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ORIGINAL ARTICLE

Clinical impacts of sacubitril/valsartan on patients eligible for cardiac resynchronization therapy

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Abstract

Aims Sacubitril/valsartan (SAC/VAL) has been used in patients with heart failure and reduced ejection fraction (HFrEF), and cardiac resynchronization therapy (CRT) could benefit the HFrEF patients with wide QRS durations. This study aimed to evaluate the clinical impacts of SAC/VAL on reverse cardiac remodelling in CRT-eligible and CRT-ineligible HFrEF patients with different QRS durations.

Methods and results The TAROT-HF study was a multicentre, observational study enrolling patients who initiated SAC/VAL from 10 hospitals since 2017. Patients with baseline left ventricular ejection fraction (LVEF) $\leq$ 35% were classified into two groups: (i) Group 1: CRT-eligible group, patients with left bundle branch block (LBBB) morphology plus QRS duration $\geq$130 ms or non-LBBB morphology plus QRS duration $\geq$150 ms; and (ii) Group 2: CRT-ineligible group. Propensity score matching was performed to adjust for confounders, and 1168 patients were analysed. Baseline characteristics were comparable between the two groups. The improvements in LVEF and left ventricular end-systolic volume index (LVESVi) were more significant in Group 2 than in Group 1 after 1 year SAC/VAL treatment (LVEF: 8.4% ± 11.3% vs. 4.5% ± 8.1%, $P < 0.001$; change percentages in LVESVi: −14.4% ± 25.9% vs. −9.6% ± 23.1%, $P = 0.004$). LVEF improving to $\geq$50% in Groups 1 and 2 constituted 5.2% and 20.2% after 1 year SAC/VAL treatment ($P < 0.001$). Multivariate analyses showed that wide QRS durations were negatively associated with the reverse cardiac remodelling in these HFrEF patients with SAC/VAL treatment.

Conclusion Despite SAC/VAL treatment, wide QRS durations are associated with lower degrees of left ventricular improvement than narrow ones in the HFrEF patients. Optimal intervention timing for the CRT-eligible patients requires further investigation.

Keywords Cardiac resynchronization therapy; Guideline directed medical therapy; Heart failure; Left bundle branch block; Reverse cardiac remodelling; Sacubitril/valsartan

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Introduction

Heart failure is associated with high mortality rates, frequent rehospitalizations, and poor quality of life.[1] Recovery of left ventricular (LV) function is an important treatment goal for patients with heart failure and reduced ejection fraction (HFrEF). Several randomized controlled trials have shown that traditional neurohormonal modulation using beta-blockers,

angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists promotes LV functional recovery.[2–6] The recent PROVE-HF study, which enrolled 794 HFrEF American patients with contemporary background heart failure treatment, clearly demonstrated the beneficial effect of LV reverse remodelling following sacubitril/valsartan (SAC/VAL) treatment.[7]

Apart from the aforementioned medical therapies, cardiac resynchronization therapy (CRT) restores electromechanical dyssynchrony, induces reverse LV remodelling, improves functional status, and reduces mortality of patients with HFrEF and QRS prolongation.[8–11] Current guidelines recommend that disease-modifying medical therapy should be given prior to the implantation of CRT, in the hopes that medical therapy alone is sufficient to improve LVEF.[12,13] However, optimal timing for CRT implantation remains controversial. Several studies demonstrated that heart failure patients with left bundle branch block (LBBB) show less LVEF improvement after traditional drug therapy than those with a narrow QRS complex, implying that the former patients may benefit more from early CRT implantation than the latter patients.[14,15] Nevertheless, these studies were conducted before the era of SAC/VAL, and data on how HFrEF patients with prolonged QRS duration respond to SAC/VAL are lacking. Therefore, this study sought to evaluate the clinical impacts of SAC/VAL on reverse cardiac remodelling in patients with different QRS durations.

Methods

Data source and patient characteristics

The study cohort was selected from the *T*reatment with *A*ngiotensin *R*eceptor neprilysin inhibitor f*O*r *T*aiwan *H*eart *F*ailure patients (TAROT-HF) study, which is a principal investigator-initiated, multicentre, and observational study of patients with HFrEF in Taiwan. This study was approved by the institutional ethics committee [CHGH-IRB: (615)106A-23]. The TAROT-HF study includes clinical data, baseline electrocardiograms (ECGs), and baseline and serial follow-up echocardiograms of more than 1700 patients with HFrEF who received SAC/VAL treatment from 10 hospitals between March 2017 and March 2021. Patients were treated with traditional guideline-directed medical therapy for more than 3 months before the initiation of SAC/VAL. The amounts of guideline-directed medical therapies (GDMT) before and after the initiation of SAC/VAL were expressed as the per cent of the European guideline-recommended target doses, for example, 10 mg daily for bisoprolol, 20 mg daily for enalapril, and 50 mg daily for spironolactone.[12] For SAC/VAL, the initiation and 1 year follow-up amounts were expressed as the percentages of standard starting doses (49/51 mg twice per day) and target doses (97/103 mg twice per day). The study design, purpose, and rationale had been completely described,[16] and data regarding LV remodelling had been published in a previous manuscript.[17] In brief, left ventricular end-diastolic volume index (LVEDVi), left ventricular end-systolic volume index (LVESVi), and LVEF were measured and calculated using the biplane Simpson's method on apical four-chamber and two-chamber views as recommended by the American Society of Echocardiography.[18] The reports were verified by expert cardiologists unaware of patients' clinical data and medications.

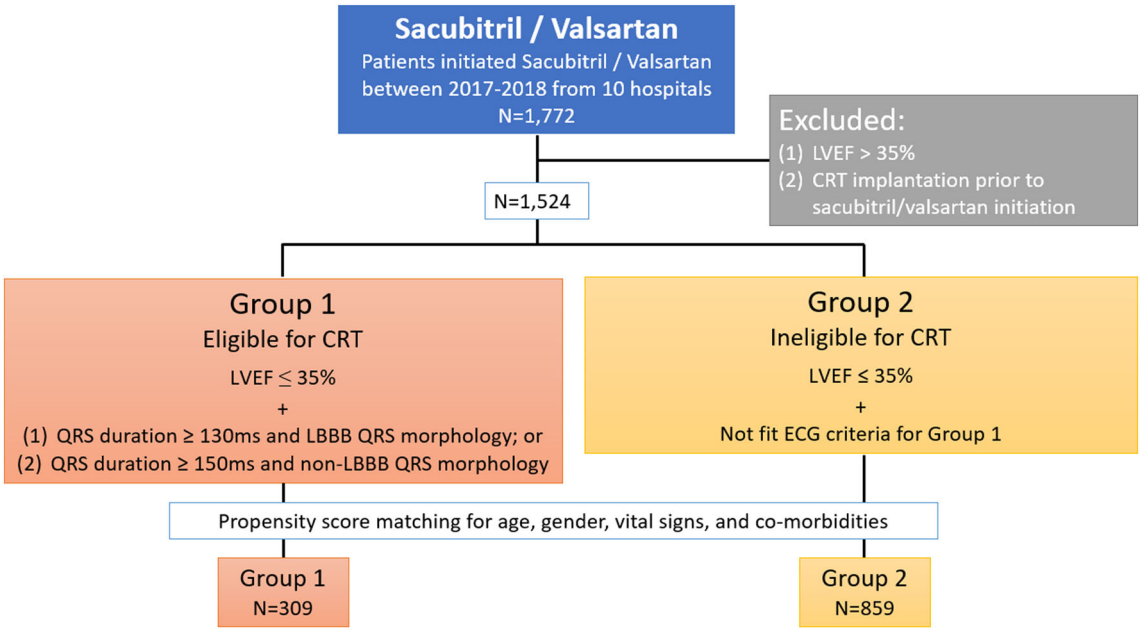
Study population

Patients were classified as Group 1: 'CRT eligible group' if they presented LVEF ≤35% plus LBBB QRS morphology and QRS duration ≥130 ms or non-LBBB QRS morphology and QRS duration ≥150 ms at baseline ECG. Patients with LVEF ≤35% but did not meet the ECG indications for CRT were classified as Group 2: 'CRT ineligible group'. Those patients with baseline LVEF 35–40% and those who already received CRT implantation before SAC/VAL treatment were excluded for analysis. The study flowchart is shown in *Figure 1*.

Study outcomes

The absolute changes in LVEF, LVEDVi, and LVESVi following SAC/VAL treatment over time were measured as continuous outcome variables. The first categorical outcome was dichotomized as post-SAC/VAL LVEF >35% vs. ≤ 35%. This threshold for 'response' was selected on the basis of guideline recommendations for CRT implantation. The second categorical outcome was to assess the proportions of heart failure with improved EF following SAC/VAL treatment, which included patients with a baseline LVEF of ≤35%, a ≥10-point increase from baseline LVEF, and a follow-up LVEF improved up to >40%.[19] The third categorical outcome was dichotomized as post-SAC/VAL LVEF ≥50% vs. <50% on the basis of the guideline designation of heart failure with preserved EF. Times to each categorical outcome were collected. Because CRT implantation would potentially affect the echocardiographic findings among patients in the Group 1, we performed a sensitivity analysis evaluating the changes in echocardiographic parameters after SAC/VAL regardless of CRT implantation. Clinical events, including heart failure hospitalization and mortality, were collected during follow-up. Serial echocardiography follow-up demonstrated changes in LVEF during the study period. Thus, clinical events that occurred when patients' LVEF measurements were ≤35%, 35–50%, and ≥50% were calculated separately.

Figure 1 Flowchart of the study.



Statistical analysis

Propensity score matching was performed to adjust for confounders. Propensity was estimated using a logistic regression model with the following covariates: age, gender, eGFR, body mass index, systolic blood pressure, HF aetiology, New York Heart Association Functional class, and 12 co-morbidities (hypertension, diabetes mellitus, dyslipidaemia, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, history of stroke, thyroid disorder, hyperuricaemia, and prior malignancy). In the matching process, the greedy, nearest-neighbour method without replacement and with a calliper of 0.01 of the propensity score was used.

Continuous and categorical variables are expressed as the mean values ± standard deviations and percentages, respectively. Differences in baseline characteristics and clinical parameters were tested using the χ^2 test for categorical variables, and continuous data were compared using the Student's *t*-test or Mann–Whitney *U* test for normally and non-normally distributed data, respectively. Two-group comparisons are summarized as Group 1 vs. Group 2 unless otherwise specified. Times to each categorical echocardiographic outcome were presented using survival analysis with the Kaplan–Meier method and log-rank test. Cox proportional hazards regression models were performed to assess the factors associated with reverse cardiac remodelling, including time to LVEF improvement to ≥50% and time to ≥15% decrease in LVESVi from baseline, presented as hazard ratios with 95% confidence intervals (CIs). The tested variables in the multivariate analysis were those with a *P*-value < 0.1 in the univariate model. Clinical events were presented as event rate per 100 patient-year. A *P*-value of <0.05 was considered to be statistically significant, and statistical analyses were performed using IBM SPSS software version 24.0 (IBM SPSS, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

After applying the inclusion and exclusion criteria, 1524 patients with baseline LVEF ≤35% who initiated SAC/VAL treatment were enrolled. Following propensity score matching, a total of 309 Group 1 and 859 Group 2 patients were included in the final analysis (*Figure 1*). Baseline characteristics of patients are shown in *Table 1*. The mean age of the study subjects and the mean LVEF were 65.8 ± 13.6 years and 28.0 ± 5.9%, respectively. Overall, the two matched groups were well balanced in baseline characteristics, except Group 1 patients had a significantly longer QRS duration than Group 2 patients (161.2 ± 21.3 ms vs. 103.2 ± 15.0 ms, $P < 0.001$). Baseline echocardiography demonstrated that Group 1 patients had significantly lower LVEF and higher LVEDV, LVESV, and left atrial diameter than Group 2 patients.

Table 1 Patient characteristics of the current study

	Group 1 (*N* = 309)	Group 2 (*N* = 859)	*P*-value
Age (years)	66.4 ± 13.7	65.5 ± 13.5	0.315
Male, *n* (%)	219 (70.9)	621 (72.3)	0.634
Body mass index (kg/m^2)	25.2 ± 4.6	25.0 ± 4.7	0.660
Ischemic cardiomyopathy, *n* (%)	127 (41.1)	396 (46.1)	0.130
Heart failure duration			0.165
<1 year	77 (24.9)	247 (28.8)	
1 to 5 years	122 (39.5)	354 (41.2)	
More than 5 years	110 (35.6)	258 (30.0)	
Estimated glomerular filtration rate (mL/min/1.73 m^2)	62.1 ± 25.4	60.3 ± 28.0	0.303
NYHA functional class III/IV, *n* (%)	125 (40.5)	336 (39.1)	0.680
Systolic blood pressure (mmHg)	118.2 ± 18.8	119.7 ± 19.4	0.240
QRS duration (ms)	161.2 ± 21.3	103.2 ± 15.0	<0.001
Past history, *n* (%)			
Diabetes mellitus	130 (42.1)	372 (43.3)	0.707
Hypertension	158 (51.1)	461 (53.7)	0.444
Percutaneous coronary intervention	95 (30.7)	305 (35.5)	0.130
Coronary artery bypass graft	41 (13.3)	93 (10.8)	0.248
Peripheral arterial disease	14 (4.5)	63 (7.3)	0.089
Prior stroke	34 (11.0)	111 (12.9)	0.380
Permanent atrial fibrillation	49 (15.9)	175 (20.4)	0.084
Dyslipidaemia	142 (46.0)	404 (47.0)	0.745
Chronic obstructive pulmonary disease	29 (9.4)	96 (11.2)	0.383
Prior hospitalization for heart failure	200 (64.7)	539 (62.7)	0.536
Chronic kidney disease	100 (32.4)	305 (35.5)	0.319
Thyroid disease	30 (9.7)	71 (8.3)	0.439
Hyperuricaemia	50 (16.2)	144 (16.8)	0.813
Prior malignancy	21 (6.8)	62 (7.2)	0.805
Echocardiography			
Left ventricular ejection fraction (%)	26.7 ± 6.0	28.5 ± 5.8	<0.001
Left atrial diameter (mm)	46.8 ± 9.2	44.4 ± 8.9	<0.001
Left ventricular end-diastolic diameter (mm)	61.2 ± 9.8	58.4 ± 8.5	<0.001
Left ventricular end-systolic diameter (mm)	51.3 ± 10.7	48.2 ± 9.8	<0.001
Left ventricular end-diastolic volume index (mL/m^2)	103.2 ± 34.9	92.6 ± 28.6	<0.001
Left ventricular end-systolic volume index (mL/m^2)	75.9 ± 30.2	65.7 ± 24.1	<0.001
Pulmonary artery systolic pressure (mmHg)	40.4 ± 14.7	38.6 ± 14.2	0.086
Severe mitral regurgitation, *n* (%)	60 (19.4)	126 (14.7)	0.050
Severe tricuspid regurgitation, *n* (%)	35 (11.3)	82 (9.5)	0.371
Heart failure treatment, *n* (%)			
Sacubitril/valsartan	309 (100.0)	859 (100.0)	1.000
Percentage of starting dose (49/51 mg twice daily)	52.4 ± 27.0	55.4 ± 27.1	0.105
Beta-blocker	238 (77.0)	649 (75.6)	0.604
Mineralocorticoid receptor antagonist	202 (65.4)	513 (59.7)	0.080
Ivabradine	63 (20.4)	164 (19.1)	0.621
Digoxin	66 (21.4)	184 (21.4)	0.982
Implantable cardioverter-defibrillator	24 (7.8)	61 (7.1)	0.699
Amount of medication before initiation of sacubitril/valsartan, percentage of target dose			
ACEi/ARB	61.8 ± 43.2	64.2 ± 44.3	0.482
Beta-blocker	41.8 ± 34.2	45.4 ± 36.1	0.186
Mineralocorticoid receptor antagonist	55.0 ± 25.9	58.8 ± 26.0	0.076
Ivabradine	54.5 ± 17.2	56.9 ± 16.3	0.340

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; NYHA, New York Heart Association.

Guideline-directed medical therapy

Before initiation of SAC/VAL treatment, both groups had similar utilization rates and amounts of GDMTs, including the initiated doses of SAC/VAL (*Table 1*). At 1 year follow-up, patients in both groups received similar dosages of heart failure medications, including SAC/VAL (49.6 ± 16.5% vs. 50.4 ± 17.2% of target doses 97/103 mg twice daily, *P* = 0.515), beta-blocker (48.0 ± 39.2% vs. 51.8 ± 44.0%, *P* = 0.260), mineralocorticoid receptor antagonist (59.6 ± 28.8% vs. 56.4 ± 27.2%, *P* = 0.198), and ivabradine (57.1 ± 16.1% vs. 58.3 ± 15.6%, *P* = 0.584).

Changes in echocardiographic parameter

A total of 4239 echocardiographic examinations were analysed. Absolute change in LVEF and percentage change

in LVESVi following SAC/VAL treatment over time are plotted in *Figure 2*. The improvement in LVEF was significantly higher (8.4% ± 11.3% vs. 4.5% ± 8.1%, $P < 0.001$), and the percentage change in LVESVi was significantly greater (−14.4% ± 25.9% vs. −9.6% ± 23.1%, $P = 0.004$) in Group 2 than Group 1 patients a year following SAC/VAL treatment. Differences in the alternations in LVEF and LVESVi remained significant at the 3 year follow-up (*P*-values <0.001 and 0.015, respectively).

Among Group 1 patients, 27 patients (8.7%) received CRT implantation within 1 year following SAC/VAL treatment (91–347 days, median 159 days following SAC/VAL treatment). In Group 1, the percentages of initial eligible-CRT patients with LVEF improving to >35% were 14.9%, 22.5%, 28.8%, and 32.3% at 3, 6, 9, and 12 months following SAC/VAL treatment, respectively. Furthermore, the percentages of LVEF improving ≥50% were 0.7%, 2.5%, 4.5%, and 5.2% at 3, 6, 9, and 12 months, respectively. *Figure 3* demonstrates the Kaplan–Meier curves for time from SAC/VAL initiation to LVEF improvement achieving three measurements in the current study: LVEF >35%, heart failure with improved EF, or LVEF ≥50%. Supporting Information, *Figure S1* demonstrates the result of the sensitivity analysis. After pooling the patients with CRT implantation after SAC/VAL, the improvements of LVEF were still more significant in Group 2 than in Group 1 patients.

Proportions and event rates of different time periods of ejection fraction

Among Group 2 patients, the mean proportions of time period of LVEF measurement <35%, 35–50%, and ≥50% over the total follow-up period were 59.9% ± 39.3%, 21.0% ± 31.2%, and 19.2% ± 31.9%, respectively. The proportion of time period of LVEF measurement <35% over the total follow-up period was significantly higher in Group 1 than Group 2 patients (75.3% ± 35.7% vs. 59.9% ± 39.3%, $P < 0.001$), whereas the proportion of time period of LVEF measurement ≥50% over the total follow-up period was significantly lower in Group 1 than Group 2 patients (7.9% ± 23.2% vs. 19.2% ± 31.9%, $P < 0.001$).

The overall incidences of all-cause mortality and cardiovascular mortality were 6.7 (95% CI 5.9–7.7) and 4.9 (95% CI 4.2–5.7) per 100-patient year, respectively. A total of 765 heart failure hospitalization events occurred in 393 patients during follow-up (24.6 events per 100-patient year, 95% CI 23.2–26.2). In general, adverse cardiac events were more likely to occur during the time period of LVEF measurement <35% and less likely to occur during the time period of LVEF measurement ≥50% (*Figure 4*). Among Group 1 patients who initially fulfilled the criteria for CRT, despite partial improvement in LVEF, the incidences of cardiovascular mortality and total heart failure hospitalization during the time period of LVEF measurement 35–50% were 3.6 (95% CI 1.6–7.9) and 17.1 (95% CI 12.5–24.3) per 100-patient year, respectively.

Factors associated with reverse cardiac remodelling

A total of 297 (25.4%) patients had LVEF improvement to ≥50%, whereas as 605 (51.8%) patients had a ≥15% decrease in LVESVi from baseline during follow-up. Multivariate Cox regression analysis is shown in *Table 2*. Female gender, shorter heart failure duration, and higher SAC/VAL initiation dosage were independently associated with better chance of LVEF improvement to ≥50%, whereas ischemic aetiology of heart failure, larger baseline LVESVi, and broader QRS duration were independently associated with lower chance of LVEF

Figure 2 Change in echocardiographic parameters following sacubitril/valsartan treatment over time. (A) Absolute change in LVEF and (B) percentage change in LVESVi (presented as mean and standard error of the mean).

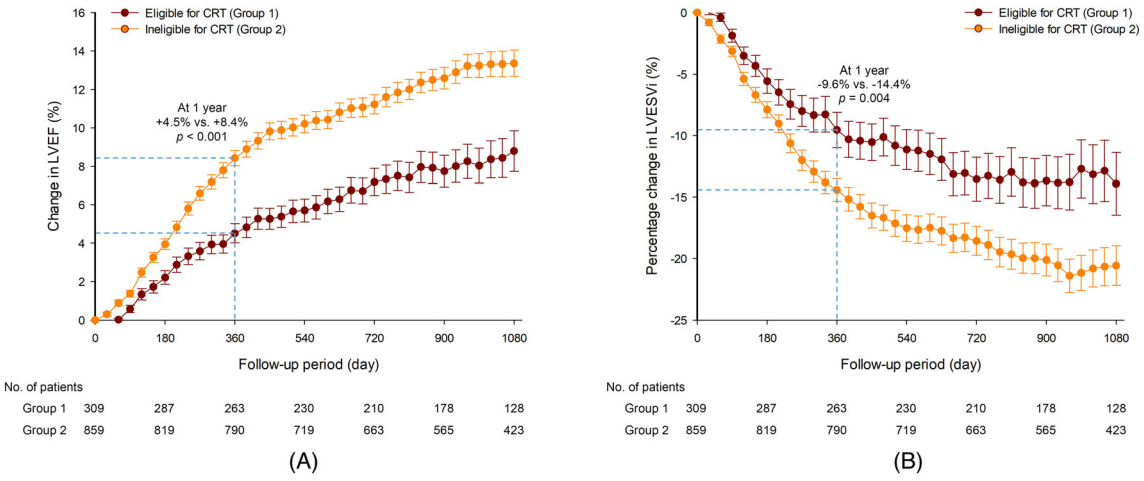
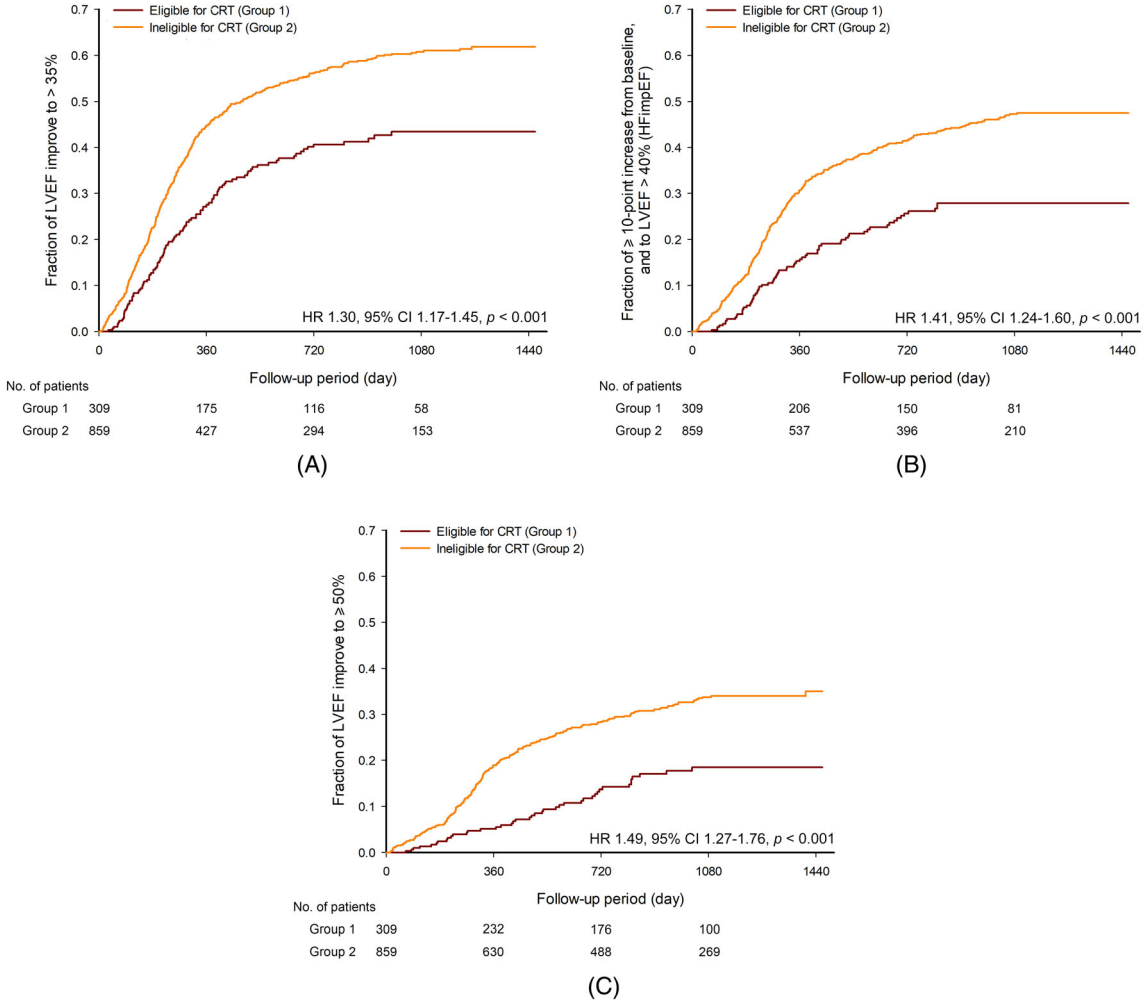


Figure 3 Kaplan–Meier survival plots of time from sacubitril/valsartan initiation to echocardiographic endpoints. (A) LVEF improves to >35%, (B) Heart failure with improved EF, and (C) LVEF improves to ≥50%, stratified by study groups. Echocardiographic data after CRT implantation were excluded.



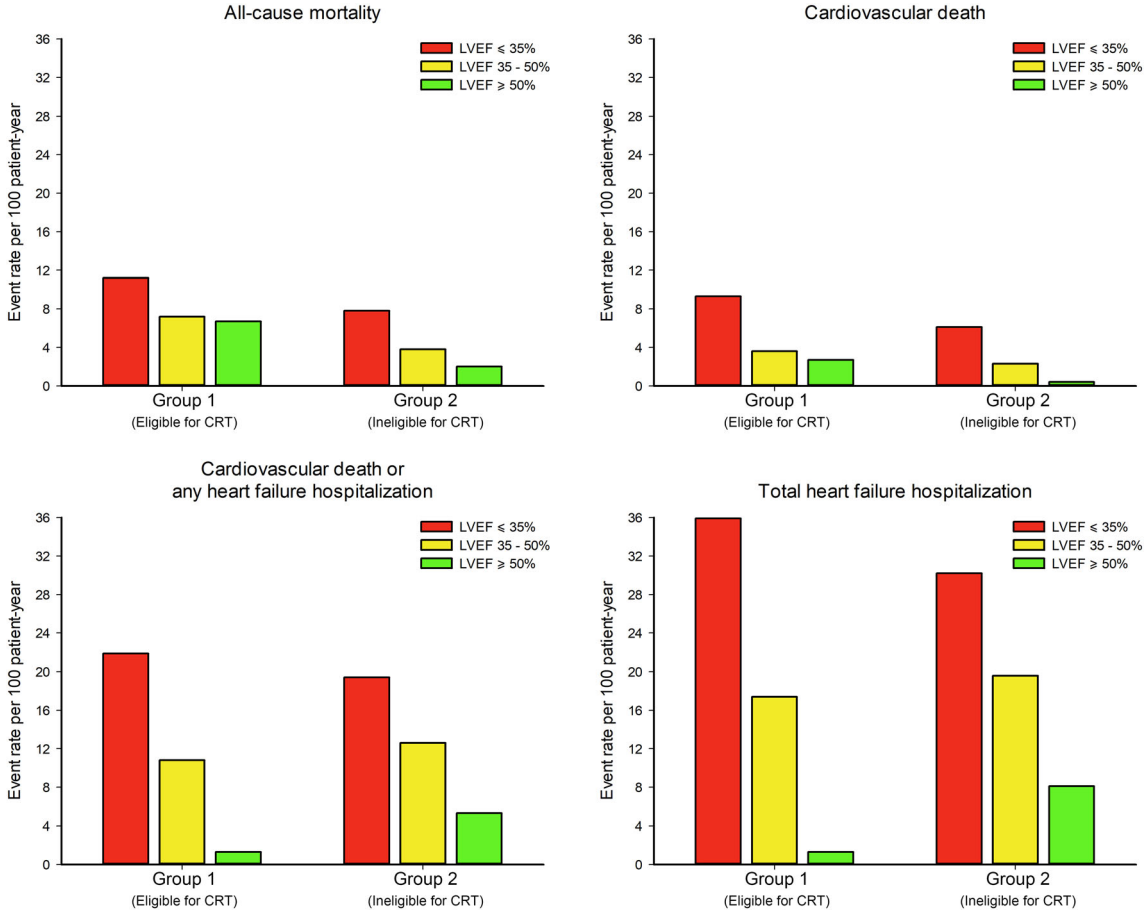
improvement to ≥50%. Multivariate analysis for ≥15% decrease in LVESVi from baseline showed similar results.

Discussion

In this multicentre study enrolling more than 1100 HFrEF patients, the major findings were (i) patients who had wide QRS duration and were eligible for CRT implantation had a smaller degree of LV structural and functional improvement than those with a narrow QRS complex and ineligible for CRT following SAC/VAL treatment and (ii) patients with partial reverse cardiac remodelling (i.e. LVEF between 35% and 50%) following SAC/VAL treatment were still at risk for adverse events.

The use of conventional GDMT can achieve LV functional recovery in many trials. In general, the use of renin–angiotensin system inhibitors in conjunction with beta-blockers may improve LVEF from 2% to 12% over the course of 6–20 months.[2–5,20,21] However, studies that analysed patients with different QRS durations revealed attenuated LVEF improvement or lack of LVEF improvement in patients with a wide QRS complex by using the conventional GDMT.[14,15] The improvement of LVEF to >35% in patients with LBBB after GDMT was observed in only 23% and 6% in the Duke University cohort[14] and the NEOLITH study,[15] respectively. Moreover, the absolute increase in LVEF following treatment was only 3.4% and 3.3% in the Duke University cohort and the NEOLITH study, respectively. As stated previously, these studies were conducted before the era of SAC/VAL. The current study fills this gap and provides evidence for the reverse remodelling effect of SAC/VAL on patients with different QRS durations. Among HFrEF patients with prolonged QRS duration, SAC/VAL treatment showed a mean 4.5% increase in LVEF over 1 year. The improvement of LVEF to >35% in patients with a wide QRS complex following SAC/VAL treatment

Figure 4 Event rate during different time periods of LVEF measurement in two study groups.



alone was observed in 81 over 251 (32.3%) patients over 1 year. This better functional improvement of LV adds to the growing body of evidence that SAC/VAL has more favourable reverse remodelling effects than conventional renin–angiotensin system inhibitors.

Moreover, our study findings echoed the results of previous studies that a wide QRS complex is independently associated with poor LVEF improvement compared with a narrow QRS complex,[14,15] even with SAC/VAL treatment. In patients who retained LVEF $<35\%$ following treatment, CRT should be implanted. In the current study, a portion of initially CRT eligible patients may have LVEF improvement to $>35\%$ but not to 50%. Although these patients were beyond the indication for CRT implantation in accordance with LVEF criteria, their risks remained high. Our data showed that cardiovascular death and/or heart failure hospitalization events were significantly higher during the time period of LVEF measurement between 35% and 50% than those during the time period of LVEF measurement $\geq 50\%$. This finding raises the question of whether or not CRT implantation could improve the clinical outcome of patients with a wide QRS complex and baseline LVEF $\leq 35\%$ if LVEF increases to 35% but $<50\%$ following SAC/VAL treatment. Randomized controlled trials designed specifically to evaluate CRT in patients with improving LVEF after pharmacological therapy are lacking. A study reported that LBBB is an independent risk factor for heart function re-deterioration in patients with recovered LVEF.[22] In our study, only 5.2% patients initially eligible for CRT implantation had LVEF improvement to $\geq 50\%$ with SAC/VAL treatment alone for 12 months, suggesting the important role of electrical dyssynchrony in a substantial portion of patients. Besides, the previous studies demonstrated that permanent atrial fibrillation may influence biventricular pacing percentage and reverse cardiac remodelling in HFrEF patients receiving CRT implantation.[23,24] Nevertheless, this study showed that the association between the effects of SAC/VAL in reverse cardiac remodelling and permanent atrial fibrillation were insignificant regardless of the QRS durations in Groups 1 and 2. Therefore, more studies were warranted to clarify the association of SAC/VAL effects in reverse cardiac remodelling and permanent atrial fibrillation in HFrEF patients with different QRS durations.

Table 2 Univariate and multivariate analyses for the factors associated with reverse cardiac remodelling

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*P*-value	Hazard ratio	95% confidence interval	*P*-value
Model 1 (QRS duration)						
LVEF improves to ≥50%						
QRS duration (per ↑10 ms)	0.85	0.81–0.89	<0.001	0.91	0.86–0.95	<0.001
Gender (female)	1.67	1.32–2.11	<0.001	1.36	1.06–1.75	0.015
Ischemic aetiology	0.52	0.41–0.67	<0.001	0.56	0.43–0.73	<0.001
Heart failure duration <1 year	2.68	2.14–3.37	<0.001	2.25	1.77–2.86	<0.001
Prior malignancy	1.58	1.09–2.31	0.017	NS	NS	NS
ICD implantation	0.50	0.28–0.90	0.020	NS	NS	NS
Systolic blood pressure (per ↑10 mmHg)	1.10	1.04–1.17	0.002	NS	NS	NS
Baseline LVEF (per ↑5%)	1.44	1.29–1.61	<0.001	NS	NS	NS
Baseline LA diameter (per ↑5 mm)	0.91	0.85–0.97	0.005	NS	NS	NS
Baseline LVESVi (per ↑10 mL/m^2)	0.77	0.72–0.81	<0.001	0.78	0.73–0.83	<0.001
SAC/VAL initiation dose (per ↑50 mg)	1.31	1.20–1.44	<0.001	1.31	1.19–1.43	<0.001
LVESVi decreases ≥15% from baseline						
QRS duration (per ↑10 ms)	0.95	0.93–0.98	0.001	0.97	0.94–0.99	0.036
Gender (Female)	1.39	1.17–1.65	<0.001	1.29	1.08–1.54	0.004
Ischemic aetiology	0.76	0.65–0.89	0.001	0.80	0.68–0.94	0.008
Heart failure duration <1 year	1.99	1.69–2.35	<0.001	1.83	1.54–2.16	<0.001
Body mass index	0.98	0.97–1.00	0.055	NS	NS	NS
Chronic kidney disease	0.84	0.71–1.00	0.045	NS	NS	NS
Systolic blood pressure (per ↑10 mmHg)	1.01	1.00–1.09	0.058	NS	NS	NS
Baseline LVESVi (per ↑10 mL/m^2)	0.95	0.92–0.98	0.002	0.96	0.93–0.99	0.020
SAC/VAL initiation dose (per ↑50 mg)	1.11	1.04–1.19	0.003	1.11	1.03–1.19	0.005
Model 2 (CRT eligibility)						
LVEF improves to ≥50%						
Eligible for CRT	0.53	0.39–0.71	<0.001	0.47	0.33–0.65	<0.001
Gender (Female)	1.67	1.32–2.11	<0.001	1.40	1.09–1.79	0.009
Ischemic aetiology	0.52	0.41–0.67	<0.001	0.52	0.40–0.67	<0.001
Heart failure duration <1 year	2.68	2.14–3.37	<0.001	2.21	1.74–2.80	<0.001
Prior malignancy	1.58	1.09–2.31	0.017	NS	NS	NS
ICD implantation	0.50	0.28–0.90	0.020	NS	NS	NS
Systolic blood pressure (per ↑10 mmHg)	1.10	1.04–1.17	0.002	NS	NS	NS
Baseline LVEF (per ↑5%)	1.44	1.29–1.61	<0.001	NS	NS	NS
Baseline LA diameter (per ↑5 mm)	0.91	0.85–0.97	0.005	NS	NS	NS
Baseline LVESVi (per ↑10 mL/m^2)	0.77	0.72–0.81	<0.001	0.77	0.72–0.82	<0.001
SAC/VAL initiation dose (per ↑50 mg)	1.31	1.20–1.44	<0.001	1.33	1.21–1.46	<0.001
LVESVi decreases ≥15% from baseline						
Eligible for CRT	0.75	0.62–0.91	0.004	0.77	0.63–0.94	0.011
Gender (female)	1.39	1.17–1.65	<0.001	1.31	1.10–1.57	0.003
Ischemic aetiology	0.76	0.65–0.89	0.001	0.80	0.67–0.94	0.008
Heart failure duration <1 year	1.99	1.69–2.35	<0.001	1.87	1.57–2.21	<0.001
Body mass index	0.98	0.97–1.00	0.055	NS	NS	NS
Chronic kidney disease	0.84	0.71–1.00	0.045	NS	NS	NS
Systolic blood pressure (per ↑10 mmHg)	1.01	1.00–1.09	0.058	NS	NS	NS
Baseline LVESVi (per ↑10 mL/m^2)	0.95	0.92–0.98	0.002	0.96	0.93–0.99	0.026
SAC/VAL initiation dose (per ↑50 mg)	1.11	1.04–1.19	0.003	1.12	1.04–1.20	0.002

The tested variables in the multivariate analysis were those with a *P*-value <0.1 in the univariate model.
CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LA, left atrial; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; SAC/VAL, sacubitril/valsartan.

Several novel heart failure medications have been introduced recently. In contrast to initiating each class of drug in a stepwise fashion, experts advocated the timely, non-stepped approach for heart failure disease-modifying treatments.[25] However, optimal timing for CRT implantation following these novel heart failure drugs remained uncertain. Our data demonstrated that reverse cardiac remodelling mostly occurred within a year following SAC/VAL treatment (*Figure 2*). This 'steep rise' appearance of remodelling trajectory was similarly reported by a Spanish group before the era of SAC/VAL.[26] Prediction of LV functional and structural recovery in patients with HFrEF may allow physicians to make accurate decisions regarding the timing of GDMT adjustment and referral for advanced heart failure treatment. In this current study, we further found that a higher dose of SAC/VAL and a shorter duration of heart failure may be associated with better progress of LVEF and LVESVi, independently. The finding was consistent with the Belgian study, emphasizing the importance of early titration and optimization of GDMT.[27] Furthermore, other factors associated with reverse LV remodelling after SAC/VAL treatment, including female gender, non-ischemic aetiology, and less severe adverse

cardiac remodelling at baseline, were similarly reported in the previous studies before the era of SAC/VAL.[28] Among 612 patients treated with implantable cardioverter-defibrillator only in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial, baseline systolic blood pressure ≥140 mmHg, serum creatinine level <1.0 mg/dL, QRS duration <170 ms, and non-ischemic aetiology predicted LV reverse remodelling at 1 year. The benefits of CRT were only significant among those with little or no reverse remodelling predictors, emphasizing the importance to deliver early CRT implantation in patients who are unlikely to experience reverse remodelling by medical therapy alone.[29]

Although heart function might continuously improve over time, prolonged waiting for LV functional and/or structural recovery might also put patients eligible for CRT at risks of adverse cardiac events. Considering the inferior reverse remodelling effect of the conventional renin–angiotensin system inhibitors among these particular populations, we proposed that SAC/VAL, instead of renin-angiotensin system inhibitors alone, should be initiated preferentially in HFrEF patients with prolonged QRS duration. Moreover, the effect of LV reverse remodelling should be reassessed 3–6 months following SAC/VAL treatment, and CRT should be implanted timely if patients' LVEF did not recover.

Several limitations inherent in the retrospective design of this study should be mentioned. First, no echocardiography core laboratory was involved in the current study. Second, all patients in the current study received SAC/VAL treatment, and no control group patients received conventional renin–angiotensin system inhibitors. Third, echocardiography data before traditional GDMT were not available, and the impacts of these traditional agents on the effect of reverse remodelling before SAC/VAL could not be assessed. Fourth, decision for CRT implantation in current study was based on real-world practice by the participating cardiologists and healthcare systems, which may lead to potential unmeasured biases.

In conclusion, among patients with baseline LVEF ≤35%, those who were eligible for CRT in accordance with ECG criteria had a smaller degree of ventricular functional improvement than those who were ineligible for CRT following SAC/VAL treatment. Timely CRT implantation should be considered for patients with prolonged QRS duration who did not response to SAC/VAL treatment.

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Conflict of interest

None declared.

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Supporting information

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

Figure S1. Kaplan–Meier survival plots of time from sacubitril/valsartan initiation to echocardiographic endpoints – (A) LVEF improves to >35%, (B) Heart failure with improved EF; and (C) LVEF improves to ≥50%, stratified by study groups. Echocardiographic data after CRT implantation were included.

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