Cost-Utility Analysis of Sacubitril/Valsartan Use Compared With Standard Care in Chronic Heart Failure Patients With Reduced Ejection Fraction in South Korea

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ABSTRACT

Purpose: Sacubitril/valsartan, the first-in-class angiotensin receptor neprilysin inhibitor (ARNI), is a possible treatment option for chronic heart failure patients with reduced ejection fraction (HFrEF). The aim of this study was to estimate the cost-effectiveness of sacubitril/valsartan use in South Korea for treating patients with HFrEF compared with that of enalapril, an angiotensin-converting enzyme inhibitor, and with angiotensin receptor blockers (ARBs).

Methods: A Markov model was designed to estimate the lifetime cost-effectiveness of treatment for patients with HFrEF. Cohorts in the alive-state incurred a monthly risk of hospitalization because of deteriorated HF, adverse events (AEs), or death. Transition probabilities of sacubitril/valsartan and enalapril were estimated by using data from the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial. The effectiveness of ARBs (eg, reduction in mortality and hospitalization rates) was assumed to be identical to that of enalapril, according to the results of the meta-analysis. However, there was no comparative evidence for AEs. We therefore conducted a Bayesian network meta-analysis and adjusted the incidence rate of AEs for ARBs. The utility for estimating quality-adjusted life years (QALYs) was elicited by the survey of the general South Korean population by using EuroQol-5 dimensions. We calculated the medical costs, including medication, monitoring, hospitalization, AEs, and terminal care, from the health care sector perspective. Costs and effectiveness were discounted by 5%. One-way sensitivity analyses and a probabilistic sensitivity analysis were conducted to determine the model robustness.

Findings: The total cost per patient for sacubitril/valsartan and enalapril was $25,832 and $18,295, respectively. Sacubitril/valsartan was associated with an ~8- month longer life expectancy compared with enalapril and a QALY gain of 0.59. As a result, the incremental cost-effectiveness ratio for sacubitril/valsartan versus enalapril was $12,722 per QALY. The incremental cost-effectiveness ratio of sacubitril/valsartan versus ARB was $11,970 with an incurred cost of $18,741 for the ARB group. The main results and those of various sensitivity analyses were lower than a threshold of $20,000.

Implications: From a health care sector perspective, sacubitril/valsartan is a cost-effective treatment for HFrEF compared with enalapril and ARBs. This finding could be helpful for cardiologists or decision makers in reaching cost-effective choices regarding the treatment selection process. (*Clin Ther*. 2019;41:1066–1079) © 2019 Published by Elsevier Inc.

Keywords: cost-effectiveness, heart failure, Markov model, sacubitril/valsartan.

INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been used

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for >2 decades to treat heart failure patients with reduced ejection fraction (HFrEF) based on clinical trials showing the efficacy of these medications.[1–5] Despite available pharmacotherapies, HF remains a leading cause of death, with an ~50% survival rate within 5 years.[6] Moreover, patients with HF who were hospitalized because of poor prognosis exhibited a high rate of readmission and mortality, and they incurred additional medical costs, which accounted for one half of the total HF-related medical costs.[7,8] Those unmet needs necessitate new medications to reduce the burden of this illness.

A large, Phase III randomized clinical trial, PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), showed an improved outcome with sacubitril/valsartan, which is the first-in-class angiotensin receptor neprilysin (ARNI), relative to that of enalapril.[9] Sacubitril/valsartan showed a significant reduction in cardiovascular (CV) death and hospitalization for HF compared with enalapril (hazard ratio, 0.80; 95% CI, 0.73−0.87; $P < 0.001$). In addition, sacubitril/valsartan significantly lowered the risk of readmission relative to that of enalapril.[10] Based on this compelling evidence, sacubitril/valsartan became available as an alternative treatment for chronic HFrEF according to the updated guidelines.[1]

Although the effectiveness of the new medication has been established, the accessibility of new medication is often associated with cost-effectiveness because this factor is an important standard for many countries using health technology assessment to reimburse medication.[11] The cost-effectiveness of sacubitril/valsartan has been shown in Western countries, including the United States, the United Kingdom, Denmark, Colombia, and the Netherlands.[12–17] HF is also a substantial health problem in the Asian population[18,19]; the cost-effectiveness of sacubitril/valsartan has not yet been proved in Asian countries, although previous studies have been conducted.[20,21]

There are additional knowledge gaps from previous studies. First, the cost-effectiveness of sacubitril/valsartan has been identified compared with that of ACE inhibitors, especially enalapril. ARBs had been restricted to patients who were intolerant to ACE inhibitors because of cough or angioedema, or already tolerating ARBs for other indications.[22] ARBs are now considered a first-line treatment for patients with HFrEF after the guidelines were revised in 2016.[1] Moreover, ARBs are used in a proportion similar to that of ACE inhibitors in Asian countries.[23] In particular, ARBs are more commonly used for patients with HF than ACE inhibitors in South Korea.[24] Consequently, evidence regarding the cost-effectiveness of sacubitril/valsartan relative to ARBs is necessary. Second, previous studies applied utility values obtained from patients with HF.[13,25] Utility is used for calculating the quality-adjusted life year (QALY), which is the final outcome of effectiveness that reflects the quality of life in pharmacoeconomic studies. Because reimbursement of a new medication is supported by public resources, the utility elicited by the general population is appropriate in terms of reflecting the perspective of the entire society.[26,27]

The goal of the current study was to determine the cost-effectiveness of sacubitril/valsartan with consideration of the unidentified points discussed earlier. A cost-utility analysis of sacubitril/valsartan compared with ACE inhibitors or ARBs was therefore conducted by using a South Korean health care setting with QALY estimated according to the utility of the general South Korean population.

MATERIALS AND METHODS

Overview of Cost-utility Analysis

According to a systematic review of cost-effectiveness studies of chronic HF treatment, among 33 studies that used decision-analytic modeling, 27 applied the Markov model.[28] A Markov model is useful when the interested disease contains a continuous risk over time, such as mortality, or the possibility of >1 major event (eg, hospitalization because of HF deterioration).[29] We used a Markov model to estimate the long-term effectiveness and costs of treatment with sacubitril/valsartan and its comparators. Health status reports were constructed reflecting the characteristics of HF referred to in the previous studies. Health status reports included the classification of alive, alive with adverse event (AE), hospitalization, or death (Figure 1).[28] "Alive" refers to a stable, chronic HF state in which the symptoms of HF are controlled by taking a therapeutic agent. Some patients who rapidly deteriorated could be hospitalized or may have experienced an AE during the alive state. In the model, clinical and cost data

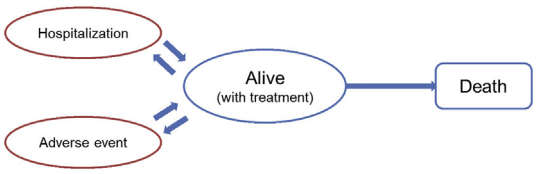

Figure 1. Health status applied to the model and the analysis framework.

were adapted to the South Korean setting and were calculated by using local data to the extent possible.

The target population was defined as patients with HFrEF according to the New York Heart Association functional classification II to IV and left ventricular ejection fraction <35%. The definition was based on the reimbursement criteria in South Korea. The study model estimated the cost and QALYs associated with each strategy throughout a lifetime (30 years) by using Microsoft Excel (Microsoft Corporation, Redmond, Washington; 2013). A 1-month cycle length was applied in accordance with the existing economic evaluation studies on chronic HF treatment.[30–32] The costs were calculated from the health care sector perspective, and all costs were expressed in 2017 US dollars ($1 = 1132.2 Korea won). A discount rate of 5% was applied to both costs and outcomes in accordance with the guidelines for economic evaluation in South Korea.[26,33]

In this study, 2 comparators were chosen with consideration of their clinical and economic aspects. The first comparator was enalapril, which is the gold standard treatment for patients with HFrEF.[34] Second, we chose ARBs, which are more commonly used in South Korea than ACE inhibitors. According to the Health Insurance Review Assessment Service guidelines for pharmacoeconomic studies, it is recommended to choose the most commonly used medication as a comparator.[26] In this study, we included candesartan and valsartan (which are approved and reimbursed for HF in South Korea) as ARBs. According to meta-analyses, ARBs and ACE inhibitors are not significantly different in reducing either mortality (odds ratio, 1.09; 95% CI, 0.92–1.29) or hospitalization (odds ratio, 0.95; 95% CI, 0.80–1.13).[35,36] Recently published Bayesian network meta-analyses also supported these results.[37,38] Consequently, we assumed that the effectiveness of ACE inhibitors and ARBs would be identical, including the reduction of mortality and hospitalization rates.[35,37,38]

Transition Probability

Mortality

A multivariate parametric survival analysis was conducted to estimate and extrapolate CV mortality beyond the trial period by using baseline characteristics and treatment allocation.[15] CV mortality was estimated by using patient-level data of 7073 patients who met the criteria of the target population from the PRADIGM-HF data (Table I). The assumption applied was that CV mortality follows a Gompertz distribution based on the visual inspection of log-cumulative hazard plots, Akaike information criterion, and Bayesian information criterion scores, as well as previous studies.[15,32] Non-CV mortality data in the South Korean population were obtained from the age- and sex-specific mortality data from life tables (Table II).[39] Death rates were converted to monthly probabilities of death by using the formula $p = 1 - e^{-r*time}$ (p, average probability of death in 1 month; r, annual death rate; time, 1/12 years in this case [because we derived monthly probabilities]).

Hospitalization Rate

Hospitalized patients may experience deterioration of health and incur additional medical costs.[8] To reflect that possibility, hospitalization risk was calculated by using a multivariable negative binomial regression model from the PRADIGM-HF trial.[15] The annual admission rates adjusted with basic characteristics of all patients were 0.36 for the sacubitril/valsartan group and 0.43 for the enalapril and ARB groups. The 1-month probability of hospitalization was calculated as 2.96% and 3.53% in the sacubitril/valsartan and enalapril/ARB groups, respectively (Table II).

AE Rate

In the current study, we considered the AEs investigated in the PARADIGM-HF trial to be applied in the model, except angioedema, which rarely occurred. The incidence rate of AEs (including

Table I. Baseline characteristics for estimating rates of cardiovascular mortality and hospitalization.

Variable	Coefficient	Baseline Characteristics	
		All Patients (N = 8399)	Included Patients* (n = 7073)
Age†	−0.094	63.8	63.5
Age^2	0.001	—	—
Female	−0.375	22%	22%
Region			
North America (reference)	—	7%	8%
Latin America	0.600	17%	17%
Western Europe	0.294	24%	24%
Central Europe	0.599	34%	33%
Asia—Pacific	−0.084	18%	18%
Race			
White (reference)	—	66%	65%
Black	0.440	5%	5%
Asian	1.012	18%	19%
Other	0.242	11%	11%
NYHA functional classification			
I/II (reference)	—	75%	74%
III/IV	0.281	25%	26%
LVEF (%)†	−0.018	29.5%	28.4%
log(eGFR)†	−0.300	4.17	4.17
log(NT-proBNP)†	0.424	7.47	7.50
Sodium†	−0.029	141.46	141.45
QRS duration†	0.002	117.36	118.4
Diabetes	0.220	35%	35%
Beta-blocker use	−0.299	93%	93%
Time since heart failure diagnosis			
≤1 y (reference)	—	30%	30%
1—5 y	0.212	38.5%	38%
>5 y	0.337	31.5%	32%
Ischemic etiology	0.139	60%	59%
Previously hospitalized for heart failure	0.144	63%	63%
EQ-5D†	−1.123	0.87	0.87
Treatment with sacubitril/valsartan	−0.256		
Constant	−12.736		

eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol-5 dimensions; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro—brain natriuretic peptide; NYHA = New York Heart Association.

* Patients who met the reimbursement criteria (NYHA functional classification II—IV and LVEF <35%) were included.

† These variables are continuous variables.

cough, hypotension, and elevated serum creatinine and potassium levels) due to sacubitril/valsartan and enalapril was calculated from the PARADIGM-HF data.[34] In contrast to effectiveness, there was an absence of evidence that compared the incidence rate of AEs between ACE inhibitors and ARBs. Therefore,

Table II. Clinical and cost data applied in the model.

Variable	Value	Reference
Clinical data		
Mortality		
Hazard ratio of cardiovascular mortality* (sacubitril/valsartan vs enalapril)	0.77 (0.69–0.87)	9
Monthly probability of noncardiovascular mortality†	0.07 (age 63.5 y) 0.10 (age 68.5 y) 0.19 (age 73.5 y) 0.34 (age 78.5 y) 0.61 (age 83.5 y) 1.07 (age 88.5 y) 1.73 (age 93.5 y)	39
Monthly probability of hospitalization		9
Sacubitril/valsartan	2.96	
Enalapril	3.53	
Monthly probability of adverse events		9
Hypotension		
Sacubitril/valsartan	0.52	
Enalapril	0.35	
Cough		
Sacubitril/valsartan	0.42	
Enalapril	0.54	
Elevated serum creatinine level		
Sacubitril/valsartan	0.12	
Enalapril	0.25	
Elevated serum potassium level		
Sacubitril/valsartan	0.60	
Enalapril	1.18	
Utility weight (mean [SD])		
Stable chronic heart failure	0.871 (0.088)	46
Stable chronic heart failure + hypotension	0.710 (0.076)	
Stable chronic heart failure + cough	0.793 (0.055)	
Hospitalization for a sudden worsening	0.215 (0.174)	
Cost data‡		
Monthly cost		
Medication cost		
Sacubitril/valsartan	124.9	49, 50
Enalapril	26.9	
ARB	32.8	
Background therapy cost (baseline/3 y)		
Sacubitril/valsartan	20.7/20.7	9, 49, 50
Enalapril or ARB	20.8/21.3	
HF management	21.7	51

Table II. (*Continued*)

Variable	Value	Reference
Cost per event		
Cost of titration for sacubitril/valsartan patients	11.0	51
Cost per adverse event		
Elevated serum creatinine level	35.5	51
Elevated serum potassium level	46.7	
Hospitalization cost	4799.2	24
Terminal cost	1824.3	53

ARB = angiotensin receptor blocker; HF = heart failure.
*Value was estimated by using a Gompertz distribution.
†Values were weighted according to the proportion of sex in cohort.
‡All costs (in US $, average exchange rate is 1132.20 KRW per USD as of August 2017).

a Bayesian network meta-analysis was conducted to estimate the incidence rate ratio (RR) of ARBs compared with that of enalapril. We reviewed the articles that reported the information for AEs based on the included studies in the previous meta-analysis for CV mortality and hopitalization.[38] Substantial data on enalapril were included from the PARADIGM-HF trial. The network diagram is given in Figure 2.[2–5,34,40–44]

In the Bayesian network meta-analysis, the probability of RR for ARBs relative to enalapril being >1 (P[RR>1]) was calculated to test the hypothesis. We interpreted that P[RR>1] >90% indicated a significantly higher incidence rate of AEs with ARBs than that with enalapril and that <10% meant enalapril had a higher incidence rate of AEs than did ARBs.[45] On the basis of the results of the P[RR>1] analysis, we determined that the incidence of cough and hypotension was not significantly different between enalapril and ARBs (Table III). Thus, the incidence rate was applied by using the number of patients who experienced each AE in the PARADIGM-HF trial. Furthermore, ARBs exhibited a significantly higher incidence rate of elevated serum

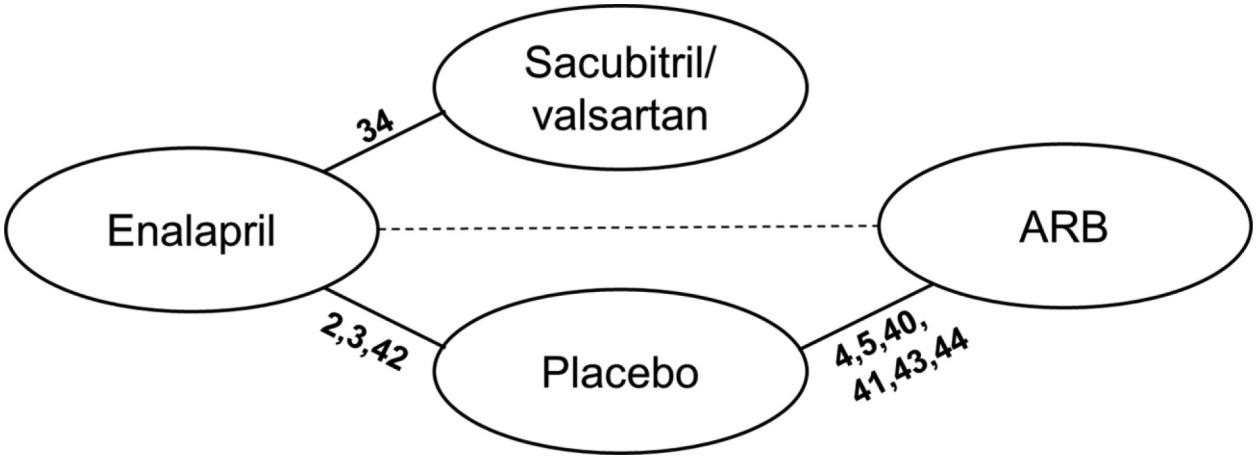

Figure 2. Network diagram for network meta-analysis. ARB = angiotensin receptor blocker. The number next to the line indicates the reference number.

Table III. Results of Bayesian network meta-analysis of adverse event incidence rate of angiotensin receptor blockers compared with that of the angiotensin-converting enzyme inhibitor.

Adverse Event	Rate Ratio		Probability of Rate Ratio >1
	Estimate	95% Credible Interval (Low–High)	
Hypotension	0.80	0.41–1.52	25%
Cough	0.38	0.05–2.05	13%
Elevated serum creatinine level	1.45	1.01–2.09	98%
Elevated serum potassium level	1.81	0.90–3.75	95%

creatinine or potassium compared with enalapril. Therefore, we adjusted the incidence rate obtained from PARADIGM-HF by using the RR of ARBs. The estimated annual rates of AEs were assumed to be the same for every month. Consequently, the values were converted by using the formula of $p = 1 - e^{-rt}$, where p = average probability of occurrence in 1 month and r = annual probability rates; the values were then input into the Markov model (Table II).

Utility

To calculate QALY as a final outcome, the utilities of each health state were applied. Referring to the guidelines for pharmacoeconomic evaluation from the Health Insurance Review Assessment Service, the value of utility surveyed from the general South Korean population according to the 5-level EuroQol-5 dimensions was used.[26,27,46] One hundred face-to-face interviewees were selected through quota sampling according to age, sex, and region from the general population. Health states of hospitalization and AEs in the alive state were surveyed to reflect the utility decremented because of the events. The following health states were surveyed: alive, hospitalization, and AEs (eg, cough, hypotension) (Table II).

Cost

The current model included the total formal medical costs paid by the National Health Insurance Service and out-of-pocket costs from the health care sector perspective.[47,48] The medical costs consisted of monthly costs paid and expenses because of clinical events such as hospitalization, AEs, and death (hereafter defined as terminal care cost). The monthly cost included the costs of medications, administration, dispensing, outpatient visit, and monitoring (Table II).

Monthly Cost

Cost of sacubitril/valsartan was determined based on the target maintenance dose (200 mg BID).[34] The unit price of sacubitril/valsartan 200 mg is $2.2, and the monthly cost was calculated as $124.9. The cost of titration was considered in the sacubitril/valsartan group. The titration cost was defined as the cost for 2 additional outpatient visits to confirm the proper regimen of sacubitril/valsartan. Medication cost of comparators was based on the price of reimbursed medication for HF in South Korea. The monthly price for enalapril was applied as $26.9 referring to the listed drug price. The price of ARBs was calculated as $32.8 by multiplying the unit price by the proportion of each medication calculated from the National Patients Sample database.[49,50]

In the model, the cost of background therapies such as beta-blockers, mineralocorticoid receptor antagonists, digoxin, lipid-lowering medications, and diuretics was also considered. The monthly price of each background therapy was calculated by adjusting the monthly price obtained from the National Patients Sample database according to the proportion of patients receiving each background therapy from PARADIGM-HF.[34,49,50]

The clinical guidelines of HF recommend that patients should be regularly checked by using radiographs, ECGs, and laboratory tests, including routine blood tests and electrolyte tests.[22] In addition, tests such as echocardiography and B-type natriuretic peptide (or N-terminal pro–B-type natriuretic peptide) tests should be performed to diagnose and monitor the prognosis of the patient. We assumed that the laboratory tests and ECG were performed annually and that the radiographs and echocardiography were performed every 6 months according to consultation with a cardiologist. The

monthly cost of outpatient visits was calculated as the unit cost of consultation per visit adjusted by frequency (eg, 3 months).[50,51]

Cost Per Event

Hospitalization cost referred to the result of a retrospective cohort study that analyzed hospitalization cost because of acute HF.[24] The value was elicited from patients with HF who had a history of hospitalization or ≥2 outpatient visits among the 6 hospitals in South Korea during 2013. For the cost of AEs, we assumed that only the patients who experienced elevated serum creatinine or potassium levels were using additional medical resources to cure the AE. We defined the cost because of AE as an additional 2-fold that of outpatient visits for counseling and conducting blood and related electrolyte tests.[51] These assumptions and definitions were based on consultation with a cardiologist.

In a previous study that examined the cost of care for patients with HF during the final 2 years of life, 27% of the total medical cost was spent in the 3 months before death.[52] Thus, we assumed that each patient in the cohort might spend $1824 for terminal care cost in the last cycle. The price referred to a report from the National Health Insurance Service of South Korea.[53]

Analysis

In the base-case analysis, the incremental cost-effectiveness ratio (ICER) represented the cost-effectiveness of sacubitril/valsartan relative to the standard of care. The willingness-to-pay threshold was set at $20,000 to interpret cost-effectiveness based on ICER.[48,54] To assess the effect of different assumptions on the model results, a series of one-way deterministic sensitivity analyses were performed to ensure the robustness of the results according to varying values. The one-way deterministic sensitivity analyses considered the following: distributions for extrapolating CV mortality, sacubitril/valsartan price (range, −10% to 10%), hospitalization cost,[50,55] utility weights from a clinical trial,[34] comparators as standard of care that included both enalapril and ARBs, discount rate, and time horizon. In the case of sensitivity analyses for comparator as standard of care, the proportion between enalapril and ARBs presented in a previous study was used.[24]

A probabilistic sensitivity analysis was conducted by using 10,000 iterations of a second-order Monte Carlo simulation with the parameters such as CV mortality, hospitalization rate, utilities, and cost. We assumed that the risk ratio of CV mortality and hospitalization rate for sacubitril/valsartan relative to enalapril followed a log-normal distribution, utility values followed a beta-distribution, and costs followed a gamma-distribution.[13,56] For determining the distribution, the mean and SE values were extracted from the PARADIGM-HF data for the risk ratio of CV mortality and hospitalization rate, and the same values were extracted from the survey data for utilities. The distribution of cost used in the value of the base-case analysis was the mean and 25% of the SEM.

RESULTS

Base-Case Analysis

The cost-effectiveness of sacubitril/valsartan use in South Korea was evaluated by applying the proper clinical and cost data (Tables I and II). According to the results, total QALYs per person over a lifetime horizon were 5.74 and 5.15 for the sacubitril/valsartan and comparator groups, respectively (Table IV). This outcome led to an incremental difference of 0.59 QALY. Calculation of life year gained without utility weights showed that the sacubitril/valsartan and comparator groups gained 6.70 and 6.02 years per patient for a lifetime period (30 years). Therefore, the sacubitril/valsartan group gained 0.68 year longer than the comparator group. The differences in total incremental costs were $7536 and $7091 for the enalapril and ARBs groups. On the basis of the incremental cost and QALYs, ICER for sacubitril/valsartan versus enalapril was $12,722 per QALY gained and versus ARBs was $11,970 per QALY. Consequently, from the health care sector perspective in South Korea, sacubitril/valsartan is a cost-effective treatment option within a threshold of $20,000.

Sensitivity Analysis

In the base-case result, the ICER of sacubitril/valsartan compared with enalapril was higher than that with ARBs. We therefore conducted one-way deterministic sensitivity analyses with enalapril as a comparator. The results are presented as a tornado diagram in Figure 3. Sensitivity analyses were

Table IV. Base-case estimates from the simulation model.

Variable	Enalapril	Sacubitril/Valsartan	ARBs	Sacubitril/Valsartan
Life years	6.02	6.70	6.02	6.70
Incremental life years	—	0.68	—	0.68
QALYs	5.15	5.74	5.15	5.74
Incremental life QALYs	—	0.59	—	0.59
Costs, $	18,295.3	25,831.7	18,740.6	25,831.7
Incremental costs	—	7536.3	—	7091.0
ICER				
Per life year gained	—	11,130.1	—	10,472.6
Per QALY gained	—	12,721.9	—	11,970.3

ARBs = angiotensin receptor blockers; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.
All costs (in US $; average exchange rate is 1132.20 KRW per USD of August 2017), life years, and QALYs were discounted at a rate of 5% annually.

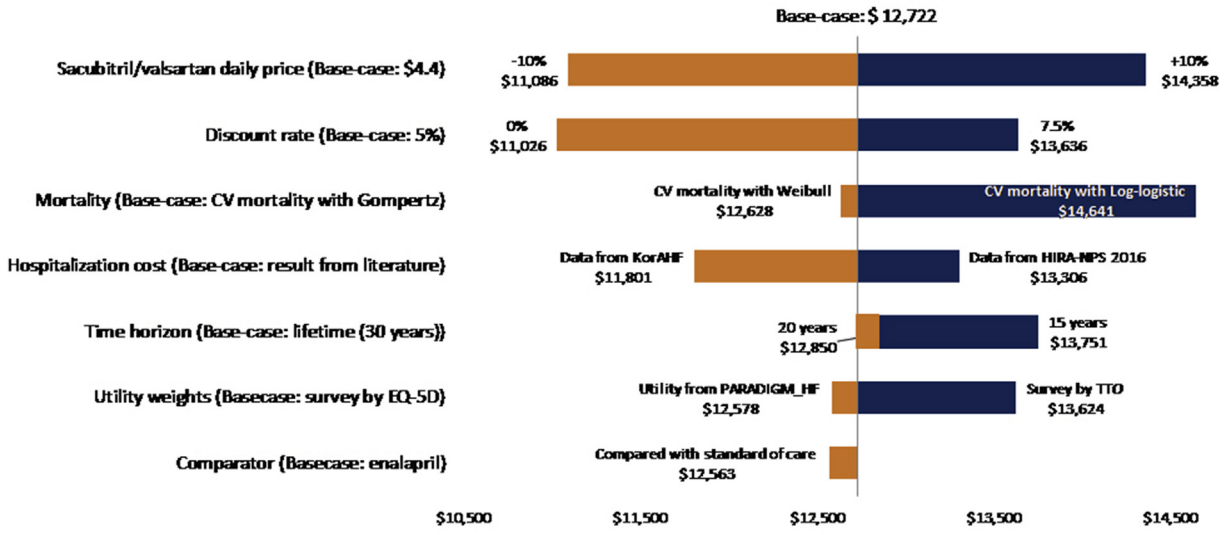

Figure 3. Tornado diagram (one-way sensitivity analysis). CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; KorAHF = Korean Acute Heart Failure Registry; HIRA-NPS = Health Insurance Review Assessment Service—National Patients Sample; PARADIGM-HF = Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; TTO = time trade-off.

performed by changing the assumptions of key model inputs. It was shown that the choice of the sacubitril/valsartan daily price had the greatest effect on ICER, but the overall variation remained stable within 20%. The distribution for CV mortality also had a considerable effect on ICER. When log-logistic distribution was applied, it showed the most appropriate statistical value but was inappropriate upon visual inspection; ICER increased to $14,641. Analysis with the variation of time horizon showed

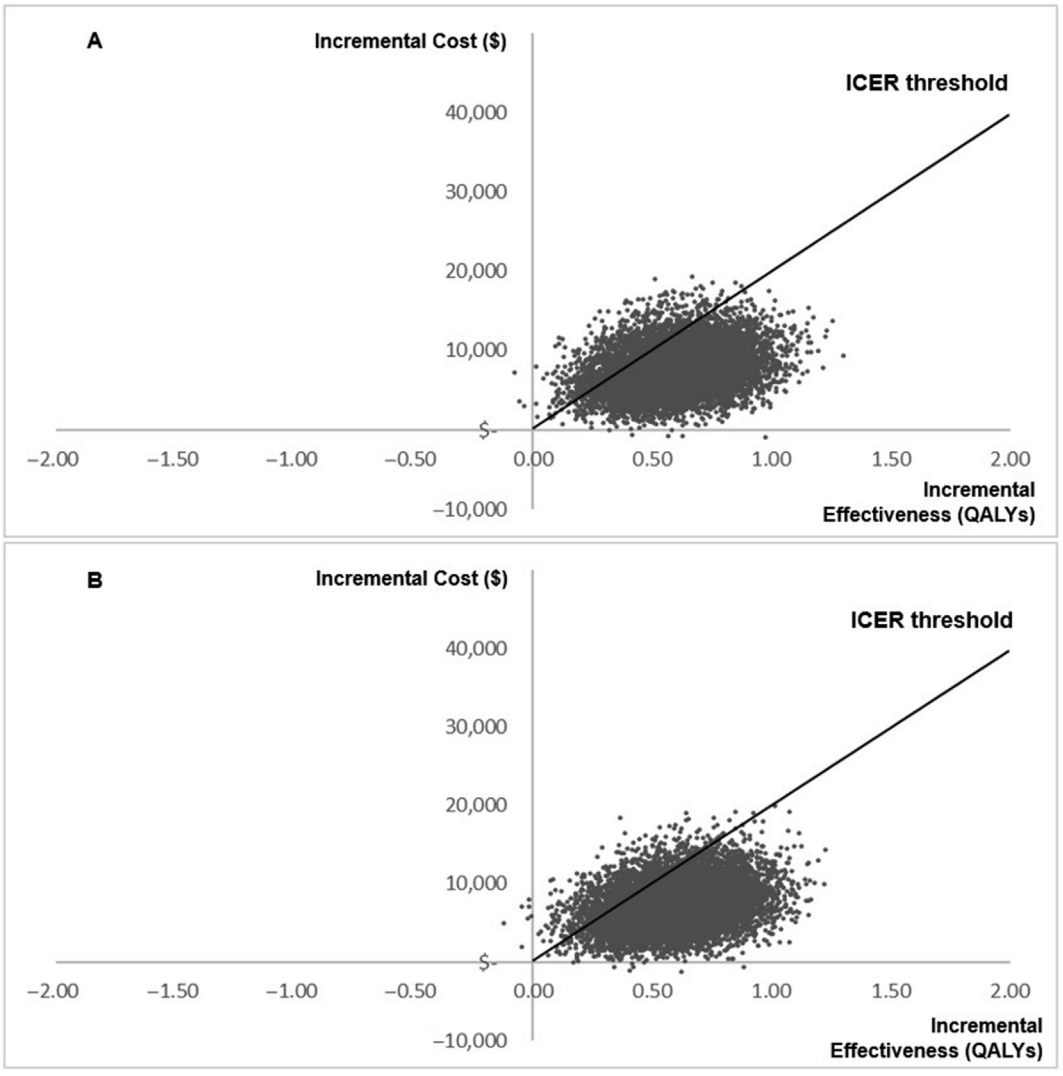

Figure 4. Illustration of probabilistic sensitivity analysis. (A) Compared with enalapril. (B) Compared with angiotensin receptor blockers. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

the following trend: the shorter the time horizon, the higher the cost per QALY. There was no result that exceeded the threshold ($20,000).

Figure 4 presents the results of the probabilistic sensitivity analysis after 10,000 iterations. Based on the ICER threshold ($20,000 per QALY), the probability that sacubitril/valsartan is cost-effective compared with enalapril was 87.6%. Compared with ARBs, the probability of the cost-effectiveness of sacubitril/valsartan was 89.0%.

DISCUSSION

The current study analyzed the cost-effectiveness of sacubitril/valsartan in South Korea compared with that of enalapril and ARBs. The ICER was estimated by using utilities obtained from the general South Korean population. Although treatment with sacubitril/valsartan is costlier than treatment with the comparators, the ICER did not exceed the South Korean threshold of $20,000 per extra QALY. This outcome might be driven by the fact that sacubitril/

valsartan significantly reduces the risk of mortality and hospitalization, which are the risk factors that deteriorate quality of life and expend additional medical costs over that of comparators.[9,34] Consequently, sacubitril/valsartan was identified as a cost-effective medication for HFrEF patients with New York Heart Association functional classification II to IV. The results of the various one-way sensitivity analyses showed that cost-effectiveness was robust with an ICER value of about one half of the South Korean threshold.

Various studies have examined the cost-effectiveness of sacubitril/valsartan compared with that of enalapril.[12–15,17,20,21] Studies in the United States and European countries, including Germany, the United Kingdom, and Denmark, reported on the cost-effectiveness of sacubitril/valsartan (ICER in the US setting, $45,017–$50,959[13,14,17]; Germany, €23,401[12]; United Kingdom, €20,400[15]; and Denmark, €22,600[15]). Those studies, although they produced ICERs that were numerically higher than those in the current study, resulted in the same decision: sacubitril/valsartan is cost-effective owing to the higher threshold in those countries than that of the current study.

On the contrary, there are several studies which suggested that sacubitril/valsartan is not a cost-effective alternative in Asian countries such as Singapore and Thailand.[20,21] The first discrepancy from the current study is the time horizon. The study from Singapore simulated the model for 10 years,[21] whereas similar studies applied a lifetime horizon.[12–15,17,20] As shown in the sensitivity analyses, the shorter the time horizon, the higher the ICER. The 10-year time horizon applied in the Singapore study with 66-year-old patients might be too short to capture the benefit of the medication, such as in delaying mortality, because patients with chronic HF who are aged 80 years are expected to live for an average of >4 years.[57] In the sensitivity analysis, we reported the variation of ICER due to the +10% and −10% of the daily price for sacubitril/valsartan. In South Korea, the medication price is readjusted by a repricing mechanism, which was introduced with consideration of the uncertainty of the price at the approval for reimbursement by using the national insurance. According to a recent study, an ~10% change in drug price was shown after the repricing mechanism was used.[58] We therefore conducted one-way sensitivity analyses to identify the impact of unit price on ICER within a 10% range and found that the price of sacubitril/valsartan is a key driver of the ICER. Considering that trend, the price of sacubitril/valsartan might have influenced its establishment as non–cost-effective in the Thailand study. The Thailand study applied a 225-fold higher cost of sacubitril/valsartan relative to that of enalapril. Such a relative ratio of medication costs is the highest among similar studies, which generally showed a 4 to 60 relative ratio. Even though the price level might vary from country to country, it seems inappropriate to compare the ICER of a previous study that applied an extremely expensive price of sacubitril/valsartan with the current result. Moreover, although the expensive price of sacubitril/valsartan was applied in the Thailand study, the calculated ICER was only $330 higher (2%) than the ICER threshold. Consequently, the results of non–cost-effectiveness need to be interpreted with caution.

The current study obtained robust results even though the comparator price was low owing to the use of generic products. Nevertheless, this study should be interpreted with caution because of the following limitations. The main limitation was associated with the uncertainty of mortality. First, we compared sacubitril/valsartan and ARBs with the assumption that ACE inhibitors and ARBs have the same effectiveness, according to various meta-analyses. This method was applied because of an absence of head-to-head trials between sacubitril/valsartan and ARBs. Although the Bayesian network meta-analysis reported that sacubitril/valsartan significantly improved survival and reduced hospitalization rates compared with ACE inhibitors and ARBs, additional clinical trials are needed to elucidate the relative effectiveness of sacubitril/valsartan and ARBs. Furthermore, this study did not consider discontinuation of drug administration. The main AEs of sacubitril/valsartan are elevated serum creatinine level, hypotension, elevated serum potassium level, and cough. Because the AEs reported in the PARADIGM-HF trial are symptoms that do not require special treatment, it may be reasonable not to consider discontinuation related to side effects. The other limitation is induced by extrapolation of

treatment effects beyond the observation period of the PARADIGM-HF trial. This factor is a common limitation shared by most economic evaluation studies in which the lifetime effect of an emerging treatment is assessed.

CONCLUSIONS

We reported the long-term cost-effectiveness of sacubitril/valsartan versus the comparators enalapril and ARBs for HFrEF in South Korea. Our results could be useful for cardiologists in choosing treatments for patients with HFrEF among sacubitril/valsartan and ACE inhibitors or ARBs. Moreover, decision makers could refer to these meaningful results that reflect the preference of the general population.

CONFLICTS OF INTEREST

Dr. Park, BS. Hong, and Dr. Lee report receiving grants from Novartis Korea Ltd during the conduct of the study. H. Kim, MPH and Dr. S. Kim are employees of Novartis Korea and report that they received personals fee during the conduct of the study. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Dr. Park contributed to simulation of the model and writing of the manuscript. Hong contributed to revising the manuscript, and administrative and technical support. H. Kim and S. Kim reviewed the manuscript and contributed to administrative support. Dr. Lee, the study supervisor, contributed to overall supervision and review of the manuscript. All authors were responsible for the study design; the collection, analysis, and interpretation of data; the writing of the manuscript; and the decision to submit for publication. All authors had full access to the data, and all authors reviewed the manuscript.

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