

Combination of ivabradine and sacubitril/valsartan in patients with heart failure and reduced ejection fraction

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Abstract

Aims Ivabradine and sacubitril/valsartan are second-line therapies for patients with heart failure and reduced ejection fraction (HFrEF) based on guideline recommendations. We aimed to evaluate the synergistic effects of these two medications.

Methods and results Patients' data were extracted from a multicentre database between 2016 and 2018. Patients were classified into (1) Simultaneous group: simultaneous prescription of ivabradine and sacubitril/valsartan within 6 weeks; (2A) Sequential group, ivabradine-first: ivabradine was prescribed first, followed by sacubitril/valsartan; and (2B) Sequential group, sacubitril/valsartan-first: sacubitril/valsartan was prescribed first, followed by ivabradine. A total of 464 patients with HFrEF were enrolled. Cardiovascular death and/or unplanned re-hospitalizations for HF were less frequent (28.6% vs. 44.8%, $P = 0.01$), and the improvement of left ventricular ejection fraction (LVEF) was significantly greater in patients from the Simultaneous group than those from the Sequential group (Δ LVEF $12.8 \pm 12.9\%$ vs. $9.3 \pm 12.6\%$, $P = 0.007$). Among Sequential subgroups, the ivabradine-first treatment decreased heart rate and increased systolic blood pressure (SBP) compared with sacubitril/valsartan-first treatment (Δ heart rate -9.1 ± 12.9 b.p.m. vs. 2.6 ± 16.0 b.p.m., $P < 0.001$; Δ SBP 4.6 ± 16.5 mmHg vs. -4.8 ± 17.2 mmHg, $P < 0.001$), whereas sacubitril/valsartan-first treatment showed a higher degree of LVEF improvement (Δ LVEF $3.6 \pm 7.8\%$ vs. $0.7 \pm 7.7\%$, $P = 0.002$) than ivabradine-first treatment. At the end of follow-up, SBP, LVEF, and left ventricular volume were comparable between two Sequential subgroups.

Conclusions Among patients with HFrEF, simultaneous rather than sequential treatment with sacubitril/valsartan and ivabradine was a better strategy to reduce adverse events and achieve left ventricular reverse remodelling. Ivabradine treatment had a more significant benefit on improving haemodynamic stability, whereas sacubitril/valsartan treatment showed a more significant effect on improving LVEF.

Keywords Heart failure; Sacubitril/valsartan; Ivabradine

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Introduction

Heart failure (HF) is a disease that consumes significant healthcare resources. It inflicts high morbidity and mortality and has a tremendous adverse impact on the quality of life.¹ Several novel HF medications had been developed in the past few years, and there was increasing importance to draw up treatment strategy in the era ahead for HF personalized medicine.²

Sacubitril/valsartan (Sac/Val) and ivabradine are considered as second-line therapies according to the ESC HF Guideline: Sac/Val is recommended to replace angiotensin-converting enzyme inhibitors (ACEIs) in ambulatory HF and reduced ejection fraction (HFrEF) patients who remain symptomatic despite optimal therapy, whereas ivabradine should be considered in symptomatic patients with left ventricular ejection fraction (LVEF) $\leq 35\%$, in sinus rhythm and with a heart rate ≥ 70 b.p.m. despite optimal treatment with a beta-blocker, a renin-angiotensin system inhibitor, and an MRA.³ These recommendations were generated based on randomized controlled trials, which separately tested the efficacies of different drugs. Incremental benefits on mortality and hospitalizations were shown in the network meta-analysis, suggesting the synergistic effects of drugs with different action mechanisms.⁴ Nevertheless, the interplay between Sac/Val and ivabradine is still not clarified since Sac/Val was not available when the SHIFT trial was conducted, and the prescription rate of ivabradine in the PARADIGM-HF study was only 2%.^{5,6}

From the view of left ventricular systolic function, Sac/Val was found to improve cardiac remodelling and attenuate cardiomyocyte cell death by inhibiting PTEN and members of the guanine nucleotide-binding protein family.⁷ Animal studies suggested that ivabradine might be associated with reducing fibrosis, improving endothelial function as well as sarcoplasmic reticulum calcium overload. Moreover, ivabradine's reverse cardiac remodelling had been linked to a decrease in heart rate, improvement in the ventricular arterial coupling, and unloading of the heart.^{8–10} From the view of haemodynamics, heart rate lowering with ivabradine had been associated with an increase of 11 mmHg indirectly measured central systolic pressure in patients with stable coronary artery disease.¹¹ In patients with HF, the increase in central pressure following ivabradine treatment might counteract the pressure-lowering effect of Sac/Val.¹² However, there was scarce data regarding the sequentially or simultaneously synergistic activities of these two drugs in managing patients with HFrEF. We aimed to evaluate these two medications' prescription patterns and effects from a large-scale multicentre HF study in Taiwan.

Methods

Study designs

The present study extracted and analysed data retrospectively from a multicentre HF cohort in Taiwan, which enrolled 1835 patients with symptomatic HF and reduced ejection fraction (HFrEF) from 10 hospitals between 2016 and 2018. The protocol of this HF cohort consisted of 50 variables per patient, comprising age, sex, HF aetiologies, systolic blood pressure, heart rate, New York Heart Association functional class, left ventricular ejection fraction (LVEF), body mass index, estimated glomerular filtration rate (eGFR), co-morbidities, drug therapy, laboratory data and use of cardiac devices. The definition of HFrEF patient is that patient with New York Heart Association class II, III, or IV HF symptoms and with LVEF of 40% or less. The study complied with the Declaration of Helsinki's ethical principles and was approved by the institutional ethics committee of each hospital. No informed consent was obtained because of the retrospective study design.

Inclusion and exclusion criteria

The inclusion criteria for the current study were (i) male or female symptomatic patients with HFrEF, age more than 20 years old; (ii) between 2016 and 2018, patients were treated with both ivabradine and Sac/Val, and their treatment durations should overlap at least 6 months; patients received standard HF treatment including renin angiotensin system inhibitor and beta-blocker unless contraindicated or not tolerated before ivabradine and Sac/Val treatment; patients were in sinus rhythm with resting heart rate 70 b.p.m. or higher before ivabradine treatment. The exclusion criteria for the current study included patients refused medical advice or lost to follow up; non-sinus rhythm (atrial pacing, atrial fibrillation, or atrial flutter) or sinus rhythm with resting heart rate less than 70 b.p.m. before ivabradine treatment. The utilizations of Sac/Val and ivabradine were based on physicians' clinical decisions, and there were no blood pressure or renal function limitations for these medications.

After implying inclusion and exclusion criteria, a total of 464 patients with HFrEF were included in this study. Patients were classified by the prescribing patterns of Sac/Val and ivabradine: Group 1: Sac/Val and ivabradine were prescribed simultaneously or within 6 weeks (Simultaneous group), and Group 2: Sac/Val and ivabradine were prescribed sequentially (Sequential group, the time interval between Sac/Val and ivabradine initiation should be more than 6 weeks). Group 2 was further divided into two subgroups: Group 2A,

ivabradine was prescribed earlier, followed by Sac/Val (Sequential group: ivabradine-first), and Group 2B, Sac/Val were prescribed earlier, followed by the prescription of ivabradine (Sequential group: Sac/Val-first). The flowchart of the current study was shown in *Figure 1*.

Patient characteristics and echocardiographic parameters

Baseline characteristics were collected at the index date before the initiation of Sac/Val and/or ivabradine. Vital signs were collected at index date, before initiating the second drug (ivabradine for Sequential group: Sac/Val-first and Sac/Val for Sequential group: ivabradine-first), and at 8 ± 2 months following treatment of both medications. Transthoracic echocardiographic studies were performed at baseline, before the initiation of Sac/Val and ivabradine, and at 8 ± 2 months following treatment of both medications by trained ultrasonographers blinded to patients' clinical data and medications. Left atrial (LA) anteroposterior diameter was measured at end-systole on parasternal views. Left ventricular end-diastolic volume index (LVEDVi), left ventricular end-systolic volume index (LVESVi), and LVEF was calculated

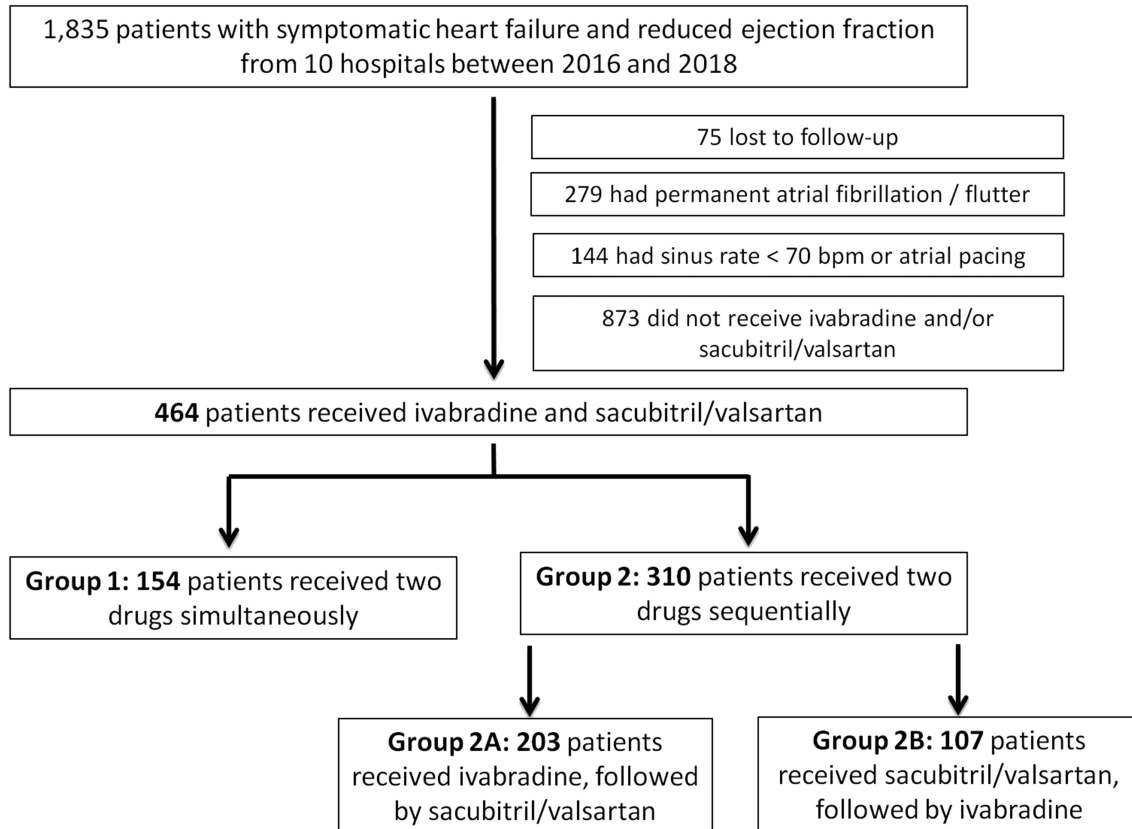
using the biplane Simpson's method on apical four-chamber and two-chamber views as recommended by the American Society of Echocardiography and the Taiwan Society of Cardiology Guidelines for Heart Failure.^{13,14} Continuous-wave Doppler of the tricuspid regurgitation trace is used to measure and estimate pulmonary artery systolic pressure (PASP).

Statistical analysis

The continuous variables were expressed as the mean value \pm standard deviation; categorical variables were reported as percentages. Descriptive summaries were presented for all patients and for subgroups of patients. Differences in baseline characteristics and clinical parameters were tested using the χ^2 test for categorical variables, and Student's *t*-test or the Wilcoxon rank-sum test was used for the comparisons between the continuous data.

Deaths from cardiovascular causes and re-hospitalization for HF events in different groups were estimated by the Kaplan–Meier method and compared using the log-rank test. The cumulative events were collected from (i) the initiation of the first HF medication (Sac/Val or ivabradine, which was initiated earlier), and (ii) from the date when both Sac/Val

Figure 1 The flowchart of the current study.



and ivabradine were prescribed. A *P*-value of <0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM SPSS, IBM Corp, Armonk, NY, USA).

Results

Baseline characteristics

A total of 464 patients with HFREF (age 59.0 ± 14.9 years old, 75.6% male, mean LVEF 28.7 ± 8.3%) were included in this study, including 154 patients initiated ivabradine and Sac/Val treatment at the same time or within 6 weeks (Group 1, Simultaneous group, the median period between ivabradine

and Sac/Val prescriptions was 5 [IQR 0–6] days) and 310 patients received these two medications sequentially (Group 2, Sequential group, the median period between ivabradine and Sac/Val prescriptions was 217 [IQR 98–416] days). The baseline characteristics of these two groups were shown in the left column of *Table 1*. Generally, patients in both groups were similar in baseline characteristics. Although the likelihood of hypertension was significantly higher in patients from the Simultaneous group than those from the Sequential group (59.7% vs. 46.8%, *P* = 0.009), baseline systolic blood pressures were not different between the two groups.

Among Group 2 patients, 203 patients received ivabradine treatment earlier, followed by Sac/Val treatment (Group 2A, Sequential group: ivabradine-first), and 107 patients received Sac/Val treatment earlier, followed by ivabradine treatment

Table 1 Baseline characteristics of study patients

	Group 1 (Simultaneous) N = 154	Group 2 (Sequential) N = 310	<i>P</i> -value	Group 2A (IVA > Sac/Val) N = 203	Group 2B (Sac/Val > IVA) N = 107	<i>P</i> -value
Age (years)	59.0 ± 15.6	59.0 ± 14.7	0.991	59.0 ± 15.0	59.0 ± 14.0	0.977
Male gender, <i>n</i> (%)	114 (74.0)	237 (76.5)	0.566	159 (78.3)	78 (72.9)	0.284
Body mass index (kg/m ²)	25.9 ± 5.2	26.0 ± 5.5	0.845	26.2 ± 5.7	25.7 ± 5.1	0.542
eGFR (mL/min/1.73 m ²)	62.4 ± 29.7	69.5 ± 46.1	0.086	71.0 ± 52.9	66.5 ± 29.2	0.413
Median NT-proBNP, pg/mL (IQR)	1817 (1031–2412)	1622 (934–2489)	0.580	1677 (944–2476)	1376 (899–2527)	0.477
LVEF (%)	28.5 ± 8.7	28.7 ± 8.1	0.778	28.3 ± 7.6	29.6 ± 9.0	0.153
LVEDVi (mL/m ²)	109.3 ± 36.7	112.0 ± 36.6	0.455	111.5 ± 34.9	113.0 ± 40.0	0.734
LVESVi (mL/m ²)	79.4 ± 33.1	81.1 ± 31.4	0.599	81.2 ± 30.1	80.9 ± 33.8	0.925
LA diameter (mm)	42.6 ± 8.7	44.0 ± 10.9	0.186	43.6 ± 9.5	44.8 ± 13.0	0.368
PASP (mmHg)	39.8 ± 16.3	37.5 ± 14.2	0.160	38.6 ± 14.9	35.6 ± 12.5	0.084
Systolic BP (mmHg)	122.1 ± 22.2	119.1 ± 19.2	0.156	117.5 ± 19.1	122.1 ± 19.1	0.012
Heart rate (b.p.m.)	88.3 ± 17.6	88.0 ± 15.3	0.834	90.2 ± 14.1	83.8 ± 16.5	<0.001
Ischaemic cardiomyopathy, <i>n</i> (%)	66 (42.9)	131 (42.3)	0.902	89 (43.8)	42 (39.3)	0.437
Co-morbidities, <i>n</i> (%)						
Diabetes mellitus	74 (48.1)	140 (45.2)	0.556	92 (45.3)	48 (44.9)	0.938
Hypertension	92 (59.7)	145 (46.8)	0.009	96 (47.3)	49 (45.8)	0.802
Prior myocardial infarction	40 (26.0)	104 (33.5)	0.097	69 (34.0)	35 (32.7)	0.821
Coronary artery disease	76 (49.4)	152 (49.0)	0.948	104 (51.2)	48 (44.9)	0.286
Peripheral artery disease	13 (8.4)	17 (5.5)	0.222	13 (6.4)	4 (3.7)	0.327
Prior stroke	17 (11.0)	40 (12.9)	0.565	23 (11.2)	17 (15.9)	0.255
Paroxysmal atrial fibrillation	17 (11.0)	50 (16.1)	0.142	33 (16.3)	17 (15.9)	0.933
Hyperlipidaemia	73 (47.4)	149 (48.2)	0.868	94 (46.3)	55 (51.9)	0.351
COPD	12 (7.8)	36 (11.6)	0.203	28 (13.8)	8 (7.5)	0.099
Chronic kidney disease	57 (37.0)	100 (32.3)	0.308	66 (32.5)	34 (31.8)	0.673
Thyroid disorder	11 (7.1)	15 (4.8)	0.310	10 (4.9)	5 (4.7)	0.921
Hyperuricaemia	28 (18.2)	57 (18.4)	0.945	36 (17.7)	21 (19.8)	0.655
Prior history of malignancy	13 (8.4)	23 (7.4)	0.706	14 (6.9)	9 (8.5)	0.612
Depression	3 (1.9)	12 (3.9)	0.404	8 (3.9)	4 (3.8)	1.000
Heart failure therapies, <i>n</i> (%)						
ACEi or ARB	0 (0.0)	158 (51.0)	<0.001	158 (77.8)	0 (0.0)	<0.001
Sac/Val	154 (100)	107 (34.5)	<0.001	0 (0.0)	107 (100)	<0.001
Beta-blocker	114 (74.0)	236 (76.1)	0.620	148 (72.9)	88 (82.2)	0.067
Ivabradine	154 (100)	203 (65.5)	<0.001	203 (100)	0 (0.0)	<0.001
MRA	104 (67.5)	212 (68.4)	0.852	145 (71.4)	67 (62.6)	0.113
Digoxin	24 (15.6)	52 (16.8)	0.766	36 (17.7)	16 (15.0)	0.533
CRT	10 (6.5)	31 (10.0)	0.210	23 (11.3)	8 (7.5)	0.282
ICD	15 (9.7)	38 (12.3)	0.422	25 (12.3)	13 (12.1)	0.966
Median time period between IVA and Sac/Val, day (IQR)	5 (0–6)	217 (98–416)	<0.001	193 (93–386)	227 (99–427)	0.082

BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IVA, ivabradine; LA, left atrial; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; Sac/Val, sacubitril/valsartan.

(Group 2B, Sequential group: Sac/Val-first). Baseline characteristics of Group 2A and 2B patients were shown in the right column of *Table 1*. Patients in Group 2A and 2B were similar in age, gender, echocardiographic parameters, renal function, and co-morbidities. Baseline systolic blood pressure was significantly lower, and heart rate was significantly higher in patients from Group 2A, comparing with those from Group 2B (117.5 ± 19.1 mmHg vs. 122.1 ± 19.1 mmHg, $P = 0.012$; 90.2 ± 14.1 b.p.m. vs. 83.8 ± 16.5 b.p.m., $P < 0.001$, respectively).

Timing and dosing of drug administrations

Ivabradine was initiated in 122 patients (26.3%) who were intolerant to beta-blockers and in 342 patients (73.7%) who had sinus rate faster than 70 b.p.m. despite the maximum tolerable dose of beta-blocker. Overall, a total of 43 Group 1 patients (27.9%) received Sac/Val and ivabradine treatment, whereas a total of 96 Group 2 patients (31.0%, $P = 0.500$) received their first medication (Sac/Val or ivabradine) following the HF hospitalization episodes. Sac/Val treatment was added in 37 Group 2A patients (18.2%), and ivabradine treatment was added in 23 Group 2B patients (21.5%, $P = 0.489$) following the repeated HF hospitalization episodes.

At baseline, daily doses of Sac/Val and ivabradine were 116.6 ± 58.3 mg vs. 115.0 ± 56.6 mg ($P = 0.820$) and 8.7 ± 2.6 mg vs. 8.7 ± 2.8 mg ($P = 0.890$) among Group 1 and 2 patients, respectively. At the end of follow-up, daily doses of ARNI and ivabradine were 176.8 ± 89.4 mg vs. 190.1 ± 100.7 mg ($P = 0.185$) and 9.4 ± 2.4 mg vs. 9.0 ± 2.7 mg ($P = 0.103$) among Group 1 and 2 patients, respectively. Detailed types and dosages of disease-modifying medications for HF were shown in Supporting Information, *Table S1*. Among Group 2 patients, types and dosages of guideline-recommended HF medications at different treatment time points were shown in *Figure 2*.

Cardiovascular death and re-hospitalization for heart failure

Figures 3 and *4* demonstrated the cumulative incidence curves of clinical events of study patients. During a mean follow-up of 27.4 ± 10.9 months, the incidence of cardiovascular death and/or first unplanned re-hospitalization for HF was 22.85 per 100-person years, and the incidence of first unplanned re-hospitalization for HF was 16.74 per 100-person years, respectively. Patients in the Group 1 had a significantly lower risk of cardiovascular death and/or first unplanned re-hospitalization for HF (16.92 per 100-person years vs. 25.70 per 100-person years, HR 0.64, 95% CI 0.46–0.90, $P = 0.01$) and first unplanned re-hospitalization for HF alone (14.66 per

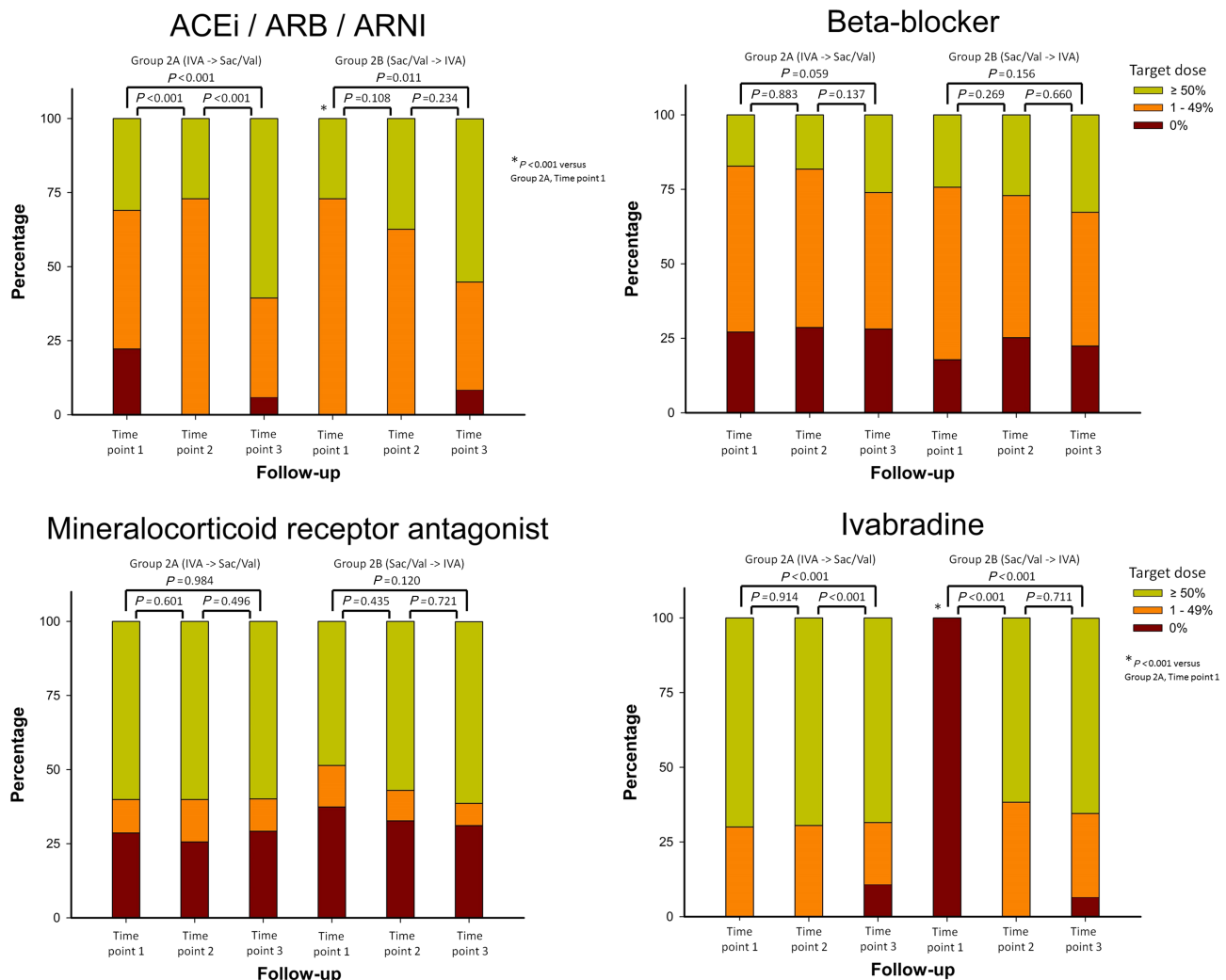
100-person years vs. 17.46 per 100-person years, HR 0.60, 95% CI 0.42–0.86, $P = 0.006$) than those in the Group 2. If the events were collected from the date when both Sac/Val and ivabradine were prescribed, the incidences of either cardiovascular death and/or first unplanned re-hospitalization for HF or HF re-admissions alone were not significantly different between the two groups.

Among Group 2 patients, the incidences of cardiovascular death and/or first unplanned re-hospitalization for HF (26.64 per 100-person years vs. 23.57 per 100-person years, $P = 0.44$) and first unplanned re-hospitalization for HF alone (17.53 per 100-person years vs. 17.27 per 100-person years, $P = 0.783$) were similar between Group 2A and Group 2B patients.

Alternations of blood pressure, heart rate, and echocardiographic parameters

Throughout the study period, systolic blood pressure did not change significantly in Group 1 and Group 2 patients (122.1 ± 22.2 mmHg to 122.0 ± 20.4 mmHg, $P = 0.945$; 119.1 ± 19.2 mmHg to 119.0 ± 17.2 mmHg, $P = 0.919$, respectively). In Group 1 patients, heart rate decreased from 88.3 ± 17.6 b.p.m. at baseline to 81.0 ± 15.5 b.p.m., and in Group 2 patients from 88.0 ± 15.3 b.p.m. at baseline to 77.6 ± 13.9 b.p.m. (both P -values < 0.001). In Group 1 patients, LVEF significantly improved from $28.5 \pm 8.7\%$ at baseline to $41.3 \pm 14.9\%$, and in Group 2 patients from $28.7 \pm 8.1\%$ at baseline to $38.0 \pm 12.7\%$ (both P -values < 0.001). The improvement of LVEF was significantly greater in Group 1 patients compared with Group 2 patients (Δ LVEF $12.8 \pm 12.9\%$ vs. $9.3 \pm 12.6\%$, $P = 0.007$). Mean percentage changes of LVEDVi and LVESVi were significantly greater in Group 1 patients comparing with Group 2 patients (LVEDVi $-14.0 \pm 24.5\%$ vs. $-7.3 \pm 31.8\%$, $P = 0.026$; LVESVi $-26.6 \pm 31.9\%$ vs. $-16.3 \pm 40.6\%$, $P = 0.008$, respectively).

Among Group 2 patients, detailed alternations of systolic blood pressures, heart rates, and echocardiographic parameters at different treatment time points were shown in *Table 2* and *Figures 5* and *6*. At baseline, systolic blood pressures were significantly lower, and heart rates were significantly higher in Group 2A patients than in Group 2B patients. Following ivabradine treatment in Group 2A and Sac/Val treatment in Group 2B, the differences between systolic blood pressure and heart rate reversed in these two subgroups. At time point 2, systolic blood pressures became significantly higher, and heart rates became significantly lower in Group 2A patients than Group 2B. Mean alternation in systolic blood pressure from time point 1 to 2 was 4.6 ± 16.5 mmHg in Group 2A patients comparing with -4.8 ± 17.2 mmHg in Group 2B patients ($P < 0.001$), whereas a change in heart rate from time point 1 to 2 was -9.1 ± 12.9 b.p.m. in Group 2A patients comparing with 2.6 ± 16.0 b.p.m. in Group 2B

Figure 2 Types and dosages of disease-modifying medications for heart failure among Group 2 patients over time.

patients ($P < 0.001$). On the other hand, following Sac/Val treatment, the degree of LVEF improvement in Group 2B patients was $3.6 \pm 7.8\%$, which was significantly greater than those in Group 2A ($0.7 \pm 7.7\%$, $P = 0.002$).

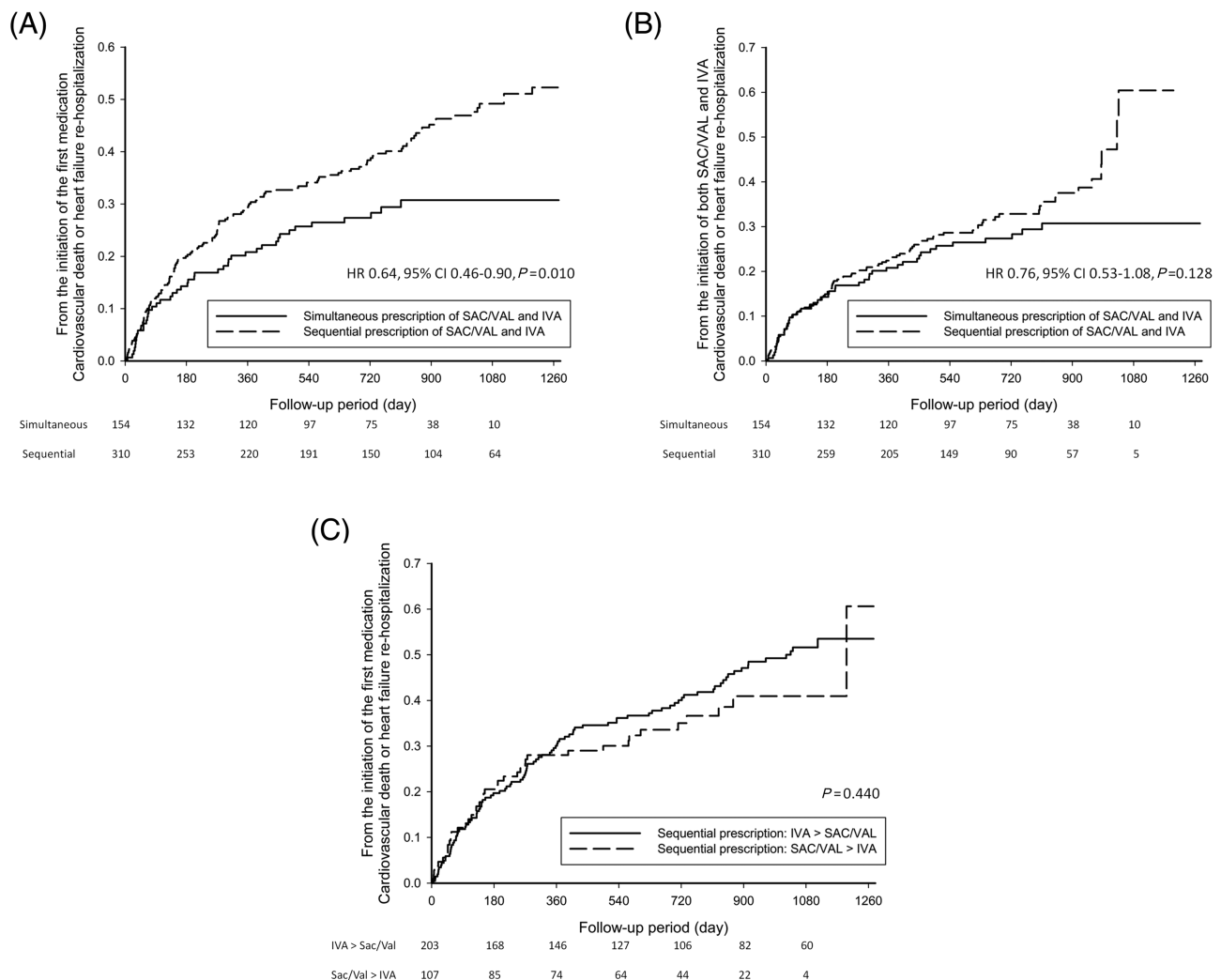
From time point 2 to 3, add-on ivabradine treatment in Group 2B patients again showed a more prominent heart rate lowering effect than add-on Sac/Val treatment in Group 2A patients (-11.3 ± 14.2 b.p.m. vs. -2.2 ± 14.7 , $P < 0.001$). In contrast, additional Sac/Val treatment in Group 2A patients demonstrated a more remarkable improvement in LVEF than additional ivabradine treatment in Group 2B patients ($8.3 \pm 10.8\%$ vs. $5.0 \pm 11.0\%$, $P = 0.012$). Overall, the changes in systolic blood pressures and heart rates from baseline to the end of follow-up were similar between Group 2A and 2B patients. Improvements of LVEF and decreases of left ventricular volumes were observed in both subgroups following either sequential treatment strategy, and there were

no significant differences in the degree of left ventricular reverse remodelling between Group 2A and 2B.

Discussion

In the past few years, two landmark randomized controlled trials^{4,5} and several real-world studies had demonstrated the beneficial effects of ivabradine and Sac/Val over standard HF treatment.^{15–18} These two medications have different action mechanisms, and it is reasonable to apply both drugs in the same patients with HF if clinically indicated. However, there is insufficient study on analysing the synergistic effect of these two novel anti-HF medications, and no data was reporting the clinical effects of different prescription patterns.

Figure 3 Kaplan–Meier curves of cardiovascular death and/or first unplanned heart failure re-hospitalizations in study patients (A, collected from the initiation of the first medication; B, collected from the prescription of both sacubitril/valsartan and ivabradine; C, in Group 2A and 2B patients).



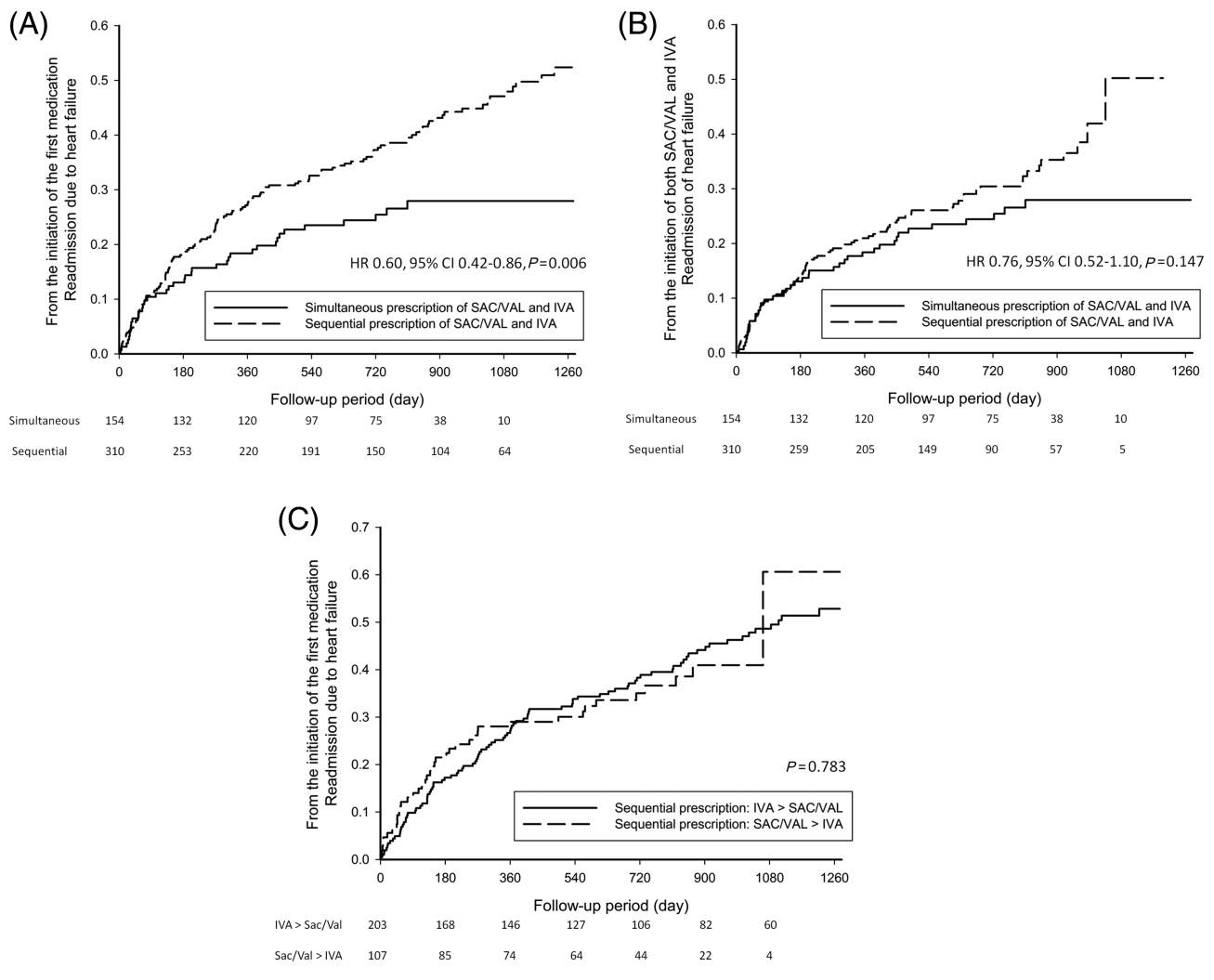
Simultaneous versus a sequential strategy of sacubitril/valsartan and ivabradine

Recurrent HF hospitalization was a strong predictor of mortality for patients with HF. Therefore, a reduction in the risk of HF re-hospitalization was one of the treatment objectives.^{19,20} Both Sac/Val and ivabradine are effective treatments to reduce HF hospitalization. In the PARADIGM-HF trial, the incidences of first unplanned re-hospitalization for HF were 21% fewer in patients treated with Sac/Val comparing with those with enalapril.⁵ In the SHIFT trial, ivabradine reduced the risks of first, second, and third HF re-hospitalizations with a relative risk reduction of 25% regarding total HF re-hospitalization.²¹ In the current study, patients who started to receive Sac/Val and ivabradine simultaneously had significantly fewer cardiovascular death and/or HF re-hospitalizations events during follow-up than

those who received these two medications one after another. Of note, when the second medication was initiated in the Sequential group, the risks of cardiovascular death and/or first unplanned re-hospitalization for HF in the patients were comparable with those in the Simultaneous group. Our finding emphasized that in patients with HF who were clinically indicated for both Sac/Val and ivabradine, timely initiation of these drugs is a better strategy to reduce future adverse outcomes.

Impaired contractility is the central pathophysiology underlying the HF syndrome, so therefore, left ventricular reverse structural remodelling is a crucial treatment target in patients with HFrEF. Ivabradine treatment demonstrated a modest but significant increase in LVEF in the BEAUTIFUL study ($2.0 \pm 7.0\%$) and SHIFT study ($2.4 \pm 7.7\%$).^{8,22} In the PROVE-HF study, which enrolled 794 patients with HFrEF from 78 outpatient sites in the USA, it also demonstrated

Figure 4 Kaplan–Meier curves of first unplanned heart failure re-hospitalizations in study patients (A, collected from the initiation of the first medication; B, collected from the prescription of both sacubitril/valsartan and ivabradine; C, in Group 2A and 2B patients).



LVEF improvement following 12 months of Sac/Val treatment by 9.4%.²³ In the current study, both simultaneous and sequential treatment strategies demonstrated a significant left ventricular reverse modelling effect, but the degree of left ventricular reverse remodelling was significantly greater in simultaneous treatment than sequential treatment. This finding suggested early and multi-pharmacologic interventions in patients with HF_{rEF} might better affect left ventricular functional recovery.

Sequential strategy: sacubitril/valsartan first versus ivabradine first

Although our findings suggested that outcomes of Sac/Val and ivabradine’s simultaneous prescription patterns were better than sequential prescription patterns in patients

indicated for both medications, there are still many concerns in real practice. Due to the rapid increase in the use of novel anti-HF medications, the increase in economic burden and the limited affordability of the healthcare system might prohibit physicians from prescribing every medication simultaneously.²⁴ In light of the different patient characteristics, physicians might prescribe different anti-HF medication types as the concept of personalized HF treatment. In the current study, baseline systolic blood pressure was significantly lower, and the heart rate was significantly higher in patients who received ivabradine first, compared with those treated with Sac/Val first. This finding suggested that physicians might be aware of tachycardia’s deleterious effect and tend to prescribe ivabradine in patients with a higher heart rate, and physicians might feel more comfortable prescribing Sac/Val in patients with relatively higher blood pressure.

Table 2 Alternations of vital signs and echocardiographic parameters following ivabradine and sacubitril/valsartan treatment

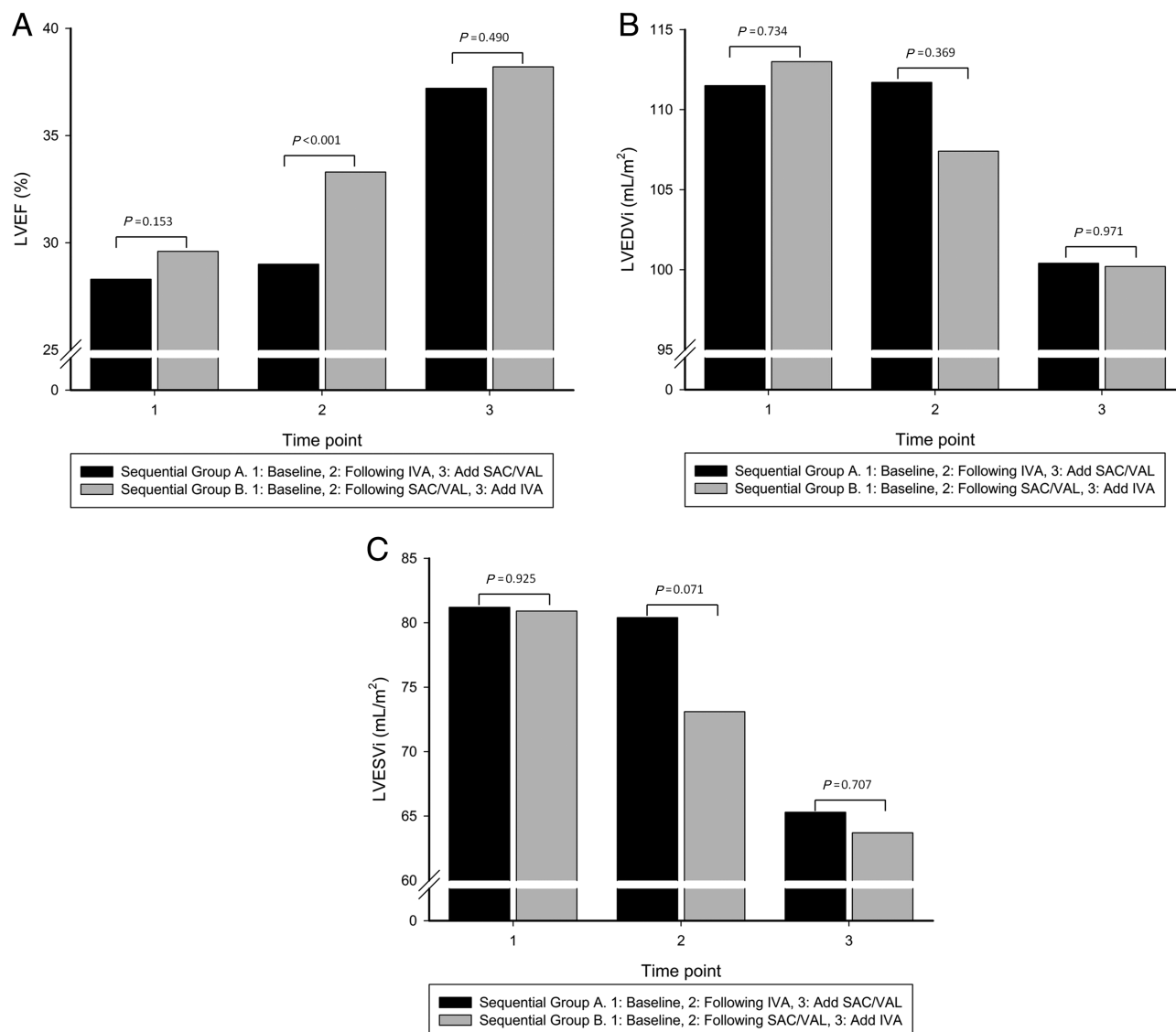
	Group 2A (IVA > Sac/Val) N = 203	Group 2B (Sac/Val > IVA) N = 107	P-value
Time point 1: Before 1st heart failure medication	Before IVA	Before Sac/Val	
Systolic BP (mmHg)	117.5 ± 19.1	122.1 ± 19.1	0.012
Heart rate (b.p.m.)	90.2 ± 14.1	83.8 ± 16.5	<0.001
LVEF (%)	28.3 ± 7.6	29.6 ± 9.0	0.153
LVEDVi (mL/m ²)	111.5 ± 34.9	113.0 ± 40.0	0.734
LVESVi (mL/m ²)	81.2 ± 30.1	80.9 ± 33.8	0.925
PASP (mmHg)	38.6 ± 14.9	35.6 ± 12.5	0.084
Time point 1→2	Add IVA	Add Sac/Val	
Time point 2: Before 2nd heart failure medication			
Systolic BP (mmHg)	122.1 ± 18.2	117.6 ± 18.2	0.040
Heart rate (b.p.m.)	81.1 ± 12.8	86.4 ± 15.6	0.003
LVEF (%)	29.0 ± 7.6	33.3 ± 10.7	<0.001
LVEDVi (mL/m ²)	111.7 ± 40.0	107.4 ± 41.2	0.369
LVESVi (mL/m ²)	80.4 ± 33.9	73.1 ± 33.5	0.071
PASP (mmHg)	36.1 ± 12.9	34.4 ± 11.8	0.269
Change from time point 1 to 2			
ΔSystolic BP (mmHg)	4.6 ± 16.5	-4.8 ± 17.2	<0.001
ΔHeart rate (b.p.m.)	-9.1 ± 12.9	2.6 ± 16.0	<0.001
ΔLVEF (%)	0.7 ± 7.7	3.6 ± 7.8	0.002
Percentage change in LVEDVi (%)	3.5 ± 33.7	-3.8 ± 21.3	0.022
Percentage change in LVESVi (%)	-8.8 ± 37.2	-18.5 ± 40.3	0.035
ΔPASP (mmHg)	-2.5 ± 11.8	-1.2 ± 9.6	0.309
Time point 2→3	Add Sac/Val	Add IVA	
Time point 3: End of follow-up			
Systolic BP (mmHg)	119.1 ± 17.3	119.0 ± 17.0	0.941
Heart rate (b.p.m.)	78.9 ± 14.4	75.1 ± 12.6	0.021
LVEF (%)	37.2 ± 12.3	38.2 ± 13.0	0.490
LVEDVi (mL/m ²)	100.4 ± 41.3	100.2 ± 40.4	0.971
LVESVi (mL/m ²)	65.3 ± 38.0	63.7 ± 33.9	0.707
PASP (mmHg)	34.9 ± 13.0	33.1 ± 11.0	0.231
Change from time point 2 to 3			
ΔSystolic BP (mmHg)	-3.0 ± 16.5	1.4 ± 18.3	0.036
ΔHeart rate (b.p.m.)	-2.2 ± 14.7	-11.3 ± 14.2	<0.001
ΔLVEF (%)	8.3 ± 10.8	5.0 ± 11.0	0.012
Percentage change in LVEDVi (%)	-7.8 ± 23.4	-4.6 ± 21.5	0.239
Percentage change in LVESVi (%)	-17.5 ± 28.8	-9.6 ± 30.7	0.024
ΔPASP (mmHg)	-1.2 ± 10.6	-1.3 ± 9.5	0.923
Overall change (Time point 1 to 3)			
ΔSystolic BP (mmHg)	1.2 ± 17.9	-2.8 ± 20.4	0.071
ΔHeart rate (b.p.m.)	-11.3 ± 17.0	-8.7 ± 18.2	0.207
ΔLVEF (%)	8.9 ± 12.5	8.6 ± 12.5	0.816
Percentage change in LVEDVi (%)	-6.1 ± 35.0	-9.5 ± 24.4	0.307
Percentage change in LVESVi (%)	-15.2 ± 43.6	-17.2 ± 28.5	0.503
ΔPASP (mmHg)	-3.7 ± 13.2	-2.5 ± 12.4	0.458

BP, blood pressure; IVA, ivabradine; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; Sac/Val, sacubitril/valsartan.

Hypotension is generally regarded as a poor prognostic factor and is also a significant barrier for the initiation and titration of HFrEF treatments in routine practice. In the PARADIGM-HF study, mean systolic blood pressure was 3.2 ± 0.4 mmHg lower in the Sac/Val group than in the enalapril group, which might limit its utilization in hypotensive patients.⁶ In the current study, one reason for not prescribing Sac/Val may have been the lower baseline systolic blood pressure observed in Group 2A patients. Recently, an algorithm for the management of hypotension in patients with HFrEF had been proposed by European experts. If hypotensive factors unrelated to HF had been excluded, doses of diuretics and guideline-recommended medical therapies for HF might need to be decreased in hypotensive patients with HFrEF.²⁵

Instead of de-escalating disease-modifying medications, ivabradine was associated with an increase in directly measured central systolic pressure and may help counter the hypotension.¹¹ Previous studies demonstrated that ivabradine's introduction might allow the introduction of a beta-blocker secondarily and/or enable increasing the beta-blocker dose more easily compared with introducing a beta-blocker directly.²⁶ In the current study, we found that in patients with HFrEF treated with ivabradine first, an increase of 5 mmHg in systolic blood pressure could help initiation and further up-titration of Sac/Val. Even in patients treated with Sac/Val first, up-titration of Sac/Val was noted after adding-on ivabradine treatment without significant change in systolic blood pressure (*Figure 2* and *Table 2*).

Figure 5 Alternations of echocardiographic parameters at different treatment time points in patients with different prescription patterns. (A) Left ventricular ejection fraction, (B) left ventricular end-diastolic volume index, (C) left ventricular end-systolic volume index.

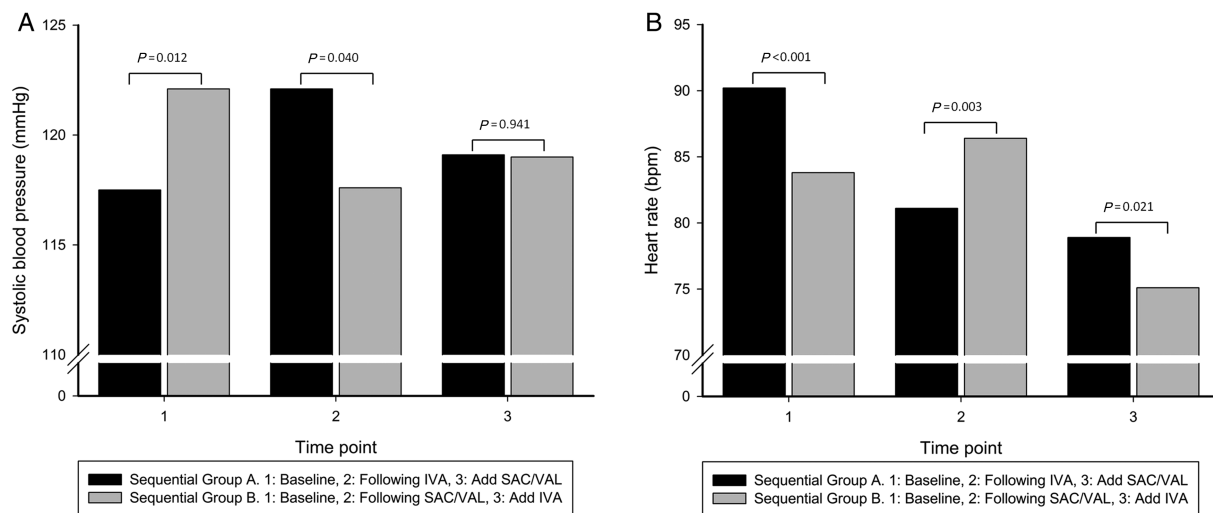


Our findings highlighted the advantage of haemodynamic stability of ivabradine treatment.

Noteworthy, the results of the current study demonstrated the synergistic effect of ivabradine and Sac/Val. At treatment time point 2, when patients in Group 2A were already treated with ivabradine, additional Sac/Val treatment demonstrated LVEF improvement of $8.3 \pm 10.8\%$, which was more prominent in Group 2B patients at the time treated with Sac/Val alone ($3.6 \pm 7.8\%$). Similarly, when Group 2B patients were already treated with Sac/Val, additional ivabradine treatment also had a more generous heart rate lowering effect than Group 2A patients at the time treated with ivabradine alone (-11.3 ± 14.2 b.p.m. vs. -9.1 ± 12.9 b.p.m.).

This study had several limitations. After screening more than 1800 patients with HFrEF, only one-fourth of patients were enrolled in the current study. These selected results of patients with HFrEF in the current study may not be generalized to other patients with HFrEF. Although baseline characteristics were generally comparable between the Simultaneous and Sequential groups, in this retrospective study, the treatment strategies were determined by each physician, and selection bias was somehow inevitable. Tricuspid annular plane systolic excursion measurements are useful for evaluating the global right ventricular function and predicting the prognosis of HF. However, these measurements were not routinely checked during the study period.

Figure 6 Alternations of vital signs at different treatment time points in patients with different prescription patterns. (A) Systolic blood pressure, (B) heart rate.



In conclusion, patients with HFrEF clinically indicated for both ivabradine and Sac/Val, simultaneously rather than sequentially prescribing Sac/Val and ivabradine, might be a better strategy to reduce future cardiovascular death and/or HF re-hospitalization events and to contribute greater left ventricular reverse remodelling. Ivabradine had a more significant effect on improving haemodynamic stability, Sac/Val had a more significant effect on left ventricular reverse remodelling, and the warranted synergistic phenomenon of these two medications was observed. Our finding demonstrated the importance of tailoring the best medication regime for individual patients with HF.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Supporting Information

5. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. *Lancet* 2010; **376**: 875–885.
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