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Heart Failure

Combined Left Ventricular Ejection Fraction and N-Terminal pro-B-type Natriuretic Peptide after Sacubitril/Valsartan for Predicting Outcomes in Patients with Heart Failure with Reduced Ejection Fraction

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Background: The aim of this study was to determine whether a combined increase of ≥ 10% in left ventricular ejection fraction (LVEF) and decrease in N-terminal pro-B-type natriuretic peptide (NT pro-BNP) to < 1000 pg/mL after treatment with sacubitril/valsartan (SAC/VAL) in patients with heart failure with reduced ejection fraction (HFrEF) translated to better treatment outcomes in a real-world Taiwanese population.

Methods: This is a single-center, prospective, non-randomized, observational study. Consecutive patients with HFrEF were treated with SAC/VAL and followed up for at least 12 months. The primary endpoint was a change in LVEF and reduction in NT pro-BNP at 12 months. The secondary outcomes were death and heart failure (HF) rehospitalization.

Results: A total of 105 patients were analyzed after 12 months of SAC/VAL treatment. The mean age was 66.0 ± 11.6 years, and the mean LVEF and NT pro-BNP were 33.6 ± 6.7% and 4462.7 ± 5851.7 pg/mL respectively. The mean LVEF significantly increased to 50.5 ± 10.3% ($p < 0.001$), while NT pro-BNP decreased to 1270.3 ± 2368.2 pg/mL ($p = 0.001$) at 12 months, with the greatest changes occurring in the first 3 months of treatment ($p < 0.001$). Five patients died and 12 were rehospitalized for HF. None of the patients in the responder group died compared to 5 deaths in the non-responder group ($p = 0.039$). Combined ≥ 10% LVEF increase and NT pro-BNP of < 1000 pg/mL was an independent predictor of death and HF rehospitalization ($p = 0.019$).

Conclusions: SAC/VAL treatment resulted in significant improvements in LVEF, reduced NT pro-BNP level, death and HF hospitalization. Taken separately, an NT pro-BNP level of < 1000 pg/mL was a better predictor than ≥ 10% LVEF increase. Combining both variables predicted fewer deaths and HF rehospitalizations. Even with failure to reach the target dose, SAC/VAL still had significantly beneficial treatment outcomes in Taiwanese patients.

Key Words: Ejection fraction • NT pro-BNP • Reverse remodeling • Sacubitril/valsartan

INTRODUCTION

Sacubitril/valsartan (SAC/VAL), a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), contains the angiotensin receptor blocker (ARB) valsartan and the neprilysin inhibitor prodrug sacubitril (AHU377). It has greater anti-remodeling effects than either valsartan or sacubitril alone, and has been shown to improve left ventricular ejection fraction (LVEF), reduce myocardial remodeling, and increase natriuretic peptide availability.[1,2] In 2015, SAC/VAL was approved in Europe and the United States for the treatment of adults with chronic heart failure with reduced ejection fraction (HFrEF) to reduce

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Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CRR	Cardiac reverse remodeling
CRT	Cardiac resynchronization therapy
CV	Cardiovascular
EF	Ejection friction
eGFR	Estimated glomerular filtration rate
GUIDE-IT	Guiding evidence-based therapy using biomarker intensified treatment in heart failure
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
LA	Left atrium
LARR	Left atrial reverse remodeling
LAV	Left atrial volume
LV	Left ventricular
LVEDD	Left ventricular end-diastolic diameter
LVEDDi	Left ventricular end-diastolic diameter index
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVRR	Left ventricular reverse remodeling
MRA	Mineralocorticoid receptor antagonist
NT pro-BNP	N-terminal pro-B-type natriuretic peptide
NYHA	New york Heart Association
PARADIGM-HF	Prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure study
PRIDE	N-terminal pro-BNP investigation of dyspnea in the emergency department study
PROTECT	pro-BNP outpatient tailored chronic heart failure therapy study
PROVE-HF	Prospective study of biomarkers, symptom improvement, and ventricular remodeling during sacubitril/valsartan therapy for heart failure
SAC/VAL	Sacubitril/valsartan
SBP	Systolic blood pressure
TITRATION	Initiating LCZ696 in heart failure patients

the risk of cardiovascular (CV) death and heart failure (HF) re-hospitalization. These approvals occurred following the results of the landmark Prospective Comparison of ARNI with angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[1] In the 2017 update for HF management, the guidelines recommend (class I recommendation) replacing an ACEI or ARB with an ARNI in patients with chronic, symptomatic, or New York Heart Association (NYHA) class II or III HFrEF to further reduce morbidity and mortality, provided that there are no contraindications to its use.[3] Taken separately, both LVEF and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are strong independent predictors of treatment outcomes in HFrEF. However, they have not been combined as a single variable with their respective cut-off values before to predict outcomes. We undertook this study to determine whether combining both variables could better predict treatment outcomes in Taiwanese patients.

METHODS

Patients

In this single-center, prospective, non-randomized, observational study, we enrolled Taiwanese patients diagnosed with HF at our hospital. They were all treated with add-on or substitution of SAC/VAL for 12 months (March 2018 to 2019). The inclusion criteria were symptomatic patients who were ≥ 18 years old, systolic blood pressure (SBP) of ≥ 100 mmHg, chronic HFrEF/NYHA class II-IV, LVEF ≤ 40%, on stable treatment with ACEIs, ARBs, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and ACEI/ARB naïve patients. Patients were excluded if they were hemodynamically unstable, had previous angioedema or hypersensitivity to ACEI, ARB or SAC/VAL treatment, severe liver impairment, or a potassium level of > 5.2 mEq/L. Variables including age, sex, comorbidities, HF etiology, vital signs, medications, serum potassium, creatinine, and NT pro-BNP levels were all collected at baseline and at every 3 months until 1 year. The cohort was subdivided into 2 groups, namely responders (≥ 10% increase in LVEF and NT pro-BNP of < 1000 pg/mL), and non-responders.

Recommended dose

The approved target dose of SAC/VAL is 97/103 mg twice daily, and treatment should be initiated at a starting dose of 49/51 mg twice daily for patients already on an ACEI or ARB. Up-titration is performed after 2-4 weeks

to the target dose as tolerated by the patient. For patients who are not receiving ACEI or ARB treatment, have severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), or moderate hepatic impairment (Child-Pugh class B), a lower starting dose of 24/26 mg twice daily with up-titration every 2-4 weeks to the target dose is recommended.[4,5] If switching from an ACEI, a washout period of 36 hours is needed. The recommended starting dose is 49/51 mg twice daily with up-titration every 2-4 weeks to the target dose.[6] We followed these dose recommendations for all of our patients on first medical contact, during hospital admission, or via our outpatient department. They were followed every 2 weeks to evaluate tolerability and need for dose titration. All patients were followed for at least 12 months in person or via telephone interviews if the patient could not make the follow-up visit or otherwise stopped coming.

Endpoints

The primary endpoint or treatment response was defined as a pre-determined cut-off percentage or value of ≥ 10% increase in LVEF[7-9] and a reduction in NT pro-BNP to < 1000 pg/mL[10,11] at 12 months respectively. The secondary outcomes were death and HF rehospitalization. CV events included all deaths, resuscitated sudden death, HF hospitalization, and worsening HF, defined as new or progressive symptoms or signs of decompensated HF and unplanned intensification of diuretics. For patients who died prior to the end of the study, and therefore having no data at 12 months, the last available data prior to death were used to classify them as responders or non-responders.

Echocardiography

Conventional echocardiography was performed by two independent certified sonographers and interpreted independently by the authors. It was performed at baseline and every 3 months until 1 year. Echocardiographic parameters analyzed included LVEF, left ventricular (LV) volume, LV mass, left atrial volume (LAV), ratio of early trans-mitral peak velocity to early diastolic peak annular velocity, peak velocities of trans-mitral early (E), late diastolic (A) LV filling, and ratio (E/A ratio), valve regurgitation, right ventricular systolic function via tricuspid annular plane systolic excursion, tricuspid regurgitation velocity, systolic pulmonary arterial pressure and inferior vena cava diameter variation. All ultrasound examinations were performed using a TOSHIBA (Aplio Artida) SSH-880CV ultrasound system.

Statistical analysis

Continuous variables are presented as mean and standard deviation for normally distributed variables. Categorical variables are presented as frequencies and percentages. The paired sample t-test and one-way ANOVA were used for normally distributed data, while the Wilcoxon signed-rank test was used for non-normally distributed data. Pearson's chi-square test or Fisher's exact test was used for categorical variables, and the Mann-Whitney *U*-test was used for continuous variables.

Multivariate Cox regression analysis was used to assess the predictive ability of individual variables for treatment outcomes, presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables strongly associated with the outcomes of HF, including age, sex, SBP, NYHA: III-IV, NT pro-BNP, creatinine, diabetes mellitus, ACEIs/ARBs, MRAs, beta-blockers, and LVEF, were subjected to univariate analysis. Variables with a p value of < 0.2 were then included in multivariate analysis. Two multivariate models were created; model 1 adjusted for change in LVEF and NT pro-BNP separately, and model 2 adjusted for both variables taken together as one variable (responders). Survival analysis for time-dependent outcomes was performed using Kaplan-Meier analysis and compared with the log-rank test. All data analysis was performed using SPSS 12.0 (SPSS Inc. Chicago, IL, USA), and p values of < 0.05 were considered significant.

RESULTS

Patients

A total of 105 patients were included in the final analysis, of whom 74 were male. The mean age of the patients was 66.0 ± 11.6 years. Forty-four patients were in NYHA class III-IV, and 57% of the patients had ischemic heart disease as the cause of HF. The mean LVEF of all patients in the study was 33.6 ± 6.7%, and the mean NT pro-BNP was 4462.7 ± 5851.7 pg/mL. Ninety-four (90%) patients were on beta-blockers, while 81 (77.1%) and 79 (75%) were on ACEIs/ARBs at baseline (before switching to SAC/VAL) and MRAs, respectively. The other basic clini-

cal characteristics are listed in Table 1.

LVEF

The mean LVEF increased from 33.6 ± 6.7% at baseline to 50.5 ± 10.3% at 12 months (p < 0.001), with the greatest increase occurring within the first 3 months of treatment (vs. 43.1 ± 9.6, p < 0.001). There were also significant decreases in both the LV and left atrium (LA) diameters, and these changes were more pronounced after 3 months of treatment (p < 0.001). The results are listed in Table 2. Seventy-one (68%) patients had a ≥ 10% change in LVEF, and 34 (32%) patients had a < 10% change in LVEF. For the ≥ 10% group, more patients (66%) obtained a < 1000 pg/mL NT pro-BNP (p = 0.031). There was only 1 death in the ≥ 10% change group compared to 4 deaths in the < 10% change group (p = 0.020). The other data are listed in Table 3.

Table 1. Baseline clinical characteristics

N = 105	
Age (yrs) (35-93)	66.0 ± 11.6
Male gender	74 (70.5)
Systolic blood pressure (mmHg)	125.4 ± 21.5
NYHA	
II	61 (58.1)
III-IV	44 (41.9)
Dilated cardiomyopathy	45 (43)
Ischemic heart disease	60 (57)
Duration of heart failure (days)	1164 ± 1504
Atrial fibrillation	23 (21.9)
Hypertension	35 (33.3)
Diabetes mellitus	49 (46.7)
eGFR (mL/min/1.73^2)	53.0 ± 21.4
eGFR	
45-60	29 (27.6)
30-45	20 (19)
< 30	13 (12.4)
Creatinine (mg/dL)	1.8 ± 1.8
Potassium (mEq/L)	4.3 ± 0.6
BUN (mg/dL)	27.3 ± 15.6
NT-pro-BNP (pg/mL)	4449.3 ± 5781.6
LVEF (%)	33.6 ± 6.7
Beta blockers	94 (89.5)
ACE-I/ARB	81 (77.1)
MRA	79 (75.2)
Diuretics	56 (53.3)
CRT	2 (2.0)
Statins	56 (53.3)
AMI	4 (3.8)

ACE-I, angiotensin converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, aldosterone receptor blocker; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

NT pro-BNP

NT pro-BNP significantly decreased at 12 months (4449.3 ± 5781.6 to 1270.3 ± 2368.2 pg/mL, p = 0.001) with the greatest decrease occurring within the first 3 months of treatment (vs. 2389.3 ± 4621.6 pg/mL, p < 0.001). After grouping the patients into ≥ 1000 pg/mL (n = 43) and < 1000 pg/mL (n = 62) groups, more patients in the ≥ 1000 pg/mL group were older with poorer renal function (p < 0.001). More patients (76%) had a ≥ 10% change in LVEF in the < 1000 pg/mL group (p = 0.031), and more patients (89%) were on MRAs (p < 0.001). There were no deaths (p = 0.006) and fewer HF rehospitalizations (p = 0.011) in the < 1000 pg/mL group. The other data are listed in Table 4.

eGFR

There was a modest improvement in the patient's eGFR from baseline to 3 months (53.0 ± 21.4 to 55.3 ± 20.2 ml/min/1.73 m^2). Although the eGFR gradually decreased to 51.8 ± 21.2 ml/min/1.73 m^2 at 1 year, the change was not statistically significant (p = 0.840). Serum creatinine remained mostly the same (p = 0.880), but potassium levels slightly increased (p = 0.014).

LVEF and NT pro-BNP: the responders

The patients were divided into two groups. The re-

Table 2. LVEF change (quantitative)

	Baseline	3 months	p value	6 months	9 months	12 months	p value
LVEF	33.6 ± 6.7	43.1 ± 9.6	< 0.001	48.1 ± 9.6	49.5 ± 10.1	50.5 ± 10.3	< 0.001
LVEDd (cm)	6.0 ± 0.8	5.7 ± 0.7	< 0.001	5.6 ± 0.8	5.5 ± 0.8	5.4 ± 0.7	< 0.001
LVEDs (cm)	5.0 ± 0.8	4.5 ± 0.7	< 0.001	4.2 ± 0.8	4.1 ± 0.8	4.0 ± 0.8	< 0.001
LAD (cm)	4.9 ± 0.6	4.7 ± 0.5	< 0.001	4.5 ± 0.6	4.5 ± 0.5	4.5 ± 0.6	< 0.001

LAD, left atrial diameter; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

Table 3. Comparison of patients using qualitative change in LVEF at 12 months

N = 105	≥ 10% change in LVEF (N = 71)	< 10% change in LVEF (N = 34)	p value
Age (yrs)	65.2 ± 12.0	67.6 ± 10.9	0.316
Male gender	52 (73.2)	22 (64.7)	0.370
Systolic BP (mmHg)	127.5 ± 22.1	120.8 ± 19.8	0.133
NYHA: III-IV	31 (43.7)	13 (38.2)	0.598
Duration of heart failure (days)	1016.9 ± 1443.8	1474.2 ± 1597.8	0.145
Atrial fibrillation	14 (19.7)	9 (26.5)	0.434
Hypertension (%)	25 (35.2)	10 (29.4)	0.555
Diabetes mellitus	34 (47.9)	15 (44.1)	0.717
eGFR			
45-60	17 (23.9)	12 (35.3)	0.224
30-45	14 (19.7)	6 (17.6)	0.800
< 30	6 (8.5)	7 (20.6)	0.077
Creatinine (mg/dL)	1.7 ± 1.7	2.1 ± 2.1	0.217
Potassium (mEq/L)	4.2 ± 0.6	4.4 ± 0.5	0.050
BUN (mg/dL)	26.1 ± 16.3	30.5 ± 13.9	0.462
NT-pro-BNP at baseline (pg/mL)	4365.5 ± 5367.8	4684.8 ± 6974.0	0.837
NT-pro-BNP: < 1000 pg/mL at 12 months (n = 62, 59%)	47 (66.2)	15 (44.1)	0.031
ACE-I/ARB	53 (74.6)	28 (82.4)	0.379
MRA	57 (80.3)	22 (64.7)	0.084
Diuretics	41 (57.7)	15 (44.1)	0.190
Statins	35 (49.3)	21 (61.8)	0.231
Death	1 (1.4)	4 (11.8)	0.020
HF rehospitalization	8 (11.3)	4 (11.8)	0.940

ACE-I, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Table 4. Comparison of patients using NT-proBNP values at 12 months

N = 105	< 1000 pg/mL (N = 62)	≥ 1000 pg/mL (N = 43)	p value
Age (yrs)	62.5 ± 11.0	71.3 ± 10.8	< 0.001
Male gender	46 (74.2)	28 (65.1)	0.316
Systolic BP (mmHg)	124.9 ± 21.0	126 ± 22.5	0.809
NYHA: III-IV	26 (41.9)	18 (41.9)	0.994
Duration of heart failure (days)	1016.5 ± 1468.7	1379.1 ± 1543.5	0.226
Atrial fibrillation	10 (16.1)	13 (30.2)	0.086
Hypertension	21 (33.9)	14 (32.6)	0.888
Diabetes mellitus	27 (43.5)	22 (51.2)	0.442
eGFR			
45-60	18 (29.0)	11 (25.6)	0.697
30-45	9 (14.5)	11 (25.6)	0.156
< 30	1 (1.6)	12 (27.9)	< 0.001
Creatinine (mg/dL)	1.2 ± 0.3	2.7 ± 2.6	0.001
Potassium (mEq/L)	4.3 ± 0.6	4.3 ± 0.5	0.875
BUN (mg/dL)	22.7 ± 9.8	33.3 ± 19.7	0.061
LVEF at baseline (%)	33.3 ± 6.9	34.0 ± 6.4	0.565
LVEF: ≥ 10% change at 12 months (n = 71, 68%)	47 (75.8)	24 (55.8)	0.031
ACE-I/ARB	46 (74.2)	35 (81.4)	0.387
MRA	55 (88.7)	24 (55.8)	< 0.001
Diuretics	35 (56.5)	21 (48.4)	0.442
Statins	30 (48.4)	26 (60.5)	0.222
Death	0	5 (11.6)	0.006
HF rehospitalization	3 (4.8)	9 (20.9)	0.011

ACE-I, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

sponder group included patients with a ≥ 10% increase in LVEF and a NT pro-BNP of < 1000 pg/mL, while the other patients were placed in the non-responder group. The patients in the responder group were younger, had less atrial fibrillation and better renal function (p = 0.003, 0.042, and 0.004, respectively). More patients were on MRAs in this group (87.2% vs. 65.5%, p = 0.010). No patient died in the responder group and 3 were rehospitalized, while there were 5 deaths and 9 rehospitalizations in the non-responder group (p = 0.039 and p = 0.144, respectively). The other data are listed in Table 5. Of the 5 deaths, only 1 patient had a ≥ 10% increase in LVEF and none had a NT pro-BNP of < 1000 pg/mL, fulfilling the non-responder criteria.

Adverse effects and clinical outcomes

Symptomatic hypotension was not noted in any of the patients during the study period, and only 1 patient had dizziness. There were 5 deaths in the overall cohort, and 2 were cardiogenic in origin. Twelve patients were re-hospitalized for HF, of whom 6 were re-hospitalized in the first 3 months of follow-up.

Predictors

In model 1, combined LVEF change of ≥ 10% and NT pro-BNP of < 1000 pg/mL (responders) was the only independent predictor of death and HF rehospitalization after adjustments for other variables [HR: 0.21 (95% CI: 0.06-0.77), p = 0.019]. SBP did not reach statistical significance (p = 0.052). However, when taken as separate variables in model 2, NT pro-BNP of < 1000 pg/mL [HR: 0.11 (95% CI: 0.03-0.40), p = 0.001], diabetes mellitus [HR: 0.29 (95% CI: 0.10-0.88), p = 0.028], and SBP [HR: 1.02 (95% CI: 1.00-1.05), p = 0.036] were independent predictors, while ≥ 10% LVEF change [HR: 0.50(95% CI: 0.18-1.37), p = 0.179] was not.

Survival curves

Responders vs. non responders

The cumulative death-free survival was significantly better in the responders than in the non-responders (log-rank: p = 0.038). There was a trend of lower rehospitalizations for HF (log-rank: p = 0.097), and a significantly lower combined cumulative risk of death or rehospitalization (log-rank: p = 0.012). The survival curves are presented in Figures 1A-C.

LVEF: ≥ 10% vs. < 10% improvement or change

Using the percent change in LVEF as the dependent

Table 5. Responders vs. non-responders

N = 105	Responders (N = 47)	Non-responders (N = 58)	p value
Age (yrs)	62.2 ± 11.5	69.0 ± 11.0	0.003
Male gender	35 (74.5)	39 (67.2)	0.420
Systolic BP (mmHg)	126.5 ± 21.2	124.4 ± 22	0.631
NYHA: III-IV	21 (44.7)	23 (39.7)	0.604
Duration of heart failure (days)	919 ± 1432.2	1364.3 ± 1541.7	0.132
Atrial fibrillation	6 (12.8)	17 (29.3)	0.042
Hypertension	18 (38.3)	17 (29.3)	0.331
Diabetes mellitus	22 (46.8)	27 (46.6)	0.979
eGFR			
45-60	11 (23.4)	18 (31.0)	0.385
30-45	6 (12.8)	14 (24.1)	0.140
< 30	1 (2.1)	12 (20.7)	0.004
Creatinine (mg/dL)	1.2 ± 0.3	2.3 ± 2.3	0.001
Potassium (mEq/L)	4.2 ± 0.6	4.3 ± 0.5	0.303
BUN (mg/dL)	22.2 ± 10.6	31.7 ± 18	0.064
Beta blockers	42 (89.4)	52 (89.7)	0.961
ACE-I/ARB	35 (74.5)	46 (79.3)	0.557
MRA	41 (87.2)	38 (65.5)	0.010
Diuretics	28 (59.6)	28 (48.3)	0.249
Statins	22 (46.8)	34 (58.6)	0.228
Death	0	5 (8.6)	0.039
HF rehospitalization	3 (6.4)	9 (15.5)	0.144

ACE-I, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

variable, patients with a ≥ 10% change were most likely to survive compared with those having a < 10% improvement (log-rank: p = 0.019). However, there was no difference in either group with regards to rehospitalization (log-rank: p = 0.750), and the combination of cumulative death or rehospitalization (log-rank: p = 0.119). The survival curves are shown in Figures 1D-F.

NT pro-BNP of < 1000 pg/mL vs. ≥ 1000 pg/mL

Using NT pro-BNP level as the dependent variable, the cumulative incidence of death, rehospitalization, and the combination of death or rehospitalization were significantly lower in the patients with an NT pro-BNP level of < 1000 pg/mL (log-rank: p = 0.005, 0.004, and < 0.001, respectively). The curves are shown in Figures 1G-I.

DISCUSSION

Cardiac reverse remodeling (CRR)

CRR refers to improvements in damaged ventricular or atrial volume, dimension, and shape, and occurs when LV geometry and/or function reverts closer to that of normal heart structure. The estimated incidence of CRR in patients with HFrEF ranges from 26-46%, and typically

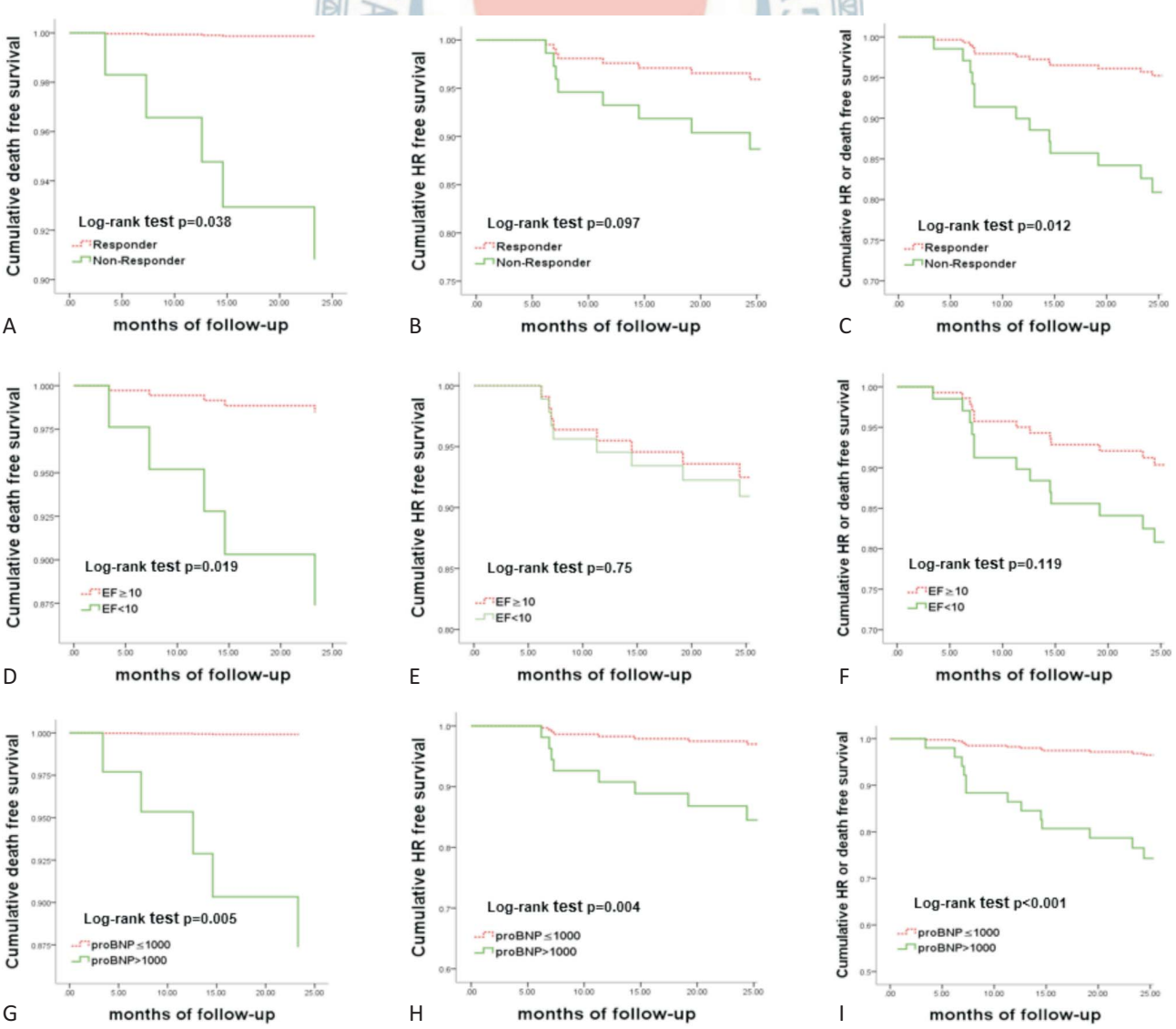

Figure 1. *Cumulative incidence of (A) Death, (B) HF rehospitalization, (C) HF rehospitalization or death using responders vs. non responders; (D-F) Using LVEF ≥ 10 vs. < 10%; (G-I) Using NT-pro BNP ≥ 1000 vs. < 1000 pg/mL. EF, ejection friction; HF, heart failure; proBNP, pro-B-type natriuretic peptide.*

occurs after intensification and titration of drug and device therapy.[12] Measures of CRR include LV end-systolic diameter, LV end-diastolic diameter (LVEDD), LV end-systolic volume, LV end-diastolic volume (LVEDV), LVEF, LV mass index, right ventricular systolic pressure, and LAV. LVRR is defined as an increase or absolute improvement in LVEF of ≥ 10% or LVEF > 50%, and a decrease of ≥ 10% in LVEDD or an LVEDD of ≤ 33 mm/m^2. LARR is defined as a decrease of > 15% in LA end-systolic volume.[7,13]

Pitfalls of LVEF

LVEF is one of the few variables in HF cardiology that is fiercely debated on whether it should remain as the gold standard. Detractors claim that LVEF calculations are inaccurate, undermined by LV chamber size, and that single measurements reveal relatively little regarding prognosis in these patients. However, the PARADIGM-HF study showed a linear relationship between LVEF and outcomes between 15-40%, with each 5% drop in ejection friction (EF) associated with a 9-10% increased risk in death or HF hospitalization. There was also a 7% increased risk in all-cause mortality in adjusted analyses, with all outcomes increasing with decreasing LVEF.[1,14]

Ejection fraction is an incomplete measure of ventricular function, as there is limited test-retest reliability due to inter- and intra-observer variability. It is preload and afterload (load) dependent which can dramatically underestimate or overestimate true myocardial function (loss of reproducibility), and poor image quality may result in foreshortening of the ventricles.[15,16] Two-dimensional echocardiography requires geometrical assumption on the LV shape to estimate LV volume, and this can lead to errors, especially when inadequate endocardial definition or low-quality images are obtained.[17] As with biomarkers, serial LVEF measurements are superior to a single point in time assessment.[18] Although considered a reasonable measure of systolic function, it is a poor measure of diastolic function. LVEF is a good predictor of cardiac events when < 45%, but has limited prognostic value when > 45%.[19]

LVEF is not an early marker of disease, as it may still be normal even in an already impaired heart. On the other hand, some patients with low LVEF do not have a worse prognosis,[20,21] suggesting that LVEF is a poor predictor of outcomes in patients with HF and acute decompensated HF. However, despite all of these shortcomings, a decline in LVEF remains and is still an important and powerful predictor of CV outcomes, as every 10% reduction in EF below 45% has been independently associated with a 39% increased risk of all-cause mortality.[19]

It is surprising that LVEF was not a predictor of treatment outcomes in this study. Possible reasons may include all of the aforementioned factors, as well as this study's limitations. However, after analyzing our data for this discrepancy, we found that some patients still had a NT pro-BNP of ≥ 1000 pg/mL despite having a ≥ 10% LVEF increase. We believe that this may have offset the beneficial effects of LVEF improvement, suggesting that NT pro-BNP may be a better predictor. Models designed to predict the combined outcome of death or hospitalization, or of hospitalization only, have poorer discriminative ability than those designed to predict death. This is due to the fact that hospitalization is more complex and difficult to predict, as the decision of who or when to admit the patient is subjective and is much more dependent on health care supply and availability.

Doses

In this study, most patients did not reach the guideline-recommended target dose, despite the intention to do so. Overall, 89% of the patients were on a 50 mg twice daily dose, while only 11% were on a 100-200 mg dose. This is unfortunate, because in the real-world less than 50% of patients with HF receive the target dosage of other disease-modifying drugs.[22-24] A 2017 HF registry in Taiwan showed that only 24.4%, 20.6% and 86.2% of patients received ≥ 50% of the target dose for ACEIs/ARBs, beta-blockers and MRAs, respectively.[25]

A conservative up-titration approach should always be considered if drug tolerance is a concern, especially in patients with poor renal function, low SBP at the outset, and/or symptomatic hypotension. In the safety and tolerability of initiating LCZ696 in heart failure patients (TITRATION) study, gradual up-titration of over 6 weeks increased the likelihood of reaching the target dose,[26] and it was also associated with better tolerance and persistence with the maximal dose in patients with lower SBP.[27] The "start low and titrate slow" approach, is still the safest method, especially in the elderly with borderline low BP or advanced heart failure.[28]

Using this strategy in our patients avoided any hypotensive episodes, increased drug compliance, and avoided drug discontinuation. Dose reductions are preferable to complete discontinuation, because patients on lower doses still have a reduced risk of death or hospitalization,[29] as in our study. In some of our patients, SBP increased after 3-4 months of treatment, suggesting improvement in cardiac output, and was similar to the TITRATION study. Up-titration should not be forced, but should be implemented according to patient safety and tolerability, allowing for temporary dose interruption or reduction.[30] Although the target dose is an important goal, individualization of therapy according to etiology, clinical profile, tolerance, and side effects is also crucial, as it is impossible to expect all patients to be on target dose.

However, in another study, dose reductions by any amount in either treatment group were associated with an increased risk of death or HF rehospitalization [HR: 2.5 (2.2-2.7), $p < 0.001$]. The primary endpoint was lowest in the group who were up-titrated to a higher dose and who remained on it, but those not reaching the target dose still had a significant and sustained benefit.[29,31] Most reductions in NT pro-BNP, which we feel is the better predictor, occurred early in the course of treatment when most patients were still receiving the lowest dose of the drug. The PROVE-HF trial was the first large-scale study of ambulatory patients with HFrEF in which a low-dose (24/26 mg) was used.[32] As with the PROVE-HF trial, even though the majority of our patients did not reach the target dose, significant benefits were still obtained.

Concerns regarding potential differences in drug tolerability and safety in Asians are warranted and were evident in this study. Differences in physical characteristics such as lower body weight and smaller size have led to the advocation of lower doses of drugs in Asians.[33] Asian patients with HF are also younger and have different risk factors compared with Western patients.[34] Treatment outcomes also differ compared with European populations.[35]

Responders and cut-off values

A clinical response to SAC/VAL is defined by cut-off values using changes in known predictors for risk stratification and prognostication in HF patients. These include NT pro-BNP and LVEF, which are two of the most powerful predictors for HF. Initially, a reduction in NT pro-BNP of $\geq 30\%$ or an increase in LVEF of $\geq 5\%$ was accepted as a meaningful clinical change.[36,37] In other studies, an LVEF change of $\geq 5\%$[36,38] or $\geq 10\%$,[7-9] follow-up LVEF of $\geq 50\%$ combined with left ventricular end-diastolic diameter index (LVEDDi)/LVEDV decrease of $\geq 10\%$,[9] or final LVEDDi of ≤ 33 mm/m^2 after 24 months of treatment[7] were also used as cut-off values. BNP cut-off values of 50,[39] 100[40] and 200 pg/mL[41] have also been used. A potential link between lowering NT pro-BNP and CRR was first demonstrated in the Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. Patients who achieved NT pro-BNP of < 1000 pg/mL were associated with significant CRR, and had the lowest frequency of CV events.[10,11]

Transformation analyses in the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) echo substudy showed that the optimal 12-month cut-point for NT pro-BNP was 1,028 pg/mL for EF, 941 pg/mL for ESVi, and 1,286 pg/mL for EDVi, approximating the prespecified NT pro-BNP target goal of 1,000 pg/mL. The extent of CRR was correlated with changes in NT pro-BNP, showing that the greater the reduction in NT pro-BNP the more extensive the CRR. Specifically, an NT pro-BNP decrease of 1,000 pg/mL corresponded to an absolute 6.7% LVEF increase and a reduction in ESVi and EDVi of 17.3 and 15.7 ml/m^2, respectively. The composite endpoint of death or HF hospitalization after 12 months was also significantly lower among the patients achieving NT pro-BNP of < 1,000 pg/mL ($p < 0.001$).[42]

NT pro-BNP has been reported to be the strongest independent predictor of first HF rehospitalization, death, and the combination of these endpoints,[43] as in our study. SAC/VAL was nearly twice as likely as enalapril to reduce NT pro-BNP to ≤ 1000 pg/mL. Moreover, whether it fell to less than a specific value, decreased by a specific percentage from baseline, or changed from a higher to a lower value, these reductions have been significantly associated with lower morbidity and mortality.[44] Even modest lowering or intermittent periods of $\leq 1,000$ pg/ml have been associated with superior outcomes.[10,45] In the NT pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, a 0% death rate was noted among patients with an NT pro-BNP of < 986 pg/mL,[46] which is also similar to our study. Therefore, based on

these findings, we defined the responders using a combination of ≥ 10% change in LVEF and NT pro-BNP of < 1000 pg/mL. We did not use a cut-off of 30% decrease in NT pro-BNP as some of our patients still had an NT pro-BNP value of > 1000 pg/mL even after a 30% reduction.

In March of 2020, we reported an in-depth evaluation of the effect of SAC/VAL on LVEF and CRR.[47] In that study, the use of SAC/VAL clearly improved LVEF and CRR parameters. In the current study, we found that the use of SAC/VAL translated to better treatment outcomes, but were more evident when NT pro-BNP levels were reduced to < 1000 pg/mL. Furthermore, we showed that combining both LVEF and NT pro-BNP with their respective cut-off values, a combination not previously reported in the literature, may be a better predictor of treatment outcomes.

Limitations

As with any observational study, our findings are observations from a clinical point of view and are limited to association and not causality. Despite multivariate analysis, residual confounding is still present. A small sample size, a single center cohort, as well as a short follow-up time are also major limitations that may limit the reliability of our results. However, the prospective design and the consecutive inclusion of patients enabled real-world representations and included numerous comorbidities which may be excluded in clinical trials. We did not have a control population, and randomization was not performed. The target dose was not achieved in most of our patients, and conventional echocardiography was the primary imaging tool for assessing CRR. Lastly, we could not completely discount the beneficial effects of other treatments for HF, that could also have led to LVEF improvements and NT pro-BNP reductions. Although this study is not powered enough and not designed to determine which variable is better in predicting clinical outcomes, our results show that NT pro-BNP may be a better predictor. Further studies are needed to evaluate this.

CONCLUSIONS

In conclusion, SAC/VAL was effective in reducing death and HF re-hospitalizations, improving LVEF and decreasing NT pro-BNP levels. Obtaining a target of ≥ 10% increase in LVEF combined with a < 1000 pg/mL NT pro-BNP value resulted in fewer deaths and rehospitalizations. Taken together, this combination may improve prediction and risk stratification in these patients. Lastly, even at low doses, SAC/VAL was still significantly beneficial in Taiwanese patients.

DECLARATION OF CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

All authors were involved in the conception, design, analysis, interpretation, revision, and final approval of the manuscript.

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