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ORIGINAL ARTICLE
Heart failure/cardiomyopathy

Different left ventricular remodelling patterns and clinical outcomes between non-ischaemic and ischaemic aetiologies in heart failure patients receiving sacubitril/valsartan treatment

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Aims Although the beneficial effect of sacubitril/valsartan (SAC/VAL) compared to enalapril was consistent across ischaemic cardiomyopathy (ICM) and non-ischaemic cardiomyopathy (NICM) groups, the PARADIGM-HF study did not analyse the effect of ventricular remodelling on patients with different aetiologies, which may affect clinical treatment outcomes. This study aimed to compare left ventricular ejection fraction (LVEF) following SAC/VAL treatment and its association with clinical outcomes.

Methods and results A total of 1576 patients were analysed. Patients were grouped by LVEF changes following SAC/VAL treatment for 8-month period. LVEF improvement ≥15% was defined as 'significant improvement', and <5% or worse was classified as 'lack of improvement'. The primary outcome was a composite of cardiovascular death and unplanned hospitalization for heart failure. Patients with NICM had lower baseline LVEF but improvement was significantly greater comparing to those with ICM (baseline 28.0 ± 7.7% vs. 30.1 ± 7.1%, $P < 0.001$, LVEF increase of 11.1 ± 12.6% vs. 6.7 ± 10.2%, $P < 0.001$). The effect of functional improvement of SAC/VAL on NICM patients showed bimodal distribution. Primary endpoints were inversely associated with LVEF changes in NICM patients: adjusted hazard ratio was 0.42 [95% confidence interval (CI) 0.31–0.58, $P < 0.001$] for NICM patients with significant improvement, and was 1.73 (95% CI 1.38–2.16, $P < 0.001$) for NICM patients but lack of improvement. Primary endpoints of ICM patients did not demonstrate an association with LVEF changes.

Conclusion Patients with NICM had higher degree of LVEF improvement than those with ICM following SAC/VAL treatment, and significant improvement of LVEF in NICM patients indicates favourable outcome.

Keywords Heart failure • Sacubitril/valsartan • Aetiology • Left ventricular ejection fraction • Reverse remodelling

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Introduction

The aetiology of heart failure (HF) was generally divided into ischaemic and non-ischaemic causes. Aetiology is one aspect of phenotyping which is an important factor to draw up treatment strategy in the era ahead for HF personalized medicine.[1] Several studies demonstrated better prognosis of non-ischaemic cardiomyopathy (NICM) patients than those with ischaemic cardiomyopathy (ICM).[2–4] Although many standard oral HF treatments such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and mineralocorticoid receptor antagonist appeared equally effective across ICM and NICM subgroups, some data purposed that implantable cardioverter-defibrillator (ICD) therapy may be less effective in patients with NICM, whereas cardiac resynchronization therapy may be more effective to reverse left ventricular remodelling in patients with NICM, comparing to those with ischaemic aetiology.[5–9]

Left ventricular reverse remodelling is associated with improved cardiac function and better outcome.[10] Although the benefit of sacubitril/valsartan (SAC/VAL) replacing angiotensin-converting enzyme inhibitor has been demonstrated and the effect was consistent across aetiologic categories in PARADIGM-HF study, the effect of left ventricular reverse remodelling of SAC/VAL on patients with different aetiologies of HF, which may significantly affect clinical treatment outcomes, was not analysed.[11,12] The present study aimed to compare left ventricular ejection fraction (LVEF) alternations following SAC/VAL treatment and its association with clinical outcomes in patients with different aetiologies of HF.

Methods

Study designs and patient characteristics

The present study extracted and analysed data from a multicentre HF cohort in Taiwan. The study complied with the Declaration of Helsinki's ethical principles and was approved by the institutional ethics committee of each hospital.

The TAROT-HF (Treatment with Angiotensin Receptor neprilysin inhibitor for Taiwan Heart Failure patients) study is a multicentre retrospective study enrolling patients with symptomatic HF and reduced ejection fraction (HFrEF), whom had been on SAC/VAL treatment from nine hospitals between 2017 and 2018. No informed consent was obtained because of retrospective study design. The protocol consisted of 50 variables per patient, comprising age, sex, HF aetiologies, systolic blood pressure, New York Heart Association functional class, LVEF, body mass index, estimated glomerular filtration rate (eGFR), comorbidities, drug therapy, laboratory data and use of cardiac devices.

A total of 1738 patients who had received SAC/VAL between 2017 and 2018 were consecutively screened. The current study's inclusion criteria were (i) male or female, age more than 20 years old, and (ii) patients with New York Heart Association class II, III, or IV HF symptoms, and with LVEF of 40% or less. The exclusion criteria for the current study included (i) patients refused medical advice or lost to follow-up, (ii) echocardiographic LVEF ≥40% before the initiation of SAC/VAL, and (iii) patients permanently discontinued SAC/VAL within 3 months after initiation. After applying the inclusion and exclusion criteria, a total of 1576 patients were enrolled for analysis. Patients were grouped by HF aetiologies as ICM and NICM groups. The flowchart of the current study was shown in *Figure 1*.

Echocardiography

Data from transthoracic echocardiographic studies were collected at baseline and at 8 ± 2 months following SAC/VAL treatment. For evaluating the relationships between echocardiographic values and SAC/VAL treatment, patients who did not have follow-up echocardiographic data, died or permanently discontinued SAC/VAL treatment before echocardiographic follow-up were excluded (*Figure 1*). 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 and the Taiwan Society of Cardiology Guideline for Heart Failure by trained ultrasonographers.[13,14] The reports were verified by expert cardiologists unaware of patient's clinical data and medications.

Left ventricular structural and functional alternations were assessed by the absolute change in LVEF and percentage change in LVESVI. LVEF improvement ≥15% was defined as 'significant improvement', and 5–15% as 'marginal improvement'. LVEF improvement <5% or worse was classified as 'lack of improvement'. Improvement in LVESVI by ≥15% was considered as 'significant left ventricular reverse remodelling'.

Study outcomes

This study's primary outcome was a composite of death from cardiovascular causes or first hospitalization for HF. Secondary outcomes included death from cardiovascular causes alone, all-cause mortality alone, and hospital readmissions due to HF alone. The patients were censored at the outcome events or at the end of the follow-up period (February 2020).

Statistical analysis

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

Incidence rates for each outcome are presented per 100 patient-years of follow-up. Event rates in ICM and NICM groups were estimated by the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to compare hazard ratios (HRs) with 95% confidence intervals (CIs) according to aetiology and LVEF changes. The HR was adjusted for the following baseline characteristic: age, gender, body mass index, systolic blood pressure, eGFR, New York Heart Association functional class, history of HF hospitalization, atrial fibrillation, hypertension, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, hyperuricaemia, prior stroke, cardiac resynchronization therapy device, ICD, prescription of beta-blocker, mineralocorticoid receptor antagonist, and ivabradine.

Multivariate logistic regression analysis was used to find potential baseline factors for significant left ventricular reverse remodelling (LVESVI improved by ≥ 15%) following SAC/VAL treatment. 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).

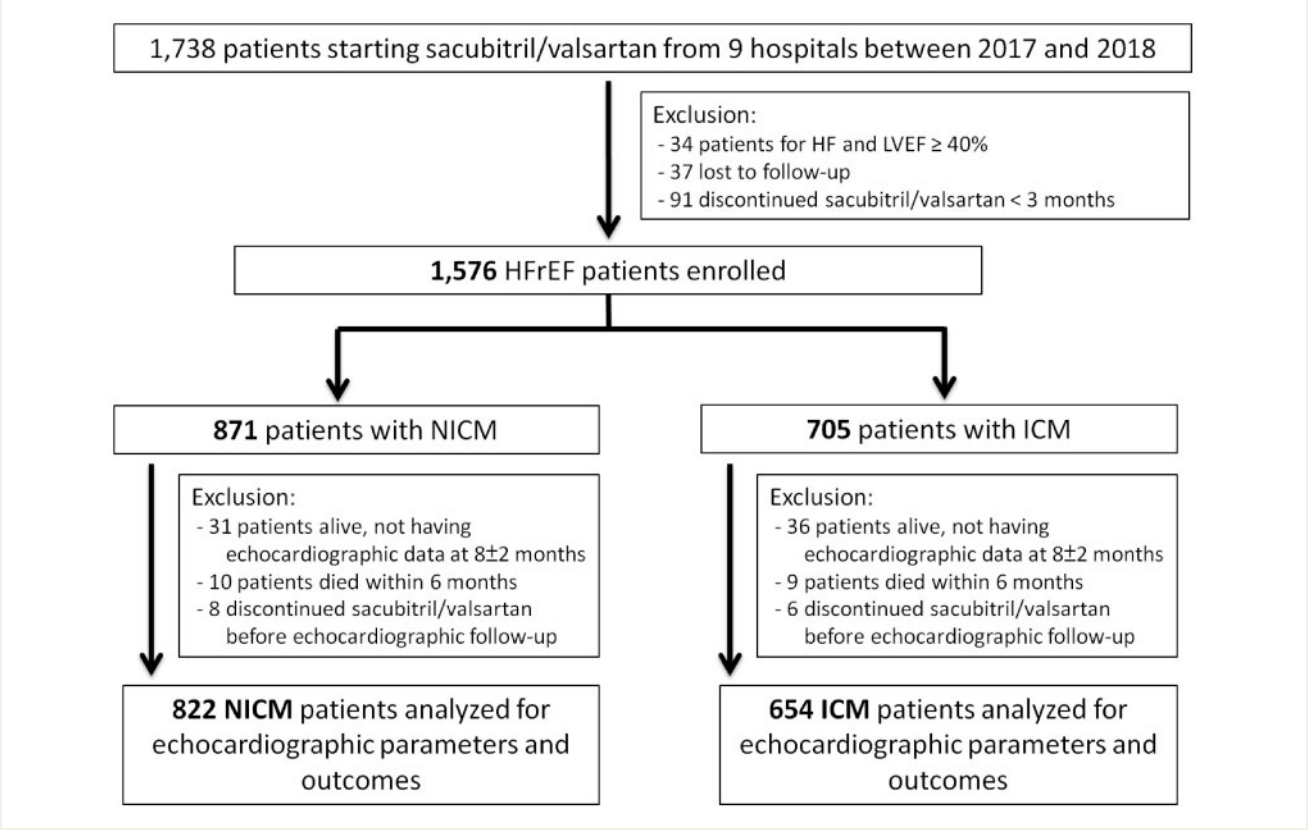

Figure 1 Flow chart of the current study.

Results

Baseline characteristics

A total of 1576 HFrEF patients were included in this study, including 871 patients with NICM and 705 patients with ICM. Patients with ICM were significantly older, thinner, more male, and prone to have associated hypertension, diabetes, dyslipidaemia, peripheral arterial disease, chronic kidney disease, and history of stroke. On the other hand, patients with NICM had higher likelihood of atrial fibrillation. Among 871 patients with NICM, 545 (62.6% of non-ischaemic patients) had idiopathic dilated cardiomyopathy, 141 (16.1%) had a hypertensive cause, 110 (12.6%) had a valvular cause, 37 (4.2%) had tachycardia-related cardiomyopathy, and 38 (4.4%) had other causes (3 viral, 5 alcoholic, 11 drug-related, 9 peripartum-related, and 10 others). *Table 1* demonstrated baseline characteristic of patients with different aetiologies of HF.

Baseline prescription rates of beta-blocker, ivabradine, and anti-arrhythmic agents were similar between ICM and NICM groups. Patients in the NICM group were more likely to receive and mineralocorticoid receptor antagonist, digoxin, anti-coagulants, and cardiac resynchronization therapy, whereas patients in the ICM group were more likely to receive nitrate, anti-platelet agents, and statin.

Functional improvement and cardiac remodelling following sacubitril/valsartan treatment

After excluding patients without having follow-up echocardiographic studies (*Figure 1*), 1476 patients (822 patients in the NICM group and 654 in the ICM group) were analysed for the echocardiographic measurements. Distributions of baseline LVEF among patients with different HF aetiologies were shown in *Figure 2A*. Patients with NICM had significantly lower LVEF value (28.0 ± 7.7% vs. 30.1 ± 7.1%, $P < 0.001$), larger left atrial diameter and larger left ventricular volume at baseline than those with ICM. The proportion of severe mitral regurgitation was also higher in patients with NICM than those with ICM (20.0% vs. 9.9%, $P < 0.001$).

Mean LVEF change by echocardiographic follow-up at 8 ± 2 months in patients with NICM was 11.2 ± 12.9%, which was significantly higher than those with ICM (6.7 ± 10.2%, $P < 0.001$). Greater degrees of decreasing left ventricular volume (Δ LVEDVI -9.3 ± 21.8 ml/m^2 vs. -4.3 ± 16.9 ml/m^2, $P < 0.001$; Δ LVESVI -14.3 ± 21.8 mL/m^2 vs. -7.9 ± 16.5 mL/m^2, $P < 0.001$), left atrial diameter and MR severity were also demonstrated in patients in NICM group than those in ICM group. Among the patients with NICM, mean LVEF improvements were more significant in patients with hypertensive cause (17.8 ± 12.7%), followed by tachycardia-related cardiomyopathy (15.4 ± 12.2%), valvular cause (11.7 ± 14.3%), other

Table 1 Baseline characteristics among patients with different heart failure aetiologies

	NICM (*n* = 871)	ICM (*n* = 705)	*P*-value
Age (y/o)	59.0 ± 15.5	66.5 ± 12.2	<0.001
Male gender	598 (68.7)	586 (83.1)	<0.001
Body mass index (kg/m2)	25.9 ± 5.3	25.2 ± 4.3	0.005
Medical history			
Diabetes	277 (31.8)	384 (54.5)	<0.001
Hypertension	409 (47.0)	440 (62.4)	<0.001
Angiographic coronary artery stenosis ≥50%	118 (13.5)	705 (100.0)	<0.001
Prior myocardial infarction	1 (0.1)	449 (63.7)	<0.001
Percutaneous coronary intervention	76 (8.7)	456 (64.7)	<0.001
Coronary artery bypass surgery	0 (0.0)	174 (24.7)	<0.001
Peripheral arterial disease	28 (3.2)	77 (10.9)	<0.001
Prior stroke/TIA	80 (9.2)	106 (15.0)	<0.001
Atrial fibrillation	317 (36.4)	211 (29.9)	0.007
Dyslipidaemia	309 (35.5)	433 (61.4)	<0.001
COPD	93 (10.7)	64 (9.1)	0.292
Previous HHF	557 (63.9)	434 (61.6)	0.329
Chronic kidney disease	237 (27.2)	282 (40.0)	<0.001
Hyperuricaemia	171 (19.6)	114 (16.2)	0.076
New York Heart Association functional class			
II	551 (63.2)	432 (61.3)	0.211
III	286 (32.8)	231 (32.8)	
IV	34 (3.9)	41 (5.8)	
Systolic blood pressure (mmHg)	122.3 ± 20.6	121.8 ± 19.1	0.632
Estimated GFR (mL/min/1.73m2)	67.4 ± 30.8	59.1 ± 35.1	<0.001
Heart failure treatment			
Sacubitril/valsartan	871 (100.0)	705 (100.0)	—
Beta-blocker	695 (79.8)	538 (76.3)	0.096
Mineralocorticoid receptor antagonist	587 (67.4)	396 (56.2)	<0.001
Ivabradine	190 (21.8)	143 (20.3)	0.459
Digoxin	207 (23.8)	114 (16.2)	<0.001
Nitrate	135 (15.5)	205 (29.1)	<0.001
Anti-platelet agents	255 (29.3)	557 (79.0)	<0.001
Anti-coagulants	279 (32.0)	150 (21.3)	<0.001
Statin	237 (27.2)	457 (64.8)	<0.001
Anti-arrhythmic agents	160 (18.4)	123 (17.4)	0.635
Cardiac resynchronization therapy	61 (7.0)	30 (4.3)	0.020
Implantable cardioverter-defibrillator	65 (7.5)	67 (9.5)	0.146

COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HHF, hospitalization for HF; ICM, ischaemic cardiomyopathy; NICM, non-ischaemic cardiomyopathy; TIA, transient ischaemic attack.

cause (10.6 ± 12.4%), and lesser in idiopathic dilated cardiomyopathy (9.2 ± 12.1%).

The detailed distribution and changes of echocardiographic measurements were shown in *Table 2* and *Figure 2B*. In patients with NICM, the proportions of significant, marginal, and lack of improvement groups were 36.9%, 23.2%, and 39.9%, while in patients with ICM, the proportions of each group were 20.3%, 29.5%, and 50.2%, respectively. The distribution of LVEF improvement following SAC/VAL treatment in patients with NICM showed a bimodal distribution, whereas patients with ICM showed a right-skewed distribution pattern (*Figure 2B*).

Significant left ventricular reverse remodelling following sacubitril/valsartan treatment: characteristics and associated factors

Significant left ventricular reverse remodelling was observed in 730 patients. Characteristics among patients with and without significant reverse remodelling following SAC/VAL treatment were shown in *Table 3*. At baseline, patients without significant reverse remodelling were more male, had lower systolic blood pressure and larger left ventricular volume, and prone to have associated ICM, peripheral

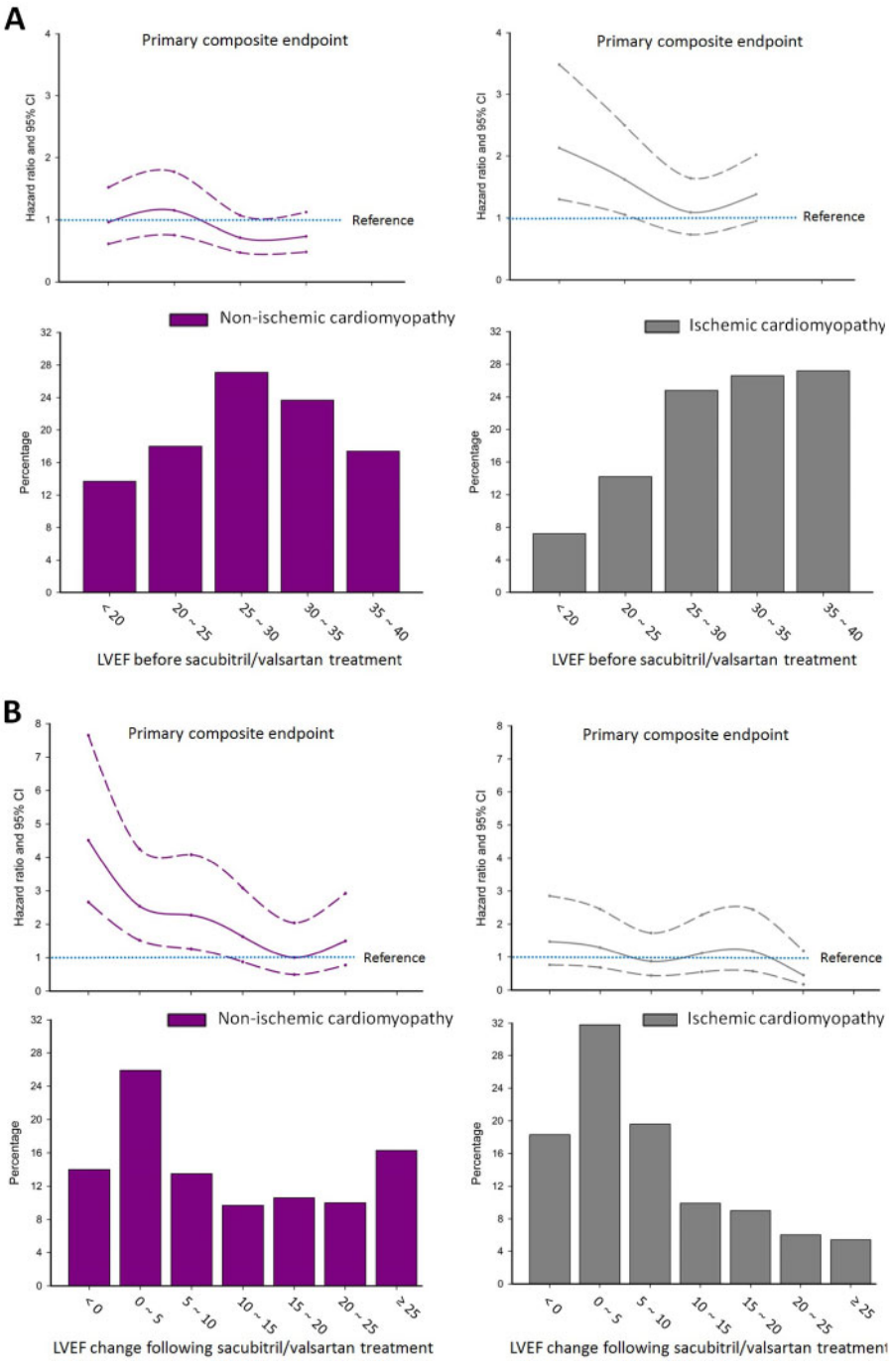

Figure 2 Hazard ratios for primary composite endpoint stratified by (*A*) baseline left ventricular ejection fraction (LVEF, reference = baseline LVEF 35–40%) and (*B*) LVEF changes following sacubitril/valsartan treatment (reference = LVEF improves of ≥25%) in patients with non-ischaemic and ischaemic cardiomyopathy.

arterial disease, and dyslipidaemia. On the other hand, patients with significant reverse remodelling tend to receive a higher initial dose of SAC/VAL and were more likely to receive ivabradine but less likely to receive ICD implantation. After multivariate analysis, female sex, non-ischaemic aetiology, lower baseline LVEDVI, free from peripheral arterial disease, not receiving ICD implantation, concomitant ivabradine treatment, and higher initial dose of SAC/VAL were associated with a better likelihood of left ventricular reverse remodelling (*Table 4*).

Table 2 Distribution of baseline LVEF, follow-up LVEF, and LVEF changes among patients with different heart failure aetiologies

	NICM (*n* = 822)	ICM (*n* = 654)	*P*-value
Baseline LVEF (%)	28.0 ± 7.7	30.1 ± 7.1	<0.001
Follow-up LVEF (%)	39.2 ± 14.4	36.8 ± 11.9	<0.001
Δ LVEF (%)	11.2 ± 12.9	6.7 ± 10.2	<0.001
Lack of improvement	328 (39.9)	328 (50.2)	<0.001
Marginal improvement	191 (23.2)	193 (29.5)	
Significant improvement	303 (36.9)	133 (20.3)	
Baseline LVEDVI (mL/m2)	98.4 ± 33.7	92.1 ± 26.4	<0.001
Follow-up LVEDVI (mL/m2)	89.1 ± 36.9	87.8 ± 27.4	0.414
Δ LVEDVI (mL/m2)	-9.3 ± 21.8	-4.3 ± 16.9	<0.001
Baseline LVESVI (mL/m2)	71.5 ± 28.9	64.7 ± 22.4	<0.001
Follow-up LVESVI (mL/m2)	57.2 ± 34.0	56.8 ± 24.9	0.820
Δ LVESVI (mL/m2)	-14.3 ± 21.8	-7.9 ± 16.5	<0.001
Baseline left atrial diameter (mm)	46.7 ± 9.5	43.5 ± 8.3	<0.001
Follow-up left atrial diameter (mm)	44.0 ± 9.9	42.4 ± 7.9	0.001
Δ Left atrial diameter (mm)	-2.8 ± 6.7	-1.1 ± 5.4	<0.001
Baseline mitral regurgitation severity			<0.001
Mild or minimal	418 (50.9)	428 (65.4)	
Moderate	240 (29.2)	161 (24.6)	
Severe	164 (20.0)	65 (9.9)	
Follow-up mitral regurgitation severity			0.015
Mild or minimal	596 (72.5)	514 (78.6)	
Moderate	158 (19.2)	105 (16.1)	
Severe	68 (8.3)	35 (5.4)	

ICM, ischaemic cardiomyopathy; Lack of improvement, LVEF improves of <5% or deteriorates; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; Marginal improvement, LVEF improves of 5–15%; NICM, non-ischaemic cardiomyopathy; Significant improvement, LVEF improves of ≥15%.

Clinical outcomes

During a mean follow-up period of 770 days, overall incidences of composite primary endpoint, cardiovascular death alone, first unplanned HF readmission alone, and all-cause mortality alone were 15.06, 3.95, 13.81, and 5.52 per 100-person years, respectively. Kaplan–Meier survival curves (*Figure 3A–D*) showed significantly lower risk of these clinical outcomes in HF patients with NICM than those with ICM. Twelve patients received heart transplantation, and four patients received left ventricular assist device (0.39 and 0.13 per 100-per years) during the follow-up period, respectively.

Figure 2A demonstrated the association between baseline LVEF and the occurrences of composite primary endpoints among patients with different aetiologies. Among patients with ICM, composite primary endpoints were higher in patients with a lesser baseline LVEF than those with relatively better baseline LVEF. On the other hand, there were no significant associations between baseline LVEF and outcomes among patients with NICM. *Figure 2B* showed the association between LVEF change and the occurrences of composite primary endpoints among patients with different HF aetiologies. The occurrences of composite primary endpoints were higher among NICM patients with lack of LVEF improvement than those with significant LVEF improvement following SAC/VAL treatment. On the contrary, the primary endpoints in HF patients with ICM were not associated with LVEF changes following SAC/VAL treatment.

Table 5 showed detailed event rates and risks of the endpoints according to HF aetiologies and LVEF changes following SAC/VAL treatment. The primary endpoint showed significant divergence in patients with NICM in line with the changes of LVEF. The adjusted HR for patients with NICM and significant improvement was 0.42 (95% CI: 0.31–0.56, $P < 0.001$), and the adjusted HR for patients with NICM but lack of improvement was 1.70 (95% CI: 1.36–2.12, $P < 0.001$). Analyses for cardiovascular death, all-cause mortality, and HF hospitalization demonstrated consistent results. Kaplan–Meier curves demonstrated that the primary endpoints were significantly different along with the changes of LVEF among patients with NICM ($P < 0.001$, *Figure 3E*), whereas the primary endpoints among the patients with ICM were similar ($P = 0.284$, *Figure 3F*).

The event rates of the primary endpoints were also analysed by different LVEF cut-off values and by the change in LVESVI. Similar results were noted comparing to the original classification, and these results were shown in the Supplementary material online, *Tables S1* and *S2*.

Table 3 Baseline characteristics among patients with and without significant left ventricular reverse remodelling following sacubitril/valsartan treatment

	Significant left ventricular reverse remodelling ($n = 730$)	Without significant left ventricular reverse remodelling ($n = 746$)	*P*-value
Age (y/o)	62.1 ± 14.5	62.5 ± 14.6	0.681
Male gender	515 (70.5)	586 (78.6)	<0.001
Body mass index (kg/m^2)	25.6 ± 5.0	25.5 ± 4.7	0.703
Medical history			
Ischaemic aetiology for heart failure	279 (38.2)	375 (50.3)	<0.001
Diabetes	306 (41.9)	311 (41.7)	0.929
Hypertension	404 (55.3)	383 (51.3)	0.123
Peripheral arterial disease	36 (4.9)	63 (8.4)	0.007
Prior stroke/TIA	90 (12.3)	85 (11.4)	0.579
Atrial fibrillation	243 (33.3)	251 (33.6)	0.884
Dyslipidaemia	326 (44.7)	373 (50.0)	0.040
COPD	77 (10.5)	73 (9.8)	0.628
Previous HHF	455 (62.3)	480 (64.3)	0.422
Chronic kidney disease	220 (30.1)	251 (33.6)	0.148
Hyperuricaemia	125 (17.1)	151 (20.2)	0.125
New York Heart Association functional class			
II	459 (62.9)	466 (62.5)	0.833
III	238 (32.6)	248 (33.3)	
IV	33 (4.5)	31 (4.2)	
Systolic blood pressure (mmHg)	123.8 ± 20.1	120.5 ± 18.9	0.001
Estimated GFR (mL/min/1.73m2)	64.3 ± 29.5	64.3 ± 36.8	0.962
LVEF (%)	29.0 ± 7.4	28.8 ± 7.6	0.637
LVEDVI (mL/m2)	93.2 ± 28.2	98.0 ± 33.1	0.003
LVESVI (mL/m2)	66.5 ± 23.9	70.5 ± 28.6	0.004
Heart failure treatment at baseline			
Sacubitril/valsartan	730 (100.0)	746 (100.0)	–
Initial dose of sacubitril/valsartan	121.9 ± 59.8	104.8 ± 51.6	<0.001
Beta-blocker	566 (77.5)	588 (78.8)	0.550
Mineralocorticoid receptor antagonist	470 (64.4)	457 (61.3)	0.214
Ivabradine	182 (24.9)	134 (18.0)	0.001
CRT	39 (5.3)	47 (6.3)	0.432
ICD	48 (6.6)	79 (10.6)	0.006
Heart failure treatment at echocardiographic follow-up			
Sacubitril/valsartan	730 (100.0)	746 (100.0)	–
Dosage of sacubitril/valsartan	186.6 ± 101.8	162.2 ± 88.6	<0.001
Beta-blocker	570 (78.1)	564 (75.6)	0.259
Mineralocorticoid receptor antagonist	440 (60.3)	461 (61.8)	0.549
Ivabradine	208 (28.5)	169 (22.7)	0.010
Revascularization (with ischaemic aetiology)	19 (6.7)	38 (10.2)	0.121
New CRT implantation	9 (1.2)	6 (0.8)	0.412

COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HHF, hospitalization for HF; ICD, implantable cardioverter-defibrillator; Significant left ventricular reverse remodelling, left ventricular end-systolic volume index improved by ≥15%; TIA, transient ischaemic attack.

Discussion

To date, the PARADIGM-HF study did not report echocardiographic follow-up data yet.[11] Recently, the PROVE-HF study, which enrolled 794 HFrEF patients from the USA, clearly demonstrated the effect of left ventricular reverse remodelling following SAC/VAL treatment.[15] The mean LVEF measurements in the PROVE-HF study increased from 28.2% at baseline to 37.8% at 12 months, whereas the mean LVEDVI measurements decreased from 86.9 mL/m^2 to 74.2 mL/m^2.

Table 4 Multivariate analysis for factors associated with significant left ventricular reverse remodelling following sacubitril/valsartan treatment

	Related to significant left ventricular reverse remodelling	Multivariate analysis	
		Odds ratio	*P*-value
Model 1			
Gender	Female	1.43 (1.12–1.84)	0.005
Heart failure aetiology	Non-ischaemic aetiology	1.55 (1.24–1.93)	<0.001
Peripheral arterial disease	No history of peripheral arterial disease	1.61 (1.03–2.50)	0.036
ICD	Not receive ICD implantation	1.62 (1.10–2.39)	0.015
LVEDVI	Lower baseline LVEDVI	0.94 (0.91–0.98) per increase 10 mL/m^2	0.001
Ivabradine	Prescription of ivabradine at baseline	1.60 (1.23–2.08)	<0.001
Initial dose of sacubitril/valsartan	Higher initial dose of sacubitril/valsartan	1.32 (1.20–1.46) per increase 50 mg	<0.001
Model 2			
Gender	Female	1.42 (1.11–1.82)	0.005
Heart failure aetiology	Non-ischaemic aetiology	1.54 (1.24–1.91)	<0.001
Systolic blood pressure	Higher baseline systolic blood pressure	1.07 (1.01–1.13) per increase 10 mmHg	0.023
Peripheral arterial disease	No history of peripheral arterial disease	1.55 (1.00–2.41)	0.049
ICD	Not receive ICD implantation	1.53 (1.04–2.26)	0.031
LVEDVI	Lower baseline LVEDVI	0.95 (0.92–0.98) per increase 10 mL/m^2	0.004
Ivabradine	Prescription of ivabradine at follow-up	1.39 (1.09–1.77)	0.009
Achieved dose of sacubitril/valsartan	Higher prescribed dose of sacubitril/valsartan at follow-up	1.13 (1.07–1.20) per increase 50 mg	<0.001

Variables adjusted for the Model 1 were age, sex, heart failure aetiology, systolic blood pressure, renal function, echocardiographic parameters, baseline heart failure treatment, and baseline characteristics shown in *Table 3*.
Variables adjusted for the Model 2 were age, sex, heart failure aetiology, systolic blood pressure, renal function, echocardiographic parameters, baseline characteristics, and heart failure treatment at follow-up.
ICD, implantable cardioverter-defibrillator; LVEDVI, left ventricular end-diastolic volume index.

Similar degrees of LVEF and LVEDVI improvements were reproduced in our study consisting of more than 1400 patients.

Using artificial neural network analysis, SAC/VAL had been found to act synergistically against cardiomyocyte cell death and left ventricular extracellular matrix remodelling. However, 50% of myocardial infarction and HF protein targets exhibited inversely correlated activities, suggesting the molecular mechanisms of SAC/VAL on reverse remodelling in these two diseases may be different.[16] In the current study, non-uniform response following SAC/VAL treatment was also observed in patients with different HF aetiologies, emphasizing the pivotal role in assessing HF aetiologies in detail before the prescription.

Although the mean LVEF changes from baseline was 11.1% in NICM group patients, the distribution of LVEF changes following SAC/VAL treatment did not follow Gaussian distribution but expressed a bimodal pattern. On the other hand, the distribution of LVEF changes in ICM group patients showed a right-skewed distribution pattern, with more than one-half of patients who did not have their LVEF improve ≥5% following SAC/VAL treatment. In a Spanish data including 1,160 HF patients before the SAC/VAL era, a steep rise of LVEF was observed in both ICM and NICM patients, but patients with NICM showed a more pronounced LVEF increasing at 1 year and during follow-up than those with ischaemic aetiology.[17] Together with our findings, these data indicated that although optimal medical therapy has been established as the cornerstone for treatment of ICM to modulate neurohumoral changes associated with adverse structural and functional remodelling of the ischaemic myocardium, non-viable myocardial scar resulted from prolonged sustained ischaemia seems less unlikely to recover following standard HF therapy.

The role of revascularization on top of medical therapy in ICM is conflicting. Some observational data and meta-analysis demonstrated that patients with ICM and myocardial viability had a significant reduction in mortality with revascularization compared to medical therapy only.[18–21] However, the Surgical Treatment for Ischaemic Heart Failure (STICH) trial demonstrated the beneficial effect of optimal medical therapy plus coronary bypass surgery over optimal medical therapy alone on patients with ICM regardless of underlying myocardial viability.[22,23] An mean increase in LVEF from baseline to month 4 in STICH trial patients with viable myocardium was 2.3 ± 0.6%, which was lesser than that in the current study (6.7 ± 10.2%) from baseline to month 8. This might be result from better reverse remodelling effect of SAC/VAL treatment than conventional renin–angiotensin system inhibitor therapy.[15,24]

Our findings and several previous studies revealed that patients with ischaemic aetiology had higher incidences of adverse outcomes than those with non-ischaemic aetiology.[2–4,25] On the other hand, when adjusted for prognostic variables including natriuretic peptide, outcomes in PARADIGM-HF study did not differ by HF aetiologies.[12]

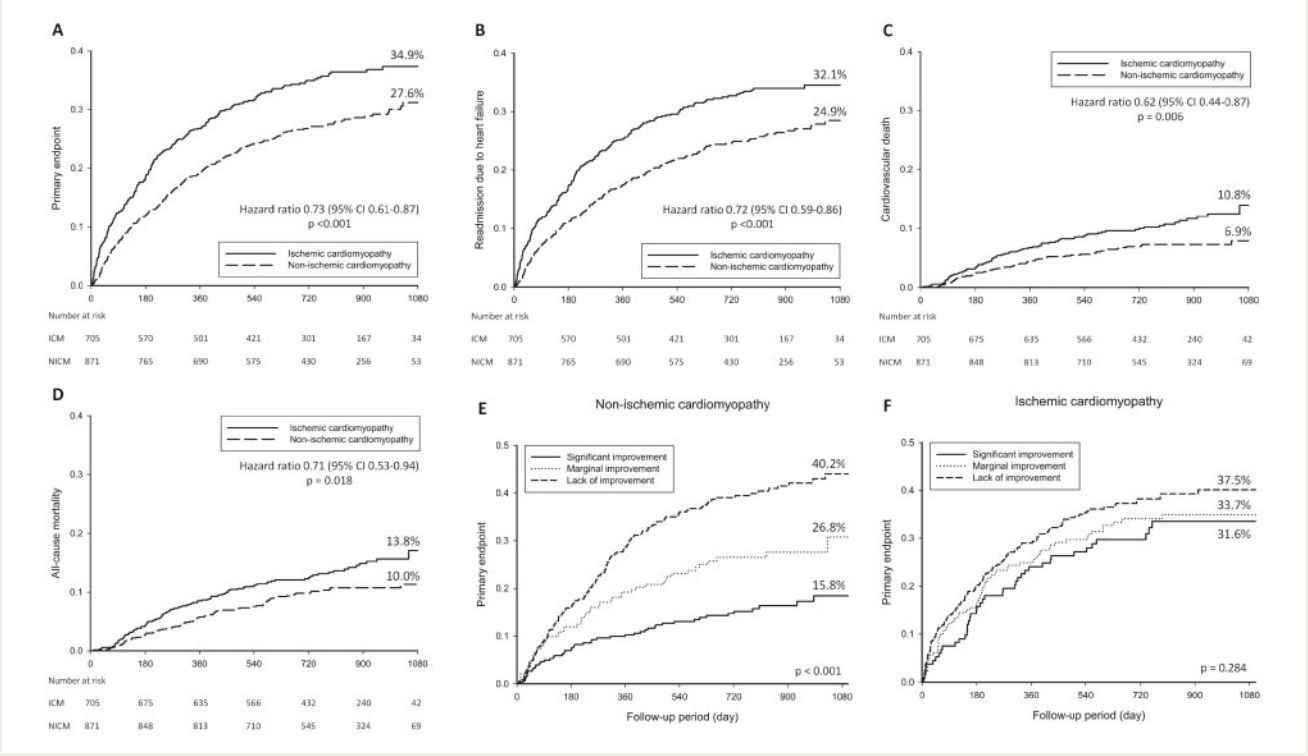

Figure 3 Cumulative incidence of clinical outcomes according to aetiology. (*A*) Cumulative incidence of the primary composite outcome, (*B*) unplanned heart failure hospitalization, (*C*) cardiovascular mortality, and (*D*) all-cause mortality. Cumulative incidence of primary composite outcome stratified according to LVEF improvement following sacubitril/valsartan treatment in (*E*) patients with non-ischaemic cardiomyopathy, and (*F*) patients with ischaemic cardiomyopathy.

However, PARADIGM-HF did not analyse the effect of ventricular remodelling of SAC/VAL on patients with different aetiologies of HF. Our study included the differences of ventricular remodelling following SAC/VAL treatment as a variable and demonstrated that the clinical outcomes in NICM patients were associated with LVEF and LVESVI changes. On the contrary, outcomes in patients with ICM among different LVEF change groups were relatively homogenous following SAC/VAL treatment. A similar finding was noted in the STICH trial: among 318 patients had paired baseline and 4-month LVEF measurement, there were no significant different in all-cause mortality or cardiovascular death between patients who had improved LVEF and those who did not have such improvement.[23] In another retrospective study divided ICM patients receiving coronary bypass surgery into two groups by whether LVEF improvement >5% or ≤5% postoperatively, incidences of cardiac death were comparable between two groups.[26] These findings highlighted that the underlying complexity of ICM and potential therapeutic benefit cannot be surmised from the simple result of ventricular reverse remodelling alone. Many factors such as comorbidities, the number and the anatomical extent of stenotic coronary arteries should be taken into consideration as well.[27] Although SAC/VAL seems to have lesser reverse remodelling effect in patients with established ICM, whether early initiation of SAC/VAL is beneficial before the maladaptive remodelling following acute myocardial infarction will be evaluated by the ongoing PARADISE-MI trial.[28]

Besides non-ischaemic aetiology, the current study also demonstrated that co-administration of ivabradine and a higher dose of SAC/VAL were associated with significant improvement in LVESVI following SAC/VAL treatment. In the era before SAC/VAL, ivabradine treatment had demonstrated a modest but significant increase in LVEF in the BEAUTIFUL study (2.0 ± 7.0%) and SHIFT study (2.4 ± 7.7%).[29,30] Since ivabradine and SAC/VAL have different action mechanisms, it is reasonable to apply both drugs in the same HF patients if clinically indicated. In a cohort consisted of 125 HFrEF patients, Martens *et al.*[24] had demonstrated that higher dosages of SAC/VAL were associated with higher degrees of left ventricular reverse remodelling. Although beta-blockers had been proven to induce beneficial reverse remodelling,[31] their prescription rates were relatively suboptimal in the current study. Several HF registries had demonstrated that the utilization of beta-blocker in real-world practice had regional diversities: highest in Western and Eastern Europe (91–92%), moderately high in Northern and Southern Europe (83–85%), moderate in USA and Asia (67–79%), and lowest in North Africa (48%).[32–34] Co-administration of multiple guideline-recommended medical therapies with up-titration to target dose should be emphasized to achieve incremental reverse remodelling effect.

Previous data showed that patients who had LVEF increasing by ≥5% following 12 months of carvedilol or metoprolol treatment would continue to improve following long-term beta-blocker

Table 5 Event rates and risks of clinical outcomes stratified by HF aetiology and LVEF changes

	N	Events	Crude rate per 100 patient-years	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	*P*-value
Primary composite endpoints						
Aetiology						
Ischaemic	654	235	17.29	1.00 (ref)	1.00 (ref)	
Non-ischaemic	822	234	13.34	0.74 (0.61–0.88)	0.77 (0.64–0.94)	0.009
LVEF improvement						
Lack of improvement	656	261	19.76	1.00 (ref)	1.00 (ref)	
Marginal improvement	382	117	14.26	0.74 (0.59–0.92)	0.66 (0.53–0.82)	<0.001
Significant improvement	438	91	9.35	0.47 (0.37–0.59)	0.44 (0.35–0.56)	<0.001
Aetiology/LVEF changes						
Non-ischaemic * lack of improvement	328	134	19.88	1.45 (1.19–1.78)	1.70 (1.36–2.12)	<0.001
Non-ischaemic * significant improvement	304	49	7.29	0.39 (0.29–0.53)	0.42 (0.31–0.56)	<0.001
CV mortality						
Aetiology						
Ischaemic	654	67	4.93	1.00 (ref)	1.00 (ref)	
Non-ischaemic	822	56	3.19	0.65 (0.46–0.93)	0.72 (0.46–1.14)	0.157
LVEF improvement						
Lack of improvement	656	97	7.34	1.00 (ref)	1.00 (ref)	
Marginal improvement	382	21	2.56	0.35 (0.22–0.56)	0.32 (0.20–0.51)	<0.001
Significant improvement	438	5	0.51	0.07 (0.03–0.17)	0.07 (0.03–0.18)	<0.001
Aetiology/LVEF changes						
Non-ischaemic * lack of improvement	328	47	6.97	2.23 (1.55–3.21)	3.29 (2.16–5.02)	<0.001
Non-ischaemic * significant improvement	304	4	0.60	0.12 (0.05–0.34)	0.14 (0.05–0.38)	<0.001
First unplanned HF readmission						
Aetiology						
Ischaemic	654	218	16.04	1.00 (ref)	1.00 (ref)	
Non-ischaemic	822	212	12.08	0.71 (0.59–0.86)	0.75 (0.61–0.91)	0.004
LVEF improvement						
Lack of improvement	656	227	17.19	1.00 (ref)	1.00 (ref)	
Marginal improvement	382	113	13.77	0.81 (0.65–1.02)	0.77 (0.61–0.97)	0.025
Significant improvement	438	90	9.25	0.52 (0.41–0.66)	0.52 (0.41–0.67)	<0.001
Aetiology/LVEF changes						
Non-ischaemic * lack of improvement	328	115	17.06	1.32 (1.06–1.63)	1.48 (1.17–1.88)	<0.001
Non-ischaemic * significant improvement	304	48	7.14	0.43 (0.32–0.57)	0.46 (0.34–0.63)	<0.001
All-cause mortality						
Aetiology						
Ischaemic	654	88	6.47	1.00 (ref)	1.00 (ref)	
Non-ischaemic	822	84	4.79	0.74 (0.55–1.00)	0.81 (0.55–1.19)	0.290
LVEF improvement						
Lack of improvement	656	126	9.54	1.00 (ref)	1.00 (ref)	
Marginal improvement	382	30	3.66	0.38 (0.26–0.57)	0.33 (0.22–0.50)	<0.001
Significant improvement	438	16	1.64	0.17 (0.10–0.29)	0.16 (0.10–0.28)	<0.001
Aetiology/LVEF changes						
Non-ischaemic * lack of improvement	328	61	9.05	1.99 (1.46–2.72)	2.60 (1.88–3.58)	<0.001
Non-ischaemic * significant improvement	304	14	2.08	0.33 (0.19–0.56)	0.36 (0.21–0.62)	<0.001

LVEF, left ventricular ejection fraction; Lack of improvement, LVEF improves of <5% or deteriorates; Marginal improvement, LVEF improves of 5–15%; Significant improvement, LVEF improves of ≥15%.

therapy, whereas those who had LVEF increasing <5% or decreasing following 1-year beta-blocker treatment tended to deteriorate later on.[35] Although SAC/VAL could modulate cardiac remodelling via limiting myocardial cell death and reducing left ventricular extracellular matrix remodelling,[16] unresponsiveness to SAC/VAL treatment in patients with NICM may imply underlying extensive myocytolysis and fibrosis, which suggest poor prognosis. Previous study had shown that in NICM patients, diffuse interstitial myocardial fibrosis quantified with T_1 mapping cardiac magnetic resonance (CMR) is independently associated with left ventricular reverse remodelling after cardiac resynchronization therapy.[36] Future study may be designed to evaluate remodelling response of SAC/VAL by pre-treatment CMR examination.

This study had several limitations. Although many factors were used for statistical adjustment in this retrospective study, some confounders may still exist. The mean follow-up period of two years was relatively short. All patients in the current study received SAC/VAL, and there were no control group patients. Patients who died before the follow-up echocardiography were excluded, so the benefit of SAC/VAL and its effect on left ventricular function might be overestimated. In patients with ICM, regional wall motion abnormalities were usually noted and might diminish Simpson's method's reliability. The intra- and inter-observer reproducibility of the echo parameters was not available because of the retrospective study design.

In conclusion, patients with NICM generally had a higher LVEF improvement degree than those with ICM following SAC/VAL treatment. Distribution of LVEF changes following SAC/VAL treatment expressed a bimodal pattern in patients with NICM and a right-skewed pattern in those with ICM. Significant improvement of LVEF in patients with NICM indicated favourable outcome, whereas lack of LVEF improvement suggested a bleak prognosis.

Data availability

Data are available from the Electronic Medical Records of Taipei MacKay Memorial Hospital, Taitung MacKay Memorial Hospital, Taipei Medical University Hospital, Hsinchu MacKay Hospital, E-Da Hospital, Taipei Veterans General Hospital, Chi-Mei Medical Center, Tri-Service General Hospital, and Cheng Hsin General Hospital, Taiwan. Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal information Protection Act", data cannot be made publicly available.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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