Indonesian Journal of Pharmacy

VOL 33 (1) 2022: 83–92 | RESEARCH ARTICLE

Budget Impact Analysis of Sacubitril/Valsartan in the Treatment of Heart Failure with Reduced Ejection Fraction (HFrEF) in Indonesia

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Info Article

Submitted: 23-11-2021
Revised: 27-01-2022
Accepted: 08-03-2022

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ABSTRACT

Based on PARADIGM-HF Clinical Trials, LCZ696, a dual-acting sodium supramolecular complex currently known as sacubitril/valsartan, was superior to enalapril in reducing the risks of death and hospitalization for heart failure (HF) in patients with heart failure and reduced ejection fraction (HFrEF). This analysis aimed to estimate the budget impact of sacubitril/valsartan in the treatment of HFrEF in Indonesia setting. A budget impact model estimated the impact with and without the use of sacubitril/valsartan for a 5-year horizon (2020 – 2024). The local data inputted in the model included age prevalence rates, drugs costs, HF hospitalization costs, and adverse events costs. The drug cost calculation of sacubitril/valsartan was from the regular price, while standard care drug costs mainly came from e-catalog price, which was reimbursement cost. The budget impact was estimated from the budget difference between the future scenario therapy and the current therapy. In the current therapy, the target population was treated without sacubitril/valsartan. Meanwhile in the future scenario therapy, the target population was treated with sacubitril/valsartan based on a market penetration rate of 6%, 12%, 18%, 24%, and 31% in the first, second, third, fourth and fifth years, respectively.

Given that the number of patients eligible for treatment was estimated as 86,594 in the first year, and the assumption that the annual increase of HF prevalence was 1.1% based on population growth, about 1,350 deaths and 3,512 hospitalizations may be avoided over five years. The scenario of implementing sacubitril/valsartan for HF treatment had an impact on an additional budget of 1%, 2%, 3%, 4%, 5% over a 5-year horizon compared to the current therapy strategy. This scenario resulted a cumulative budget impact of IDR 735 billion over five years. This analysis estimates the impact of sacubitril/valsartan application in the treatment of patients with HF and reduced ejection fraction as input for Indonesia healthcare payer in implementing the strategy for HF treatment.

Keywords: sacubitril/valsartan, heart failure with reduced ejection fraction, budget impact analysis, health technology assessment

INTRODUCTION

Chronic heart failure is a clinical condition involving the reduction of blood circulation function to provide the body needs (Ponikowski *et al*., 2016). About 50% of chronic heart failure is heart failure and reduced ejection fraction (HFrEF). HFrEF is a serious health problem related to high morbidity and mortality. It was estimated that chronic heart failure affected about 23 million persons around the world and about 20% of people aged over 40 years old would suffer from chronic heart failure for their entire life (Bui *et al*., 2011). Chronic heart failure affected about 6 million people and is responsible for 1 – 2% of

hospitalizations treatment in the USA and Europe (Ambrosy *et al*., 2014). Progressivity of heart failure is exacerbated by some harmful neurohormonal pathways. In the last three decades, therapy for prevention or changing these pathways includes the use of angiotensin-converting enzyme (ACE) inhibitor, β-blocker, and mineralocorticoid receptor antagonists, in which these therapies have proven to decrease the mortality and morbidity of patients with HFrEF (Ponikowski *et al*., 2016).

Sacubitril/valsartan (LCZ696), angiotensin receptor neprilysin inhibitor, compared with enalapril has proven to reduce mortality due to cardiovascular disease as well as hospitalization events due to chronic heart failure based on PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) study. The study compared angiotensin receptor neprilysin inhibitor (ARNI) with ACE-inhibitor to measure the impact on mortality and morbidity of heart failure patients. Furthermore, the study was a multicenter, phase III, prospective, double-blind, randomized control trial comparing the effect of sacubitril/valsartan and enalapril on mortality and morbidity in patients with HFrEF. PARADIGM-HF shows that compared with enalapril, therapy with sacubitril/valsartan significantly reduced mortality as well as hospitalization due to heart failure (McMurray *et al*., 2014).

Sacubitril/valsartan has been approved for the treatment of patients with HFrEF in Indonesia since 2017. However, at the time when the study was conducted, sacubitril/valsartan was not included yet in the national formulary for use in patients under National Health Insurance. In accordance with Ministry of Health regulation, selection of drug for included in the national formulary must consider the health technology assessment results. Budget impact analysis is a part of health technology assessment study. This study aimed to explore the economic implications of sacubitril/ valsartan in the treatment of patients with HFrEF from the perspective of Indonesian healthcare payers using budget impact analysis. Comparator in this study was ACE inhibitor that was listed in national formulary including captopril, ramipril, imidapril, lisinopril, and perindopril. The result of this study is expected to provide information for health policy decision-making regarding the implementation of sacubitril/ valsartan in the national health system.

MATERIAL AND METHODS

Study design

The study was a pharmacoeconomic study applying budget impact analysis. The budget impact analysis reported the expected total budget impact associated with the introduction of sacubitril/valsartan each year. Other outcomes will also be reported, include disaggregated costs, hospitalizations avoided, and deaths avoided.

The target population was adults with HFrEF and NYHA class II-IV using the data of the national population combined with national prevalence estimation. The intervention was therapy with sacubitril/valsartan (ACEi, ARB, ARNI) versus therapy without sacubitril/valsartan (ACEi and ARB), used in combination with background therapies (e.g., β-blockers (BB), mineralocorticoid receptor antagonists (MRA). Sacubitril/valsartan was proposed to be a substitute therapy for ACEi or ARB. The perspective of analysis was from Indonesian health care payer, with a 5-year time horizon, no discounting was applied in this study.

Model overview and assumptions

This study used the existing model developed by Novartis. The model structured (Fig. 1) can be described as a 'prevalence-based' model which considered the total population with HFrEF (rather than modelling explicitly the number of patients entering and exiting the population of interest each year). The population considered for this budget impact model comprises adult chronic HFrEF patients and NYHA class II-IV; this population is the same as that considered by PARADIGM-HF, and therefore likely to represent the population for which marketing authorization for sacubitril/valsartan is issued.

For this budget impact analysis, it is assumed that all other pharmacological treatments (e.g., background therapies) were identical regardless of the primary treatment prescribed. Furthermore, it is assumed that any differences in non-pharmacological interventions (e.g., implantation and management of cardioverter-defibrillator (ICDs) and cardiac resynchronization (CRT) therapy would be implicitly captured in 'all-cause hospitalization' and could therefore be excluded from this analysis.

The budget impact model predicts events and outcomes for populations prescribed each treatment over the modeled time horizon: all-cause mortality, all-cause hospitalization, adverse events (AEs), and episodes of care to titrate treatments.

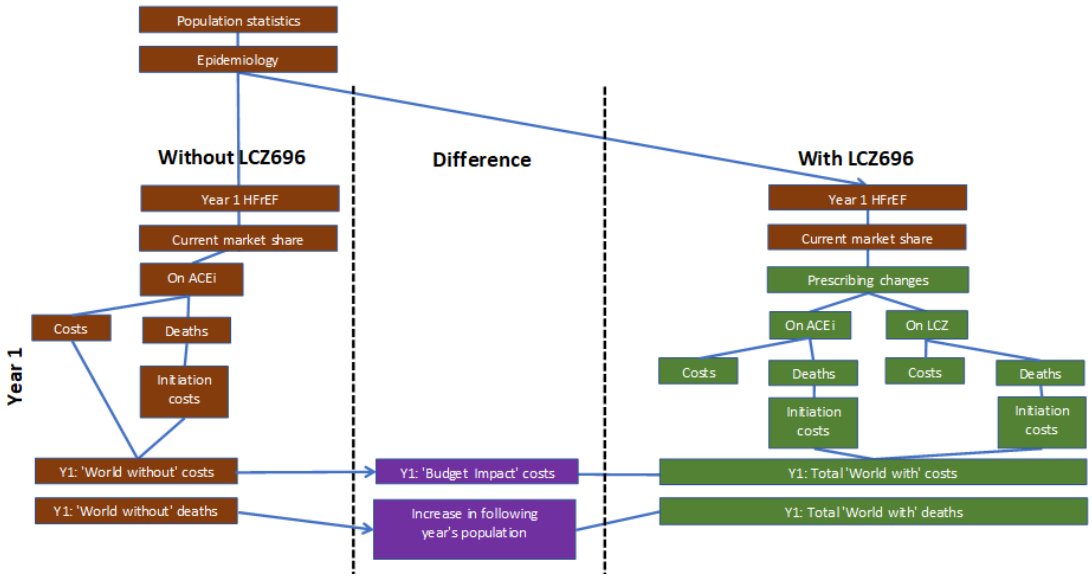

Figure 1. Model schematic for budget impact analysis

Table I. Input Data

Input data of prevalence of heart failure in Indonesia			
Age (years old)	**Population size**	**Prevalence**	
Men	**Number**	**%**	**Number**
15-44	63,990,000	0.20	127,980
45-54	16,740,000	0.20	33,480
55-64	11,070,000	0.40	44,280
65-74	5,130,000	0.50	25,650
75+	2,160,000	0.40	8,640
Women	**Number**	**%**	**Number**
15-44	62,640,000	0.20	125,280
45-54	16,740,000	0.20	33,480
55-64	11,340,000	0.40	45,360
65-74	5,670,000	0.50	28,350
75+	2,970,000	0.40	11,880
Total	198,450,000	0.24	484,380

Input data of target population numbers					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
ACEi	42,164	39,907	37,595	35,228	32,803
ARB	39,234	37,134	34,982	32,779	30,524
LCZ696	5,196	10,506	15,932	21,476	27,140
Additional patients from LCZ696 survival benefit	0	102	296	573	927
Number of patients	86,594	87,648	88,805	90,056	91,394

Input data of estimated market share of sacubitril/valsartan					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Not previously on treatment	0%	0%	0%	0%	0%
ACEi intolerance	0%	1%	2%	3%	4%
Switched from ACEi/ARB	6%	11%	15%	20%	25%
Population growth due to LCZ696 survival benefit	0%	0%	0%	1%	1%
Total LCZ696 market share	6%	12%	18%	24%	31%

Table II. Input data of probabilities of adverse events

Probabilities of each adverse event	Hypotension (%)	Cough (%)	Angioedema (%)	Hypercreatinemia (%)	Hyperkalemia (%)
ACEi	12	3	0.1	5	14
ARB	7	7	0	0	2.1
LCZ696	18	9	0.1	5	12

Tabel III. Input data of costs

Primary pharmacological therapies cost	Market share (%)	Price (28 days)
ACEi		
Captopril	52.1	20,118
Enalapril	0.6	403,200
Imidapril	5.4	70,840
Lisinopril	15.7	163,520
Perindopril arginine	6.8	168,546
Ramipril	19.4	16,520
ARB		
Candesartan	19.4	333,984
Irbesartan	12.2	270,368
Losartan	5.5	357,357
Telmisartan	36.9	85,260
Valsartan	25.2	209,538
ARNI		
LCZ696 50mg	100	822,696
Background therapy costs		**Pack price (IDR)**
Beta-blockers		1,716
Aldosterone antagonists		528
Digoxin		104
Lipid lowering medications		1,243
Diuretics		155
Aspirin		105
Anticoagulants		4,098
Costs of treatment		**Unit costs (IDR)**
Outpatients visit costs		839,600
GP visit cost		75,000
NT-proBNP test cost		320,160
Hospitalizations costs		6,693,200
Costs for each adverse event (IDR)		**Unit cost (IDR)**
Cost per GP visit		75,000
Cost per outpatient contact		150,000
Cost per ER visit		275,000
Cost per lab test (haematology)		40,000

Parameter input for the model used both local and international data sources. Parameter input for drug effectivity used international data which is the same data as model template. Epidemiological data including prevalence of chronic heart failure and the number of populations to calculate target population was from Indonesia data, as well as data of drugs price and cost of adverse treatment other hospitalization costs. Sensitivity analysis was performed using univariate sensitivity analysis, in which the model parameters were varied using arbitrary adjustment factors between 75% as lowest value to 125% as highest value from base case of 100%.

Input data

Three input data which consist of data about HF prevalence and the number of Indonesian populations for estimating input data of the target population that is eligible to receive the drugs examined in this study, the number of target population receiving the drugs yearly over a 5-year time horizon, and input data of estimation of sacubitril/valsartan market share each year over 5 years (Table I).

The number of populations was in the year 2019 based on data of National Statistics Bureau (National Statistics Bureau of Indonesia, 2019), meanwhile HF prevalence was from the result of basic health research (Riskesdas) in 2013 (Ministry of Health of Indonesia, 2014).

The number of target population was calculated using prevalence (Table I) and multiplied with the proportion of HFrEF as much as 50%, the proportion of NYHA II-IV as much as 81.3% (Tromp *et al*., 2019), and estimation of patients who is eligible to receive treatment as much as 87%. The number of target population in the first year that was inputted in the model was 86,594 patients and increased every year according to the population growth. This number consisted of number of populations receiving ACEi, ARB, LCZ696, and additional patients from LCZ696 survival benefit because one of benefit of LCZ696 was death avoiding.

In the first year, the estimation of market share was 6% and increased each year according to the assumption of increasing number of HF treatments and the rise of switching from standard care to sacubitril/valsartan.

Cost data inputs

The budget impact model includes the following costs: primary pharmacological therapies, background therapies, hospitalization, monthly management, adverse events (AE), and initial cost associated with titrating sacubitril/valsartan.

Primary pharmacological therapies cost per ACEi/ARB is calculated using the costs of all available ACEi/ARB therapies. It is assumed that all patients are titrated up to the maximum dose of sacubitril/valsartan (200 mg). Background therapies included: beta-blocker, aldosterone antagonists, digoxin, lipid-lowering medications, diuretics, aspirin, anticoagulants, adenosine diphosphate antagonists.

The annual all-cause hospitalization cost is taken by using a weighted average of all hospitalizations observed in targeted hospitals. Background medical resource use included outpatient visits (cardiology visits, general practitioner (GP) visits), and other resource use (rehabilitation center, skilled nurse facility, home health care visits, outpatient tests).

Costs of treatment included outpatients visit costs, GP visit cost, NT-proBNP test cost, and hospitalizations costs. The NT-proBNP test cost was the cost for test to diagnose heart failure. In the study, the test was assumed to be conducted once per patient.

The adverse events considered in the study for sacubitril/valsartan and ACEi as observed in PARADIGM-HF consist of hypotension, cough, angioedema, elevated serum creatinine, and elevated serum potassium. Patients experiencing hypotension require 2 additional GP visits. Patients experiencing cough require 2 additional GP visits and a blood test. Patients experiencing milder angioedema ("no treatment or use of antihistamines only") require 2 outpatient visits in addition to the cost of antihistamines. Patients experiencing more severe angioedema ("use of catecholamines or glucocorticoids without hospitalization") require an ER visit and a follow-up GP visit in addition to the cost of glucocorticoids. Patients hospitalized for angioedema are captured within the hospitalization model and are not considered here. Patients with elevated serum creatinine require 2 additional GP visits and a blood test. Patients with elevated serum potassium require 2 additional GP visits and a blood test. It is assumed that sacubitril/valsartan titration would require two additional GP visits (aligned with PARADIGM-HF).

RESULT AND DISCUSSION

This study simulated the budget impact of implementing sacubitril/valsartan in the treatment of HFrEF in Indonesia setting using the existing BIA model developed and applied in the previous study. Information from budget impact analysis results is important to give insight for the policymaker particularly for budg*et al*location in implementing the new health program under the national health insurance scheme. To our knowledge, this is the first budget impact analysis that was conducted specifically in Indonesian with HFrEF and that compared sacubitril/valsartan with standard therapy for the treatment of HFrEF.

Tabel IV. Outputs of hospitalization and death avoided

Output	Year 1	Year 2	Year 3	Year 4	Year 5
Annual Hospitalizations avoided	273	514	727	916	1082
Cumulative Hospitalizations avoided	273	787	1,514	2,430	3,512
Annual Deaths avoided	102	194	277	353	423
Cumulative Deaths avoided	102	296	573	927	1,350

Table V. Budget impact estimation of implementation of sacubitril/valsartan in Indonesia setting

Annual budget impact (in Billion IDR)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Without LCZ696: Annual total expenditure	3,102	3,136	3,170	3,205	3,240
With LCZ696: Annual total expenditure	3,144	3,226	3,313	3,405	3,501
Annual Budget Impact	43	90	142	199	260
Cummulative budget impact (in Billion IDR)					
	Year 1	Year 2	Year 3	Year 4	Year 5
Without LCZ696: Cumulative expenditure	3,102	6,238	9,408	12,613	15,853
With LCZ696: Cumulative expenditure	3,144	6,370	9,683	13,087	16,589
Cumulative Budget Impact	43	133	275	474	735
	1%	2%	3%	4%	5%

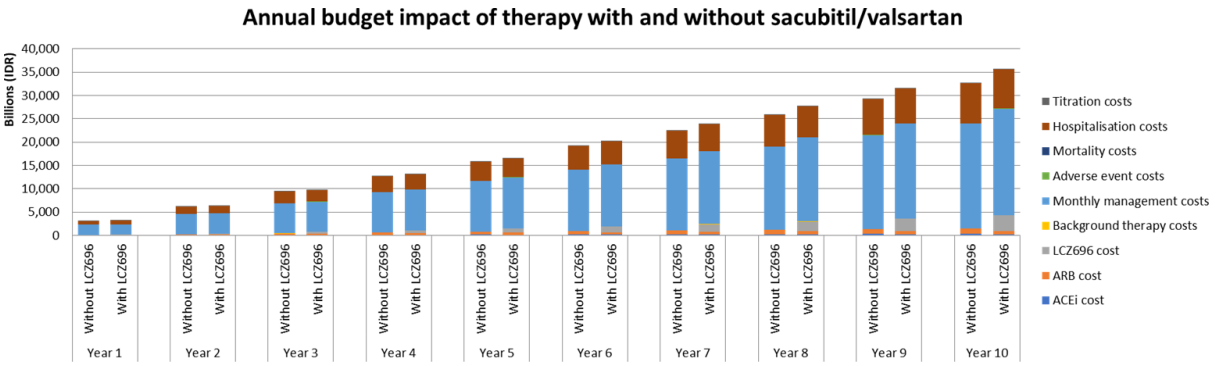

Figure 2. Budget impact of therapy with and without sacubitril/valsartan

The budget impact analysis in this study was estimated by comparing the treatment of HFrEF with sacubitril/valsartan and without sacubitril/valsartan (use standard therapy of ARB and ACEi). The budget impact model used in this study employed the efficacy of sacubitril/valsartan resulted from PARADIGM-HF Clinical Trials. The study compared sacubitril/valsartan with enalapril. In our study, sacubitril/valsartan was compared with other ARB drugs since enalapril was not available yet in Indonesia.

The epidemiological output of model simulation included hospitalization prevention and death prevention annually for 5 years (Table IV). The number of hospitalization and death avoided increased by year over 5 years. The number of hospitalizations accounted for 3,512 over 5 years, meanwhile, the number of deaths avoided accounted for 1,350 over 5 years.

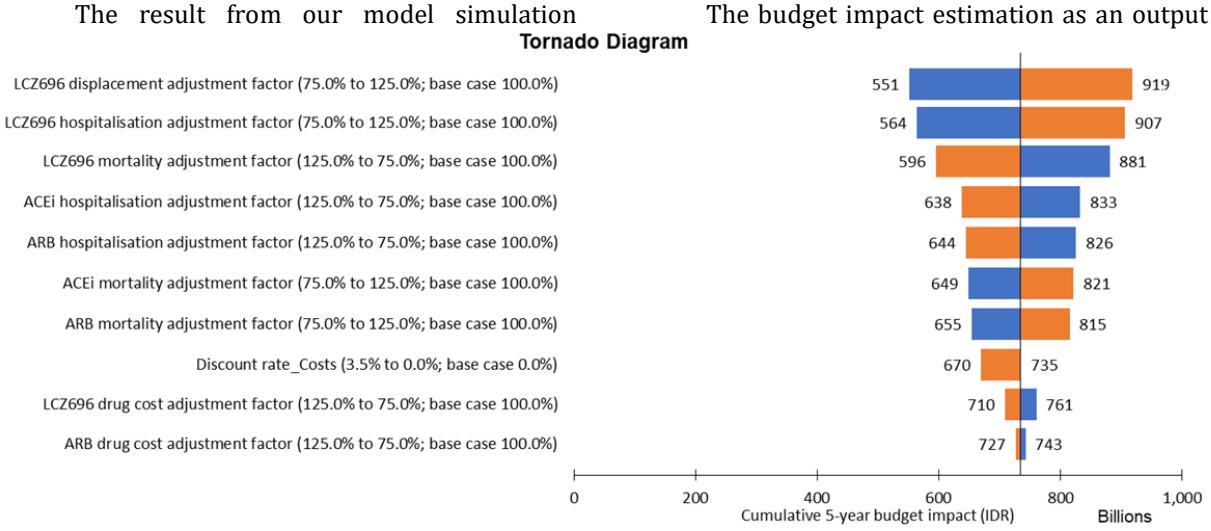

Figure 3. Tornado diagram resulted from one-way sensitivity analysis of budget impact of therapy with and without sacubitril/valsartan

suggested that implementing sacubitril/valsartan for treatment of HFrEF in Indonesia would avoid 3,512 hospitalizations (3% reduction) and 1,350 deaths (2% reduction) due to HFrEF over 5 years. A previous study conducted in Morroco revealed that treatment with Sac/Val compared to enalapril, saved 351 deaths, and avoided 1,228 hospitalizations (Kooli *et al*., 2018). Another study conducted in French stated that if 100,000 patients are treated with sacubitril/valsartan, about 4,500 deaths and 39,000 hospitalizations may be avoided over 5 years (Cariou *et al*., 2017). Another study found that with optimal usage of sacubitril/valsartan for the treatment of HFrEF patients in Ireland, 187 deaths and 187 hospitalizations could be avoided (O'Brien *et al*., 2018). A study from Canada found the potential that prescription of sacubitril/valsartan to all eligible patients with HF could prevent 2,820 all-cause mortality events, 3,698 30-day heart failure readmissions, and 3,222 cardiovascular deaths (Huitema *et al*., 2020). Finding from Argentina reported optimal usage of sacubitril/valsartan therapy was estimated to prevent 2,144 deaths each year (Bianculli *et al*., 2017). Another analysis in Portugal stated that sacubitril/valsartan may potentially avoid 287 sudden deaths versus enalapril in a 5-year period of time (Afonso-Silva & Laires, 2020). The difference in epidemiological model outputs might be due to the different assumptions and data inputted in the model such as the prevalence of HFrEF, market share, and probabilities of adverse events.

The budget impact estimation as an output of the BIA model simulation is presented in Table 5 in terms of annual and cumulative budget impact over 5 years. The annual budget impact in the first year was IDR 43 billion and increased by year and reached IDR 260 billion the fifth year. The cumulative budget impact over 5 years was about IDR 735 billion. The additional budget for implementing sacubitril/valsartan compared to the current treatment was about 5%. Fig. 2 shows the annual budget of therapy with sacubitril/valsartan and without sacubitril/valsartan along with the proportion of each cost component. It is seen that the biggest proportion of cost was monthly management cost and followed by hospitalization cost. The difference in budget between therapy with sacubitril/valsartan and without sacubitril/valsartan was driven mostly by the additional cost of sacubitril/valsartan.

Finding from our study revealed that treatment with sacubitril/valsartan compared without sacubitril/valsartan for HFrEF patients required an additional budget of IDR 735 billion over 5 years (5%). This amount might be considered as a small or big impact depends on the affordability and priority of the policymaker. For comparison, the result from budget impact analysis of sacubitril/valsartan in Germany found that the maximum annual increase in the budget was €88 million which translates to an increase in SHI expenditures of <0.04% per year (Gandjour & Ostwald, 2018). Another budget impact analysis conducted in Chile setting estimated the impact of

the implementation of sacubitril/valsartan for the treatment of HFrEF on the Chilean health system's budget varies from 1.60% and 1.42% annually for the first and second year respectively (Rojas *et al*., 2016). An analysis from the Australian Healthcare perspective found that the use of sacubitril/valsartan led to an additional 6 months of life gained per patient, translating to $27,954 per years of life saved (YoLS) and A$40,513 per quality-adjusted-life-years (QALY) gained (Chin *et al*., 2020). Meanwhile, a study in South Korea reported that the total cost per patient for sacubitril/valsartan was $25,832 and sacubitril/valsartan was associated with an 8-month longer life expectancy compared with enalapril (Park *et al*., 2019). Lastly, a study from Moroccan concluded that from the hospital perspective, sacubitril/valsartan introduction into HF treatment strategy has the potential to generate substantial savings over 5 years of more than 8.1m MAD (Kooli *et al*., 2018). The varied findings among studies were due to different assumptions used in the model as well as costs which can be very different among countries.

The difference of budgets between therapies with sacubitril/valsartan compared without sacubitril/valsartan were mainly due to the difference of drug costs because of the replacement of standard therapy with sacubitril/valsartan and the difference of hospitalization costs as the benefit of hospitalization reduction because of the use of sacubitril/valsartan. A study in Italy showed that treatment with sacubitril/valsartan was associated with lower indexed rates of hospitalizations and hospitalization-related costs (Correale *et al*., 2019). Another study in the US stated that treatment for the untreated heart failure patients with valsartan would reduce hospitalization costs from $135 million to $43 million owing to averted heart failure-related hospitalizations and shortened length of stay for the remaining hospitalizations (Smith *et al*., 2007). The study from Russia reported budget impact analysis results that indicate during three years in case of sacubitril/valsartan usage budgetary burden can be reduced by more than 220,000 rubles per patient and leads to savings of more than six billion rubles in terms of the whole population (Zyryanov *et al*., 2018). On the other hand, a study in the US also mentions that inpatient initiation of sacubitril/valsartan was estimated to save up to $449 per person for 1 year or $2,550 per person over 5 years compared with continuation of enalapril (Gaziano *et al*., 2020). The adverse effects of sacubitril/valsartan were slightly more prevalent than other drugs, however the costs for these adverse effects were much smaller if compared with other costs such as hospitalization costs and monthly management costs due to the heart failure.

Sensitivity analysis was conducted using *one-way sensitivity analysis* by replacing the base case of some input parameters with the lowest value (75% lower from the base case value) and the highest value (125% from the base case value). The result of sensitivity analysis is presented as a Tornado diagram (Fig. 3). The most sensitive parameter was the LCZ696 displacement adjustment factor. Meanwhile, the most stable parameter was the ARB drug cost adjustment factor. The difference of estimated cumulative budget impact from the base case value resulted from sensitivity analysis ranged from 0 to 25%. Results from sensitivity analysis might give partly explanation that the different value of parameter input within the range 75 – 125% from base case provided deviation of cumulative budget impact to a maximum of 25%. This results showed that the model was quite robust as indicated by the deviation of budget impact was proportional with the range of input value for sensitivity analysis.

Our study has limitations as other modeling analyses to deal with uncertainty that might lead to bias of the study results. The validity of the results is influenced by the validity of several variables such as the accuracy of model assumption, the validity of parameter input in which our study used a different sources of data namely primary data from observational data and secondary data from hospital billing, tariffs, literature review, and expert opinion/assumption. The data sources also came from different settings both local and international. To improve the validity of study results, collecting as much as valid data from local setting of Indonesia must be encouraged.

CONCLUSION

This study provides an estimation of the impact of sacubitril/valsartan application in the treatment of patients with HF and reduced ejection fraction as input for Indonesia healthcare payer in implementing the strategy for HF treatment. Using a model to simulate the implementation of the new strategy which was sacubitril/valsartan for HFrEF treatment compared to current strategy therapy in Indonesia resulted about 1,350 deaths and 3,512 hospitalizations avoidance over five years. The new strategy had the impact of an additional budget of 5% over a 5-year horizon compared to the current

therapy strategy and cumulative budget impact as IDR 735 billion over 5 years. Sensitivity analysis indicated that the model was quite robust and hence the results were consistent. Finding from this study might be a consideration for government of Indonesia in implementing health program for heart failure treatment.

ACKNOWLEDGEMENT

This work was funded by Novartis. The authors would like to thank the Director and staff of Binawaluya Heart Hospital for their support and collaboration to make this study possible.

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