended every 3–6 months for patients with HFrEF thereafter in the absence of clinical events and the onset of HF.

2.3 Definition

Symptomatic HFrEF was defined as left ventricular ejection fraction $<$40% and experienced symptoms of HF such as shortness of breath, swollen ankles, and fatigue, as well as signs of HF including increased jugular venous pressure, crackling sounds in the lungs, and swelling in the extremities [9]. HF hospitalization was defined as the occurrence of HF events of NYHA functional classes II–IV in the absence of other alternative diagnoses. Symptoms of HF were defined as the need for medical treatment with NYHA functional class II–IV symptoms. Cardiovascular (CV) mortality was defined as sudden death related to arrhythmias, HF, and myocardial infarction. All-cause mortality was defined as death due to any cause.

2.4 Study Endpoint

The study endpoints were hospitalization for HF, CV mortality, and all-cause mortality during one-year follow-up period.

2.5 Statistical Analyses

Data were presented as the mean $\pm$ standard deviation, median and interquartile range, or numbers (percentages). Median with the interquartile range presented if data were not normally distributed. The clinical characteristics of the two groups were compared using Student's *t*-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Statistical significance was defined as $p < 0.05$. All analyses were performed using statistical software (SPSS for Windows, Version 22, IBM Corp., Armonk, NY, USA).

3. Results

3.1 Baseline Characteristics and Demographics between the ARNI and SGLT2i-First Groups

In the ARNI-first group, the mean age was 60 $\pm$ 14.7 years, and the prevalence in men was 74.7%. In the SGLT2i-first group, the mean age was 60 $\pm$ 11.6 years, and the prevalence in men was 67.1% (Table 1). A shorter interval of combination with another medication was noted in the ARNI-first group (ARNI-first vs. SGLT2i-first; 74 [49–100] days vs. 112 [86–138]; $p = 0.044$). A higher prevalence of adding another medication within 1 month was noted in the ARNI-first group (ARNI-first vs. SGLT2i-first; 60.0% vs. 32.9%; $p < 0.001$). The average age and prevalence in men did not differ between the two groups. Hemodynamic conditions (systolic blood pressure and heart rate), etiologies of HF, comorbidities, baseline renal function, and NT-proBNP, and medication were not significantly different between the two groups. A higher mean dose of ARNI presented in the ARNI-first group (ARNI-

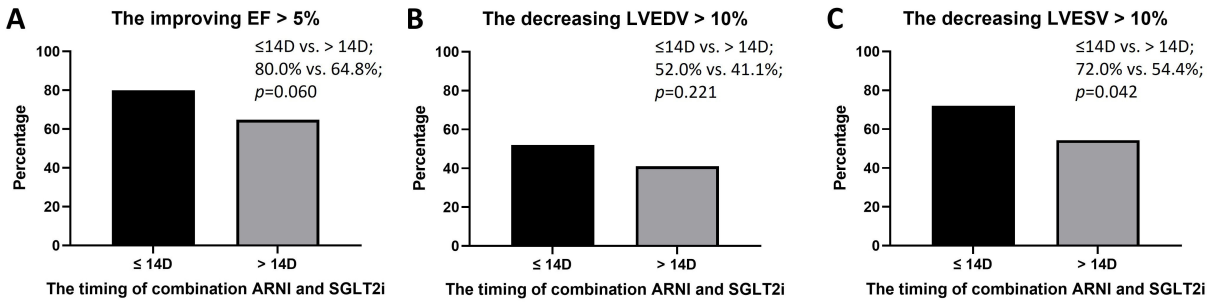

Fig. 1. The improving ejection fraction, decreasing left ventricular end-diastolic volume, and decreasing left ventricular end-systolic volume when early combination (≤14D) compared to late combination (>14D). (A) A non-significant trend of improving ejection fraction >5% presented when early combination (≤14D) compared to late combination (>14D) (≤14D vs. >14D; 80.0% vs. 64.8%; $p = 0.060$). (B) The decreasing left ventricular end-diastolic volume >10% did not differ between early combination (≤14D) and late combination (>14D) groups (≤14D vs. >14D; 52.0% vs. 41.1%; $p = 0.221$). (C) The decreasing left ventricular end-systolic volume >10% showed significant higher when early combination (≤14D) compared to late combination (>14D) group (≤14D vs. >14D; 72.0% vs. 54.4%; $p = 0.042$). Abbreviation: EF, ejection fraction; LVEDV, left ventricular end-systolic volume; LVESV, left ventricular end-systolic volume; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; D, day.

first vs. SGLT2i-first; 199.5 ± 125.6 mg vs. 147.5 ± 102.7 mg; $p = 0.005$).

3.2 Baseline and Follow-Up Echocardiographic Parameters between the ARNI and SGLT2i-First Groups

The baseline and follow-up left ventricular performances are listed in Table 2. At the baseline phase, the mean LVEF, LAD, LVESV, LVEDV, E/A, mitral E/E', lateral E/E', and RV S' did not differ between the two groups. A numerically higher prevalence of mitral regurgitation ≥III was noted in the ARNI-first group. In the follow-up phase, the mean LVEF, LAD, LVESV, LVEDV, E/A, mitral E/E', lateral E/E', and RV S' did not differ between the two groups. There was no significant difference in the change in LVEF, LAD, LVESV, and LVEDV between the ARNI-first group and SGLT2i-first groups.

3.3 Clinical Outcomes between the ARNI and SGLT2i-First Groups

The incidence of HF hospitalization, CV mortality, and all-cause mortality were higher in the ARNI-first group; however, they did not achieve a significant difference when the ARNI-first group was compared with the SGLT2i-first group (Table 3).

3.4 The Follow-Up of Renal Function and NT-proBNP between the ARNI and SGLT2i-First Groups

Follow-up serum creatinine levels and estimated glomerular filtration rate (eGFR) did not differ between the two groups (Table 4). The decrease in eGFR was not significantly higher in the SGLT2i-first group. A non-significant trend of lower NT-proBNP levels was noted in the SGLT2i-first group (ARNI-first vs. SGLT2i-first; 1383 [319–2507] pg/mL vs. 570 [206–1314] pg/mL; $p = 0.055$). A significantly higher discontinuation rate of diuretic agents was noted in the SGLT2i-first group (ARNI-first vs. SGLT2i-first; 6.8% vs. 17.5%; $p = 0.039$).

3.5 The Improving EF, Decreasing LVEDV, and Decreasing LVESV when Early Combination (≤14D) Compared to Late Combination (>14D)

Fig. 1A showed non-significant trend of improving EF >5% when early combination (≤14D) compared to late combination (>14D) (≤14D vs. >14D; 80.0% vs. 64.8%; $p = 0.060$). The decreasing LVEDV > 10% did not differ between ≤14D and >14D groups (Fig. 1B), but the decreasing LVESV >10% showed significant higher in the early combination (≤14D) group (≤14D vs. >14D; 72.0% vs. 54.4%; $p = 0.042$) (Fig. 1C).

4. Discussion

In clinical practice, the sequence of new emerging medications remains a difficult decision for physicians, especially in patients with HFrEF and poor hemodynamic conditions. Most patients with HFrEF also present with cardiorenal syndrome and may not receive all four pillar-directed medical therapies at the same time. According to the guidelines of the European Society of Cardiology, the triad of an ACEIs/ARNI, a β-blocker, and an MRA is recommended as cornerstone therapy, and SGLT2i are recommended for all patients with HFrEF already treated with the above medications [9]. In contrast, the American College of Cardiology/American Heart Association HF Guidelines recommend ACEI/ARB/ARNI, a β-blocker, MRA, and SGLT2i as first-line therapy for patients with symptomatic HFrEF [10]. Currently, ARNI and SGLT2i sequences are not recommended. In our study, reverse LV remodeling and renal function progression did not differ between the two groups, but better LV remodeling presented

Table 2. Baseline and follow-up echocardiographic parameters.

Variable	Group 1	Group 2	*p* value
	ARNI first	SGLT2i first	
Number	95	70	
Left ventricular performance (Baseline)			
Mean LVEF (%)	34.37 ± 12.22	35.73 ± 11.94	0.481
Mean LAD (cm)	4.4 ± 0.9	4.3 ± 0.7	0.534
Mean LVEDV (mL)	190.05 ± 66.19	180.66 ± 65.66	0.376
Mean LVESV (mL)	127.41 ± 52.67	117.01 ± 54.23	0.226
AR grade ≥III	3 (3.2)	1 (1.4)	0.638
MR grade ≥III	16 (16.8)	5 (7.1)	0.097
TR grade ≥III	10 (10.5)	3 (4.3)	0.241
TRPG (mmHg)	34.5 ± 15.8	28.2 ± 11.9	0.077
E/A	1.61 ± 1.01	1.79 ± 1.15	0.473
Mitral E/E'	20.15 ± 7.62	18.82 ± 8.84	0.439
Lateral E/E'	13.65 ± 5.89	12.91 ± 5.21	0.530
RV S'	10.15 ± 2.77	10.36 ± 2.61	0.731
Left ventricular performance (Follow-up)			
Mean LVEF (%)	47.91 ± 16.52	50.89 ± 14.56	0.618
Improving EF ≥40% (%)	51 (63.7)	41 (63.1)	0.933
Mean LAD (cm)	4.1 ± 0.8	4.1 ± 0.8	0.688
Mean LVEDV (mL)	176.53 ± 65.02	161.11 ± 56.46	0.134
Mean LVESV (mL)	97.36 ± 59.18	89.50 ± 52.97	0.406
AR grade ≥III	4 (4.2)	0 (0)	0.138
MR grade ≥III	7 (7.4)	2 (2.9)	0.304
TR grade ≥III	3 (3.2)	1 (1.4)	0.638
TRPG (mmHg)	27.44 ± 18.74	23.41 ± 10.19	0.412
E/A	0.94 ± 0.49	1.17 ± 1.10	0.186
Mitral E/E'	14.73 ± 6.58	14.13 ± 7.77	0.702
Lateral E/E'	11.82 ± 7.84	10.75 ± 4.37	0.458
RV S'	11.27 ± 2.91	11.38 ± 2.81	0.868
The change of LVEF (%)	10.90 (5.26 to 19.04)	11.85 (5.46 to 16.19)	0.358
Improving EF >5% (%)	55 (71.4)	44 (68.8)	0.853
The change of LAD (cm)	–0.3 (–0.6 to –0.1)	–0.2 (–0.5 to 0.1)	0.461
The change of LVEDV (mL)	–12.00 (–22.00 to 4.57)	–11.47 (–35.00 to 5.97)	0.723
Decreasing LVEDV >10% (%)	35 (45.5)	28 (44.4)	0.905
The change of LVESV (mL)	–25.20 (–46.48 to –1.89)	–25.90 (–35.50 to –10.95)	0.943
Decreasing LVESV >10% (%)	43 (55.8)	42 (66.7)	0.225

Data are expressed as mean ± standard deviation or median and interquartile range (if data were not normally distributed) or numbers (percentages). Student's *t*-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables.

Abbreviation: ARNI, angiotensin receptor neprilysin inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient; RV, right ventricle.

in early combination (≤14D) subgroups. However, a non-significant trend of lower NT-proBNP levels and a higher percentage of discontinuing diuretic agents were observed in the SGLT2i-first group. It is reasonable to accept better symptomatic control and decongestion if SGLT2i is used first for symptomatic patients with HFrEF.

4.1 The Progression of Renal Function in HFrEF

In patients with HFrEF, several factors may affect renal function, including cardiac pump failure related to lower blood supply and increased congestion, chronic activation of the adrenergic system and renin-angiotensin-aldosterone system (RAAS), and direct and indirect effects of anti-HF medication [11,12]. Approximately 30% of the patients with HF also have chronic kidney disease, and worsening renal function occurs in approximately 25% of the cases, with a deleterious effect on outcomes [13]. Additionally, renal function may also be affected by age, and comorbidities, including atherosclerosis, diabetes mellitus, hypertension, and renal dysfunction, are associated with poor out-

Table 3. Clinical outcomes during one-year follow-up period.

Variable	Group 1	Group 2	*p* value
	ARNI first	SGLT2i first	
Number	95	70	
HF hospitalization (%)	21 (22.1)	11 (15.7)	0.327
CV mortality (%)	3 (3.2)	1 (1.4)	0.638
All-cause mortality (%)	7 (7.4)	3 (4.3)	0.520

Data are expressed as mean ± standard deviation or median and interquartile range (if data were not normally distributed) or numbers (percentages). Chi-square test for categorical variables.

Abbreviation: ARNI, angiotensin receptor neprilysin inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; HF, heart failure; CV, cardiovascular.

Table 4. The follow-up of renal function and NT-proBNP.

Variable	Group 1	Group 2	*p* value
	ARNI first	SGLT2i first	
Number	95	70	
Creatinine (mg/dL)	1.22 ± 0.53	1.25 ± 0.61	0.748
eGFR (mL/min/1.73 m^2)	66.42 ± 25.69	64.10 ± 22.58	0.604
The change of eGFR	–1.63 ± 17.24	–3.47 ± 16.18	0.551
NT-proBNP (pg/mL)	1383 (319–2507)	570 (206–1314)	0.055
Discontinue diuretic (%)	6 (6.8)	11 (17.5)	0.039

Data are expressed as mean ± standard deviation or median and interquartile range (if data were not normally distributed) or numbers (percentages). Student's *t*-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables.

Abbreviation: NT-proBNP, N-terminal pro-B-type natriuretic peptide; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; eGFR, estimated glomerular filtration rate.

comes [14]. Acute worsening renal function after starting RAAS inhibitors occurs in approximately 13% of the patients with HF, more so in the older hypertensive patients, following exposure to iodinated contrast, during acute illness, heart failure exacerbation, hypotension, and dehydration [15–17]. According to recent studies on SGLT2i for HF, a lower risk of kidney failure and slower progression of renal function were observed when the SGLT2i group was compared with the control group [18,19]. In our study, no patients needed emerge hemodialysis and experienced renal death. The progression of renal function did not differ between ARNI and SGLT2i-first strategy groups. Therefore, sequential combination of ARNI and SGLT2i may be feasible for the patients with symptomatic HFrEF.

4.2 Lower Blood Pressure in the Patients with HFrEF

Among the patients with HFrEF, a low proportion of patients received the target dose (or received at least 50% of the target dose), partly due to hypotension [20]. In the PIONEER-HF study, ARNI could safely be initiated in patients with SBP >100 mmHg for 6 hours, without using vasodilators or increasing the dose of intravenous diuretics in the preceding 6 hours, and no use of inotropes in the preceding 24 hours [21]. When the SBP is 100–120 mmHg, ARNI should be initiated at a low dose to prevent hypotension [20]. SGLT2i does exhibit a modest blood pressure lowering effect and approximately 1–4 mmHg in patients with HF, and the volume status of such a population on diuretics should be reevaluated owing to the risk of over-diuresis and hypotension [22]. The risk of hypotension and acute worsening of renal function may allow physicians to choose one medication first. The expert also suggested that SGLT2i could be initiated on at a minimum dose of RAAS inhibitors and β-blockers without systemic hypotension [20]. In our study, a higher prevalence of discontinuing diuretic agents and trend toward lower serum NT-proBNP levels were observed in patients with HFrEF and SGLT2i-first strategies. Better effect of decongestion was expected in the SGLT2i-first group. The mechanisms of improving decongestion of SGLT2i are related to reduction of interstitial fluid volume, natriuresis and osmotic diuresis, and neurohumoral and inflammation attenuation [23].

4.3 The Combination of ARNI and SGLT2i for HFrEF

In a retrospective study of diabetic patients with HFrEF, those with the initiation of sacubitril/valsartan pre-

sented a more prominent improvement in LV performance than those with the initiation of SGLT2i, and the combination of ARNI and SGT2i showed significant improvement in cardiac function and prognosis in this population [24]. Another real-world study also found that treatment with a combination of SGLT2i and ARNI was associated with a lower risk of composite HF hospitalization or all-cause mortality and was well tolerated [25]. The subgroups with SGLT2i presented better results than those without SGLT2i [26]. A meta-analysis concluded that SGLT2i and ARNI demonstrated similar effects (indirect comparison hazard ratio 0.93, 95% confidence interval 0.82–1.06, p-value = 0.28), while the combination of SGLT2i and ARNI resulted in a better cardiovascular protective effect [25]. In our study, the sequence of ARNI and SGLT2i did not affect reverse LV remodeling and renal function progression and did not present with acute kidney injury. The SGLT2i-first strategy may provide better decongestion. Early combination may provide better LV remodeling effect.

4.4 Study Limitations

This study had several limitations. First, it was a retrospective, nonrandomized study with limited size, and we could not rule out selective bias. Second, the timing of adding another medication based on the judgement of physicians and a shorter interval was noted in the ARNI-first group. Third, echocardiographic examination was performed every 3–6 months for patients with HFrEF if no new events. However, we still provide important information for clinical practice regarding the sequence of ARNI and SGLT2i implementation in patients with symptomatic HFrEF.

5. Conclusions

In patients with symptomatic HFrEF, SGLT2i-first strategy may provide a higher possibility of discontinuing diuretic agents than the ARNI-first strategy. Changes in LV performance, progression of renal function, and clinical outcomes did not differ between the two groups. Early combination ($\leq$14D) provided better LV remodeling.

Availability of Data and Materials

The study data are available from the corresponding author upon reasonable request.

Author Contributions

W-CL did data curation, formal analysis, investigation, and methodology. Z-CC critically reviewed the study proposal. W-TC, C-SH, C-TL, P-SH, S-CH, C-HL, C-YC, and Z-CC participated in the interpretation of data. W-CL wrote original draft. J-YS participated in writing and technical editing of final manuscript and also contributed conception as well as the design of the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This retrospective study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved for human research by the Institutional Review Committee of the Chi Mei Medical Center (Number: 11104-008).

Acknowledgment

The authors thank Chi Mei research team for data collection for this study.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. European Journal of Heart Failure. 2015; 17: 884–892.

[2] Ouwerkerk W, Teng TK, Tromp J, Tay WT, Cleland JG, van Veldhuisen DJ, *et al*. Effects of combined renin-angiotensin-aldosterone system inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction: insights from BIOSTAT-CHF and ASIAN-HF registries. European Journal of Heart Failure. 2020; 22: 1472–1482.

[3] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al*. Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England Journal of Medicine. 2014; 371: 993–1004.

[4] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2019; 381: 1995–2008.

[5] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al*. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England Journal of Medicine. 2020; 383: 1413–1424.

[6] Novikov A, Vallon V. Sodium glucose cotransporter 2 inhibition in the diabetic kidney: an update. Current Opinion in Nephrology and Hypertension. 2016; 25: 50–58.

[7] Tsampasian V, Baral R, Chattopadhyay R, Debski M, Joshi SS, Reinhold J, *et al*. The Role of SGLT2 Inhibitors in Heart Failure: A Systematic Review and Meta-Analysis. Cardiology Research and Practice. 2021; 2021: 9927533.

[8] McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. Circulation. 2021; 143: 875–877.

[9] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726.

[10] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA Guideline for the

Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895–e1032.
[11] Damman K, Testani JM. The kidney in heart failure: an update. European Heart Journal. 2015; 36: 1437–1444.
[12] Mewton N, Girerd N, Boffa JJ, Courivaud C, Isnard R, Juillard L, *et al*. Practical management of worsening renal function in outpatients with heart failure and reduced ejection fraction: Statement from a panel of multidisciplinary experts and the Heart Failure Working Group of the French Society of Cardiology. Archives of Cardiovascular Diseases. 2020; 113: 660–670.
[13] Damman K, Tang WHW, Testani JM, McMurray JJV. Terminology and definition of changes renal function in heart failure. European Heart Journal. 2014; 35: 3413–3416.
[14] Ruocco G, Palazzuoli A, Ter Maaten JM. The role of the kidney in acute and chronic heart failure. Heart Failure Reviews. 2020; 25: 107–118.
[15] Onuigbo MAC, Onuigbo NTC. Late onset renal failure from angiotensin blockade (LORFFAB): a prospective thirty-month Mayo Health System clinic experience. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2005; 11: CR462–CR469.
[16] Onuigbo MAC, Onuigbo NTC. Late-onset renal failure from angiotensin blockade (LORFFAB) in 100 CKD patients. International Urology and Nephrology. 2008; 40: 233–239.
[17] Beldhuis IE, Streng KW, Ter Maaten JM, Voors AA, van der Meer P, Rossignol P, *et al*. Renin-Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction: A Meta-Analysis of Published Study Data. Circulation. Heart Failure. 2017; 10: e003588.
[18] Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, *et al*. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation. 2021; 143: 298–309.
[19] Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, *et al*. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation. 2021; 143: 337–349.
[20] Yamaguchi T, Kitai T, Miyamoto T, Kagiyama N, Okumura T, Kida K, *et al*. Effect of Optimizing Guideline-Directed Medical Therapy Before Discharge on Mortality and Heart Failure Readmission in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction. The American Journal of Cardiology. 2018; 121: 969–974.
[21] Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, *et al*. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. The New England Journal of Medicine. 2019; 380: 539–548.
[22] Honigberg MC, Vardeny O, Vaduganathan M. Practical Considerations for the Use of Sodium-Glucose Co-Transporter 2 Inhibitors in Heart Failure. Circulation. Heart Failure. 2020; 13: e006623.
[23] Hernandez M, Sullivan RD, McCune ME, Reed GL, Gladysheva IP. Sodium-Glucose Cotransporter-2 Inhibitors Improve Heart Failure with Reduced Ejection Fraction Outcomes by Reducing Edema and Congestion. Diagnostics. 2022; 12: 989.
[24] Kim HM, Hwang IC, Choi W, Yoon YE, Cho GY. Combined effects of ARNI and SGLT2 inhibitors in diabetic patients with heart failure with reduced ejection fraction. Scientific Reports. 2021; 11: 22342.
[25] Yan Y, Liu B, Du J, Wang J, Jing X, Liu Y, *et al*. SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta-analysis. ESC Heart Failure. 2021; 8: 2210–2219.
[26] Hsiao FC, Lin CP, Tung YC, Chang PC, McMurray JJV, Chu PH. 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. 2021; 330: 91–97.