Original Article

Outcomes of Heart Failure with Reduced Ejection Fraction Patients Receiving Sacubitril/Valsartan in Real-World Practice

Panyapat Jiampo MD[1], Theeravet Pattayanant MD[2], Pornthip Yoonaisil MD, MSc[3], Pawana Watansawad RN[4]

[1] Division of Cardiology, Department of Medicine, Bhumibol Adulyadej Hospital, Bangkok, Thailand

[2] Department of Medicine, Bangchak Hospital, Bangkok, Thailand

[3] Department of Nutrition Center, Phyathai 3 Hospital, Bangkok, Thailand

[4] Bhumibol Adulyadej Hospital, Bangkok, Thailand

Objective: To describe clinical outcomes and NT-pro-brain natriuretic peptide (NT-proBNP) level of patients with chronic heart failure with reduced ejection fraction (HFrEF) receiving sacubitril/valsartan (Sac/Val) in real world setting.

Materials and Methods: The present research was a single-center, retrospective, non-interventional study in adult patients with HFrEF that received Sac/Val at Bhumibol Adulyadej Hospital. Data were extracted from the hospital's database and electronic medical records. All patients fulfilling the inclusion criteria were identified and included into the present study. The present study was approved by the Ethics Committees of Bhumibol Adulyadej Hospital.

Results: During the two years of the present study, two patients died from cardiovascularly (CV) death. The New York Heart Association (NYHA) class was changed from baseline to 12-month (2.0±0.4) and 24-month (1.8±0.1), p<0.001. Left ventricular ejection fraction (LVEF) was significantly inclined at 24-month compared to baseline. The rate of heart failure and related hospitalization within one year declined from baseline at 19 visits/year to 12-month at 6 visits/year, and 24-month at 5 visits/year. The mean of NT-proBNP level was significantly reduced from baseline at 2,802.3±3,106.7 to 12-month at 2,203.8±4,051.1, and 24-month at 1,157.6±1,069.9 (p=0.03). Total hospitalization due to any cause was decreased from baseline at 26 visits/year to 12-month at 24 visits/year, and 24-month at 12 visits/year. Numbers of emergency room visit, ICU/CCU admission, length of stay for admission, and direct medical cost of heart failure (HF) treatment were diminished from baseline.

Conclusion: Sac/Val can reduce hospitalized HF and level of NT-proBNP. Its efficiency in Thai patients with HFrEF was similar to real world data.

Keywords: Heart Failure with reduced ejection fraction, Sacubitril/Valsartan, Angiotensin receptor blocker/neprilysin inhibitor (ARNI)

Received 2 May 2022 | Revised 27 June 2022 | Accepted 8 July 2022

J Med Assoc Thai 2022;105(9):872-5

Website: http://www.jmatonline.com

Heart failure (HF) is associated with increased mortality and hospitalization rates, especially among the elderly[1,2]. The problems were currently considered due to high cost of care for both pharmacological and non-pharmacological treatment[3]. Neurohormonal modulation is the cornerstone in HF with reduced ejection fraction (HFrEF) management to reduce cardiovascularly (CV) death and HF hospitalization[4].

Sacubitril/valsartan (Sac/Val) is the first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) therapy recommended by major guideline for HFrEF treatment[5,6]. It has been approved for treatment of HFrEF in Thailand since August 2016 and included in the Thai HF treatment guidelines since 2019[7]. It has been available at Bhumibol Adulyadej Hospital in Bangkok since February 2017. However, Asian population was under-representative in determining the impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial, which was around 18% in the ARNI group[8]. The researchers would like to describe clinical outcomes and NT-proBNP level of Thai patients with chronic HFrEF receiving Sac/Val in a real-world setting.

Materials and Methods

The present study design was a single-center,

Correspondence to:

Jiampo P.

Division of Cardiology, Department of medicine, Bhumibol Adulyadej Hospital, Bangkok 10220, Thailand.

Phone: +66-2-5347322

Email: panyapat@gmail.com

How to cite this article:

Jiampo P, Pattayanant T, Yoonaisil P, Watansawad P. Outcomes of Heart Failure with Reduced Ejection Fraction Patients Receiving Sacubitril/Valsartan in Real-World Practice. J Med Assoc Thai 2022;105:872-5.

DOI: 10.35755/jmedassocthai.2022.09.13478

retrospective, non-interventional study in adult patients with HFrEF that received Sac/Val at Bhumibol Adulyadej Hospital. Data were extracted from the hospital's database and electronic medical records. All patients fulfilling the inclusion criteria were identified and included in the present study. Study period was February 2017 to February 2020. The present study was approved by the Ethics Committees of Bhumibol Adulyadej Hospital (Institutional Review Board No.91/63).

Inclusion criteria were male or female aged 20 or above who had documented HF diagnosis with Left ventricular ejection fraction (LVEF) of less than 40% by echocardiography within six months and prior received Sac/Val for at least three months. Exclusion criteria were patients with HF primarily resulting from pericardial disease and congenital heart disease or lost to follow-up before completion of at least three months.

The main outcomes composed of CV death, LVEF, The New York Heart Association (NYHA), HF-related hospitalization, and NT-proBNP level at 12-and 24-month. The other outcomes were all-cause of death, total hospitalization, and healthcare resource utilization including numbers of emergency room visits, IPD, intensive care unit (ICU)/cardiac care unit (CCU) admission, length of staying for admission (days), and direct medical cost of HF treatment.

Statistical analyses were performed with IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as mean (SD). Categorical data were presented as number and percentage. Paired t-test was used to compare difference of outcome changes between baseline and 12-month, and baseline and 24-month. A p-value of less than 0.05 was considered statistically significant. Repeated measure analyses were applied to determine change overall across the three-time points at baseline, 12-month, and 24-month.

Table 1. Baseline characteristic of patients with chronic HFrEF who received sacubitril/valsartan in real-world practice

Characteristic	Total number (n=50)
Age (year); mean±SD	69.4±12.6
Sex: male; n (%)	34 (68)
Healthcare reimbursement scheme; n (%)	
Direct disbursement	48 (96)
Universal health coverage	2 (4)
Previous hospitalization due to heart failure within 1 year (visit/year)	19
Previous ICU/CCU admission due to heart failure within 1 year (visit/year)	10
Medical history; n (%)	
Diabetes mellitus	22 (44)
Hypertension	26 (52)
Dyslipidemia	22 (44)
Obesity	3 (6)
Stroke	4 (8)
Coronary arterial disease	27 (54)
Atrial fibrillation	17 (34)
Other cardiac arrhythmia	0 (0)
Chronic kidney disease	9 (18)
Liver disease	0 (0)
Anemia	22 (44)
Asthma or chronic obstructive pulmonary disease	2 (4)
Heart failure medication; n (%)	
Sacubutril/valsartan	50 (100)
ACEI/ARB	0 (0)
Beta-blocker	34 (68)
Mineralocorticoid receptor antagonist	14 (28)
Ivabradine	7 (14)
Diuretic	35 (70)
Digoxin	8 (16)

SD=standard deviation; ICU=intensive care unit; CCU=cardiac care unit; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

Results

Between February 2017 and February 2020, 53 patients were diagnosed with chronic HFrEF and received Sac/Val at Bhumibol Adulyadej Hospital. Three patients were lost to follow-up. Finally, 50 patients were included in the eligibility study. Baseline characteristics are shown in Table 1. The mean age was 69.4±12.6 years with 68% males. Participants reported at 54% with coronary arterial disease and 52% with hypertension.

Efficacy outcomes from baseline to 12-month and 24-month follow-up are shown in Table 2. In the two years of the present study, two patients died from CV death from brainstem stroke and sudden cardiac death. The NYHA class was changed from baseline of 2.4±0.5) to 12-month of 2.0±0.4, and 24-month of 1.8±0.1 ($p<0.001$). LVEF was significantly inclined at 24-month compared to baseline ($p<0.001$). The rate of HF-related hospitalization within one year declined from baseline at 19 visits/year to 12-month at six visits/year, and 24-month at five visits/year. The Mean of NT-proBNP level was significantly reduced from baseline at 2,802.3±3,106.7 to 12-month at 2,203.8±4,051.1, and 24-month at 1,157.6±1,069.9, ($p=0.03$). Hospitalization due to any cause was decreased from baseline at 26 visits/year to 12-month at 24 visits/year, and 24-month at 12

Table 2. Efficacy outcomes from baseline to 12-month and 24-month follow up of patients with chronic HFrEF who received sacubitril/valsartan in real-world practice

Efficacy outcomes	Baseline	12-month	24-month	P[a]	P[b]	P[c]
Clinical characteristics						
NYHA class; n (%)						
• I	0 (0)	4 (8)	12 (24.0)			
• II	33 (66)	41 (82)	34 (68.0)			
• III	17 (34)	4 (8)	4 (8.0)			
• IV	0 (0)	0 (0)	0 (0.0)			
NYHA class; mean±SD	2.3±0.5	2.0±0.5	1.8±0.5	<0.001	<0.001	<0.001
LVEF (%); mean±SD	26.3±9.6	33.0±14.5	35.3±15.0	0.08	<0.001	0.08
Heart rate (bpm); mean±SD	75.6±19.3	75.1±15.1	74.8±15.3	0.86	0.73	0.94
Systolic blood pressure (mmHg); mean±SD	121.1±17.4	118.5±16.7	124.1±19.2	0.37	0.28	0.13
Body mass index; mean±SD	24.3±5.2	24.4±5.7	24.4±6.0	0.75	0.77	0.92
NT-proBNP (pg/mL); mean±SD	2921±3464	1906±2285	1258±1204	0.24	0.01	0.03
Estimated GFR (mL/minute/1.73 m^2); mean±SD	55.5±22.9	57.6±18.8	55.7±21.9	0.39	0.83	0.67
ALT (U/L); mean±SD	25.0±15.7	21.8±14.0	21.9±10.2	0.60	0.23	0.57
Sodium (mmol/L); mean±SD	140.5±2.3	141.0±2.7	140.0±3.5	0.23	0.25	0.07
Potassium (mmol/L); mean±SD	4.2±0.5	4.2±0.5	4.2±0.8	0.79	0.80	0.96
Chloride (mmol/L); mean±SD	102.0±3.2	103.5±2.8	103.5±3.3	<0.01	<0.01	<0.01
Bicarbonate (mmol/L); mean±SD	25.9±5.0	25.6±4.6	25.0±3.0	0.77	0.31	0.50
Clinical outcomes						
Death from cardiovascular disease; n (%)	0 (0)	0 (0)	2 (4)			
Death from any cause; n (%)	0 (0)	0 (0)	2 (4)			
Hospitalization due to heart failure (visit/year)	19	6	5			
Hospitalization due to any cause (visit/year)	26	24	12			
Healthcare resource utilization						
Emergency room visit, visit/year	12	2	3			
ICU/CCU Admission, visit/year	10	0	1			
Length of stay for admission, days	213	52	51			
Direct medical cost of heart failure treatment	2,288,807	555,664	327,724			
Any medication-related adverse events						
Volume depletion	0 (0)	0 (0)	0 (0)			

SD=standard deviation; NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; NT-proBNP=NT-pro-brain natriuretic peptide; GFR=glomerular filtration rate; ALT=alanine aminotransferase; ICU=intensive care unit; CCU=cardiac care unit

[a] Outcomes at 12-month compared baseline, Paired t-test; [b] Outcomes at 24-month compared baseline, Paired t-test; [c] Change overall across the three-time points, Repeated measure analyses

visits/year. Numbers of emergency room visit, ICU/CCU admission, length of stay for admission, and direct medical cost of HF treatment were diminished from baseline.

Discussion

The present study was a single-center, retrospective, non-interventional study. The baseline characteristics composed of age, prevalence of major comorbidities, NYHA class, LVEF similar to the prospective comparison of ARNI with ACEI to PARADIGM-HF[8]. However, there were three different baseline characteristics of gender, HF medication, and NT-proBNP. The participants were 68% male, which less than the PARADIGM-HF that had a 79% male population. This may describe the population in real-word practice. HF medications, B-blockers, and MRAs, was lower than PARADIGM-HF trial. NT-proBNP were higher than PARADIGM-HF, which mean that the participants had poor prognosis of HF.

The main outcome of CV death was lower than PARADIGM-HF at 4.0% versus 13.3%. HF related hospitalization was also decreased corresponding to PARADIGM-HF, and a previous study in Taiwan[9], and in Thailand[10]. In addition, NYHA class was significantly improved after 1-year and 2-year follow up compared to baseline in correspondence

with improving both LVEF and NT-ProBNP. Whilst LVEF was significantly inclined, NT-proBNP was significantly declined after 2-year follow-up. Previous studies showed early benefit of ARNI treatment with improved LVEF[11,12]. NT-proBNP could predict the risk of major adverse outcomes in patients during treatment with ARNI[13]. Emergency visit, ICU or CCU admission, and length of stay for admission were decreased, along with the direct medical cost of HF treatment. Medical-related adverse events were not reported. The estimated glomerular filtration rate (GFR) was not changed significantly, corresponding to the previous study[14]. The present study supported the use of sacubitril/valsartan in Thai patient, corresponding to a previous study in Asian population[15].

There were limitations that needs to be addressed. First, the design was single-arm retrospective study based on a claims database and had multiple unadjusted confounding factors. Second, the number of participants was small for a real-world study.

Conclusion

Sac/Val can reduce hospitalized HF and level of NT-proBNP. Its efficiency in Thai patients with HFrEF was similar to real world data.

What is already known on this topic?

Sal/Val was superior to enalapril in reducing the risks of death and decreasing hospitalization for heart failure from clinical trial.

What this study adds?

Sac/Val can reduce hospitalized heart failure and level of NT-proBNP. Its efficiency in Thai patients with HFrEF was similar to the real-world data.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev 2017;3:7-11.
2. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail 2020;22:1342-56.
3. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME Med J 2020;5:1-6.
4. Greenberg B. Medical management of patients with heart failure and reduced ejection fraction. Korean Circ J 2022;52:173-97.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776-803.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
7. Buakhamsri A, Chirakarnjanakorn S, Sanguanwong S, Porapakkham P, Kanjanavanich R. Heart Failure Council of Thailand (HFCT) 2019 heart failure guideline: pharmacologic treatment of chronic heart failure-part I. J Med Assoc Thai 2019;102:240-4.
8. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
9. Hsiao FC, Wang CL, Chang PC, Lu YY, Huang CY, Chu PH. Angiotensin receptor neprilysin inhibitor for patients with heart failure and reduced ejection fraction: Real-world experience from Taiwan. J Cardiovasc Pharmacol Ther 2020;25:152-7.
10. Rattanavipanon W, Sotananusak T, Yamaae F, Chandrsawang A, Kaewkan P, Nathisuwan S, et al. Real-world experience of angiotensin receptor/neprilysin inhibitor (ARNI) usage in Thailand: a single-center, retrospective analysis. BMC Cardiovasc Disord 2021;21:324.
11. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, et al. Ejection fraction improvement and reverse remodeling achieved with sacubitril/valsartan in heart failure with reduced ejection fraction patients. Am J Cardiovasc Dis 2017;7:108-13.
12. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovasc Ther 2018;36:e12435.
13. Myhre PL, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, et al. B-type natriuretic peptide during treatment with sacubitril/valsartan: The PARADIGM-HF trial. J Am Coll Cardiol 2019;73:1264-72.
14. Shi Y, Wang Y, Chen J, Lu C, Xuan H, Wang C, et al. Effects of angiotensin receptor neprilysin inhibitor on renal function in patients with heart failure: a systematic review and meta-analysis. Postgrad Med J 2021.
15. Dewan P, Docherty KF, McMurray JJV. Sacubitril/valsartan in Asian patients with heart failure with reduced ejection fraction. Korean Circ J 2019;49:469-84.