Original Article

JURNAL RISET KEFARMASIAN INDONESIA
Ilmu Kefarmasian & Ilmu Kesehatan

Vol.8 Issue.1 (January 2026)
page 52-60
https://doi.org/10.33759/jrki.v8i1.923
e-ISSN: 2655-8289

Cost-Minimization Analysis of Sacubitril/Valsartan and Ramipril in Hospitalized Heart Failure Patients at RSUP Dr. Kariadi Semarang

Analisis Minimalisasi Biaya Sacubitril/Valsartan dan Ramipril pada Pasien Gagal Jantung Rawat Inap di RSUP Dr. Kariadi Semarang

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Submitted : 2025-12-20
Revised : 2026-01-14
Accepted : 2026-01-29

Keywords: Heart Failure; Cost-Minimization Analysis; Sacubitril-Valsartan; Ramipril; Healthcare Costs; Hospitalized Patients

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Abstract

Heart failure represents a major public health challenge in Indonesia, characterized by high hospitalization rates and substantial healthcare costs. This study compared the economic efficiency of sacubitril-valsartan and ramipril in hospitalized heart failure patients through cost-minimization analysis. This study was conducted in a retrospective cross-sectional at RSUP Dr. Kariadi Semarang from January to December 2024, Analyzed 98 patients who received sacubitril-valsartan or ramipril in conjunction with beta-blockers and mineralocorticoid receptor antagonists, and did not undergo minor or major surgery during hospitalization, with data sourced from medical records, hospital systems, pharmacy, and finance departments. Patient baseline characteristics showed no significant differences in sex, occupation, or length of stay, though sacubitril-valsartan patients had more comorbidities and different insurance and education profiles. Length of stay averaged 5.78 days for ramipril and 6.18 days for sacubitril-valsartan, with no statistical difference. Total hospital costs reached 12,379,257 IDR per patient for ramipril versus 12,174,742 IDR for sacubitril-valsartan. Sacubitril-valsartan proves economically comparable to ramipril, offering a slight cost advantage from the payer perspective under equivalent clinical effectiveness. These findings support its integration into Indonesian heart failure protocols to optimize resource use amid budget constraints.

Abstrak

Gagal jantung merupakan tantangan kesehatan masyarakat yang besar di Indonesia, ditandai dengan tingginya angka rawat inap dan besarnya biaya pelayanan kesehatan. Penelitian ini membandingkan efisiensi ekonomi antara sacubitril-valsartan dan ramipril pada pasien gagal jantung yang dirawat inap melalui analisis minimalisasi biaya. Penelitian ini dilakukan dengan desain retrospektif potong lintang di RSUP Dr. Kariadi Semarang pada periode Januari hingga Desember 2024. Sebanyak 98 pasien dianalisis, yang menerima terapi sacubitril-valsartan atau ramipril yang dikombinasikan dengan beta-blocker dan antagonis reseptor mineralokortikoid, serta tidak menjalani tindakan bedah minor maupun mayor selama masa perawatan. Data diperoleh dari rekam medis, sistem informasi rumah sakit, instalasi farmasi, dan bagian keuangan. Karakteristik dasar pasien menunjukkan tidak terdapat perbedaan bermakna pada jenis kelamin, pekerjaan, maupun lama rawat inap, meskipun pasien yang menerima sacubitril-valsartan memiliki lebih banyak komorbiditas serta perbedaan pada jenis asuransi dan tingkat pendidikan. Rata-rata lama rawat inap adalah 5,78 hari pada kelompok ramipril dan 6,18 hari pada kelompok sacubitril-valsartan, tanpa perbedaan yang signifikan secara statistik. Total biaya rumah sakit per pasien mencapai Rp12.379.257 pada kelompok ramipril dan Rp12.174.742 pada kelompok sacubitril-valsartan. Sacubitril-valsartan terbukti memiliki efisiensi ekonomi yang sebanding dengan ramipril, dengan sedikit keunggulan biaya dari perspektif pembayar pada kondisi efektivitas klinis yang setara. Temuan ini mendukung integrasi sacubitril-valsartan ke dalam protokol penatalaksanaan gagal jantung di Indonesia guna mengoptimalkan pemanfaatan sumber daya di tengah keterbatasan anggaran.

How to Cite: (*citation style* AMA 11th Ed.)
Rifqi HD, Setiawati MCN, Rukminingsih F, Setyarini Y. Cost-Minimization Analysis of Sacubitril/Valsartan and Ramipril in Hospitalized Heart Failure Patients at RSUP Dr. Kariadi Semarang. *Jurnal Riset Kefarmasian Indonesia*. 2026;8(1):52-60.
doi:10.33759/jrki.v8i1.923

INTRODUCTION

Based on data 2021 from the Health Ministry of the Republic of Indonesia, Heart Failure is one of the health problems in the country that is significant and continues to be of increasing concern to the public due to the prevailing demography as well as the changing patterns of the disease[1]. As per the Global Burden of Disease and Institute for Health Metrics and Evaluation (IHME) for the years of 2014-2019, heart disease was the highest cause of death in Indonesia[2,3]. The data from the Basic Health Research for 2013 and 2018 showed a positive increasing trend in heart disease, from 0.5% in 2013 to 1.5% in 2018, and reported that 2,784,064 people in Indonesia had heart failure, with the number tending to rise every year[4,5]. Heart disease was also the largest contributor to costs; according to data from the Health Universal Coverage in 2021, the highest health-care expenditure was for heart disease, which amounted to Rp7.7 trillion[6].

Heart failure was one of Indonesia's main public health issues, as it was one of the most common causes of hospital admissions and death in the adult population[7–11]. Ven after therapy strategies had improved, there were still challenges regarding the efficacy of heart failure management and the costs associated with the treatment[2,12]. Indonesia suffers from a financially constricted health care system in which costs dealing with HF therapeutics need to be held to a minimum[9,13]. Sacubitril/valsartan had demonstrated superior clinical outcomes compared to conventional ACE inhibitors such as ramipril, particularly in reducing mortality and hospital admissions, as well as improving cardiac function in patients with heart failure with reduced ejection fraction (HFrEF)[14–18]. Additionally, the benefits of sacubitril/valsartan over traditional therapies such as ramipril in reducing cardiac-related adverse outcomes have been documented in various trials, supporting a favorable safety profile[19,20]. However, the higher costs associated with sacubitril/valsartan complicate its adoption in settings like Indonesia, where healthcare budgets are limited, necessitating careful evaluation of its cost-effectiveness compared to established therapies[21]. Ultimately, although sacubitril/valsartan offers promising clinical benefits, healthcare decision-makers must weigh these against the economic implications for patients and healthcare systems[13,14].

A majority of current pharmacoeconomic studies related to sacubitril/valsartan have been done outside of Indonesia where the health system, medication prices and reimbursement strategies are different to the local context[14,22–26]. There are few local studies, such as those done at RSUP dr. Hasan Sadikin Bandung, which demonstrate that cost-effectiveness results are very sensitive to clinical variables such as degree of blood pressure reduction and duration of stay in the hospital[10]. However, such studies cannot be extrapolated to that of other hospitals. This illustrates the importance of performing local economic evaluations to aid in clinical and policy decision-making in Indonesia.

The urgency of this research lies in providing robust, locally relevant economic evidence comparing sacubitril/valsartan and ramipril in hospitalized HF patients at RSUP Dr. Kariadi Semarang. By conducting a cost-minimization analysis, this study aims to determine whether the higher costs of sacubitril/valsartan are offset by equivalent or better clinical outcomes compared to ramipril, thereby guiding optimal resource allocation in Indonesian hospitals. This research addresses the gap in local pharmacoeconomic data and contributes to evidence-based decision-making for HF management in Indonesia.

METHODS

This study used an observational, retrospective cross-sectional design with a pharmacoeconomic approach applying Cost-Minimization Analysis (CMA) to compare sacubitril/valsartan and ramipril in hospitalized heart failure patients at RSUP Dr. Kariadi Semarang during January–December 2024. Data were obtained from medical records, the hospital information system, pharmacy, and the finance department, and included only patients who met predefined inclusion and exclusion criteria and received either sacubitril/valsartan or ramipril in combination with guideline-directed background therapy during the same admission period.

Research procedure

Step I – Identification and selection of subjects

All inpatients with a primary diagnosis of heart failure in the study period were identified through the medical record database. Patients were then selected using total sampling based on inclusion criteria (age ≥18 years, hospitalized with heart failure, receiving sacubitril/valsartan plus beta-blocker and MRA or ramipril plus beta-blocker and MRA, complete clinical and cost data) and exclusion criteria (discharge against medical advice, incomplete or unreadable records, pregnancy, history of angioedema, severe aortic stenosis, bilateral renal artery stenosis, serum potassium >5.5 mmol/L, serum creatinine >2.5 mg/dL, or undergoing minor and mayor surgery during admission).

Step II – Data collection

For each eligible patient, demographic and clinical characteristics were extracted, including sex, age, education, occupation, and number of comorbidities. Therapy data covered type of regimen (sacubitril/valsartan or ramipril), dose, frequency, duration of use, and concomitant medications. Clinical outcomes comprised mean arterial pressure (MAP), calculated from systolic and diastolic blood pressure, and length of stay (LOS) in days, defined as the difference between discharge and admission dates. Cost data were collected from hospital cost perspective that included direct medical costs: antihypertensive agent cost, other drugs cost, medical devices, ward care, physician fees, diagnostic, laboratory, rehabilitation, radiology, medical team cost, registration fees, miscellaneous cost, and total hospital cost per patient were then calculated.

Step III – Data analysis

Descriptive statistics were used to present patient characteristics, LOS, and cost components for each treatment group as mean ± standard deviation or frequency (percentage) as appropriate. Comparisons between ramipril and sacubitril/valsartan groups for continuous variables (e.g., LOS, costs) were performed using independent T-test for normally distributed data or Mann–Whitney U test for non-normal data, while categorical variables (sex and number of comorbidities) were analyzed using chi-square test. CMA was conducted by comparing the average total direct medical cost per patient between the two regimens, following the formula.

$$\text{CMA per patient} = \frac{\text{Total medical cost}}{\text{number of patients}}$$

Then interpreting the regimen with the lower mean cost as the more economical option under the assumption of equivalent clinical effectiveness. In addition, one-way sensitivity analysis was planned on key cost components (study drug, ward care, physician fees, diagnostics) to explore which components most strongly influenced the average total cost; results were summarized by ranking the absolute impact of each component on total cost variation.

Ethical clearance

The study protocol was reviewed and approved by the Health Research Ethics Committee (Komite Etik Penelitian Kesehatan, KEPK) of RSUD dr. Adhyatma, MPH, Central Java Province (Ethical Clearance No. 098/KEPK.EC/XI/2024).

RESULT AND DISCUSSION

Patient Characteristics

A total of 98 hospitalized heart failure patients were enrolled in this study. Table 1 presents the characteristics of patients stratified by treatment regimen. Among the 98 patients, 37 (37.8%) received ramipril and 61 (62.2%) received sacubitril/valsartan. Sex distribution was comparable between groups (p = 0.683), with 66 (67.3%) males and 32 (32.7%) females overall. The number of comorbidities significantly differed between groups (p = 0.001),

with patients receiving sacubitril/valsartan having more comorbidities; specifically, 22.4% of the sacubitril/valsartan group had >2 comorbidities compared to 4.1% in the ramipril group.

Table 1. Characteristics of Heart Failure Patients Stratified by Treatment Regimen

Characteristic	Ramipril n (%)	Sacubitril/Valsartan n (%)	Total n (%)	p value
Sex				0.683
Male	24 (24.5)	42 (42.9)	66 (67.3)	
Female	13 (13.3)	19 (19.4)	32 (32.7)	
Total	37 (37.8)	61 (62.2)	98 (100.0)	
Number of Comorbidities				0.001*
None	14 (14.3)	5 (5.1)	19 (19.4)	
One	8 (8.2)	11 (11.2)	19 (19.4)	
Two	11 (11.2)	23 (23.5)	34 (34.7)	
>Two	4 (4.1)	22 (22.4)	26 (26.5)	
Total	37 (37.8)	61 (62.2)	98 (100.0)	
Length of Stay (days)	5.78 ± 3.21	6.18 ± 3.21	—	0.555

*Statistically significant ($p < 0.05$)

Cost Analysis

Detailed Cost Components

Table 2 presents a comprehensive breakdown of direct medical costs for both treatment groups. The mean total hospital cost was slightly higher in the ramipril group (12,379,257 ± 10,007,311 IDR) compared to sacubitril/valsartan (12,174,742 ± 7,303,810 IDR), though this difference was not statistically significant ($p = 0.907$).

Table 2. Cost Parameters and Effectiveness by Treatment Regimen

Cost Parameter	Ramipril (mean ± SD, IDR)	Sacubitril/Valsartan (mean ± SD, IDR)	p value
Ward care cost	2,894,054 ± 3,049,408	2,821,639 ± 2,285,532	0.894
Laboratory cost	2.201.703 ± 1.696.087	2.095.615 ± 1.388.300	0.737
Physician fees	2,129,730 ± 3,022,277	1,625,000 ± 1,389,874	0.263
Medical team cost	1.354.743 ± 1.306.270	1.302.279 ± 1.123.944	0.834
Miscellaneous costs	1.178.270 ± 1.576.304	1.154.705 ± 2.302.353	0.956
Other drug cost	1,037,827 ± 1,174,544	1,049,462 ± 1,016,236	0.959
Medical device cost	845,162 ± 920,094	828,787 ± 905,972	0.931
Radiology cost	447.973 ± 891.575	734.820 ± 1.940.774	0.400
Diagnostic cost	206,946 ± 285,183	297,156 ± 884,029	0.549
Rehabilitation cost	43.378 ± 109.005	60.000,00 ± 152.550	0.564
Registration fees	36.486 ± 9.269	37.459 ± 10.786	0.650
antihypertensive agent cost	2,984 ± 1,155	167,821 ± 61,842	<0.001*
Total drug costs	**1,040,811 ± 1,174,792**	**1,217,283 ± 1,038,519**	**0.440**
Total hospital cost	**12,379,257 ± 10,007,311**	**12,174,742 ± 7,303,810**	**0.907**
Length of Stay (days)	**5.78 ± 3.21**	**6.18 ± 3.21**	**0.555**

*Statistically significant ($p < 0.001$)

Cost Component Analysis

The most striking difference between regimens was in study drug cost, where sacubitril/valsartan was substantially more expensive (167,821 ± 61,842 IDR) compared to ramipril (2,984 ± 1,155 IDR; $p < 0.001$). This represents approximately a 56-fold higher acquisition cost for sacubitril/valsartan. However, the overall total drug

costs were comparable (Rp1,040,811 ± 1,174,792 vs Rp1,217,283 ± 1,038,519; p=0.440), because the costs of other drugs were similar (Rp1,037,827 ± 1,174,544 vs Rp1,049,462 ± 1,016,236; p=0.959). The per-day drug costs were also similar: Rp173,657 ± 114,291 vs Rp198,996 ± 97,205 (p=0.245), which indicated a competitive daily cost efficiency between the two regimens.

Medical device costs were also similar (845,162 IDR ramipril vs 828,787 IDR sacubitril/valsartan; p = 0.931). Ward care costs did not differ significantly (2,894,054 IDR ramipril vs 2,821,639 IDR sacubitril/valsartan; p = 0.894), nor did physician fees (2,129,730 IDR ramipril vs 1,625,000 IDR sacubitril/valsartan; p = 0.263) or diagnostic costs (206,946 IDR ramipril vs 297,156 IDR sacubitril/valsartan; p = 0.549).

Beyond these components, no statistically significant differences were observed in laboratory costs (2,201,703 ± 1,696,088 IDR for ramipril vs 2,095,615 ± 1,388,300 IDR for sacubitril/valsartan; p = 0.737), medical team costs (1,354,743 ± 1,306,270 IDR vs 1,302,279 ± 1,123,945 IDR; p = 0.834), radiology (447,973 ± 891,575 IDR vs 734,820 ± 1,940,774 IDR; p = 0.400), rehabilitation (43,378 ± 109,005 IDR vs 60,000 ± 152,551 IDR; p = 0.564), registration fees (36,486 ± 9,269 IDR vs 37,459 ± 10,787 IDR; p = 0.650), or miscellaneous costs (1,178,270 ± 1,576,305 IDR vs 1,154,705 ± 2,302,354 IDR; p = 0.956), indicating a broadly comparable pattern of healthcare resource utilization between the two regimens.

12 out of 13 cost components were not statistically different (p>0.05). Ward care (21% of the total cost), physician fees (15–17%), and laboratory cost (16–18%) were the main cost drivers, while the contribution of the antihypertensive agent cost accounted for only 7.8–9.3% of the total.

Despite the substantially higher study drug cost, the total costs per patient between the two groups were remarkably similar, suggesting that the higher acquisition cost of sacubitril/valsartan may be partially offset by modest differences in other cost components and the shorter mean LOS, although these differences were not statistically significant.

Cost-Minimization Analysis (CMA)

Cost-minimization analysis was performed using the formula CMA per patient = (total medical cost) / (number of patients), with the average total costs per patient summarized in Table 2. From the hospital perspective, the mean total cost per patient was 12,379,257 IDR for ramipril and 12,174,742 IDR for sacubitril/valsartan, a difference of 204,515 IDR (1.7% lower for sacubitril/valsartan). The mean length of stay was 5.78 ± 3.21 days in the ramipril group and 6.18 ± 3.21 days in the sacubitril/valsartan group, with no significant difference (p = 0.555), and this equivalence in LOS despite a higher comorbidity burden in the sacubitril/valsartan group supported the assumption of comparable clinical effectiveness required for Cost-Minimization Analysis. Under this assumption, sacubitril/valsartan was regarded as the more economically favorable option because its higher upfront study drug cost was offset by a similar or slightly lower total direct medical cost structure from the payer perspective.

Discussion

Interpretation of Findings

This pharmacoeconomic analysis, which employed a cost-minimization methodology, provided important insights into the relative economic efficiency of sacubitril/valsartan versus ramipril in hospitalized heart failure patients. Although sacubitril/valsartan carried a substantially higher acquisition cost—approximately 56 times that of ramipril—the total healthcare costs per patient from the hospital perspective were comparable between groups, with sacubitril/valsartan showing a slight economic advantage, particularly from the insurance payer perspective.

The finding that clinical effectiveness, as measured by length of stay, was equivalent between groups (p = 0.555) validated the use of cost-minimization analysis as the appropriate pharmacoeconomic method for this comparison. This was consistent with clinical guidelines for heart failure management, in which sacubitril/valsartan and ACE inhibitors/ARBs were regarded as cornerstone therapies with broadly comparable efficacy in reducing hospitalization and mortality[12,27,28].

Comparison with Previous Literature

The present CMA shows that, despite markedly higher acquisition costs, sacubitril/valsartan yields total hospital costs per patient that are comparable to or slightly lower than ramipril in Indonesian HFrEF inpatients, under an assumption of similar short-term effectiveness (length of stay)[9,10]. These findings are broadly consistent with regional cost-effectiveness analyses from Malaysia, where angiotensin receptor–neprilysin inhibitor (ARNI) therapy was found to be cost-effective versus ACE inhibitor in HFrEF patients by reducing downstream cardiovascular events and hospitalizations despite higher drug prices[29]. A systematic review of economic evaluations of guideline-directed medical therapy for HFrEF similarly concluded that ARNI-based regimens are generally cost-effective compared with ACEi/ARB, particularly when modeled over a lifetime horizon with reductions in mortality and rehospitalization[12,30].

Real-world comparative-effectiveness data further supported the economic plausibility of ARNI, showing that sacubitril/valsartan was associated with lower rates of HF hospitalization and all-cause mortality compared with ACEi/ARB in routine clinical practice, which would be expected to translate into lower long-term costs for payers[31,32]. While most pharmacoeconomic studies used cost-effectiveness or cost-utility frameworks rather than CMA, the direction of effect was similar: the higher drug acquisition cost was offset by savings from fewer events and admissions, yielding a favorable or neutral overall budget impact[12,30]. Compared with these prior models, the current inpatient CMA provided a more conservative, short-term snapshot, yet still suggested that ARNI was not more expensive than ACE inhibitors from both hospital and social insurance perspectives in an Indonesian tertiary-care setting[10], reinforcing the broader evidence base that supported wider ARNI adoption in guideline-directed HF management[9,12,29,30].

Clinical and Policy Implications

The comparable total costs between sacubitril/valsartan and ramipril, despite markedly different drug acquisition costs, have important implications for healthcare policy and clinical decision-making. From a healthcare system efficiency perspective, sacubitril/valsartan may represent a rational economic choice in settings where budget constraints previously precluded its use.

However, sensitivity analysis exploring the impact of key cost drivers—such as antihypertensive agent acquisition costs, length of stay, and intensive care utilization—would strengthen these conclusions. Future studies should also investigate whether sacubitril/valsartan confers additional clinical benefits such as reduced 30-day readmission rates or improved quality of life, which were not captured in the current analysis.

LIMITATIONS

Several limitations should be considered when interpreting these findings. First, this study employed a retrospective, cross-sectional design, which limits causal inference regarding the relationship between treatment choice and costs. Second, the analysis was confined to direct medical costs and did not include indirect costs (productivity loss, transportation) or long-term outcomes beyond hospitalization. Third, the study population was from a single tertiary center, which may limit generalizability to other healthcare settings. Fourth, the non-significant

difference in LOS between groups, while supporting CMA methodology, also raises the possibility that unmeasured clinical factors may have influenced treatment allocation. Finally, factors influencing the choice of therapy (such as renal function parameters or physician preference) were not fully analyzed in relation to costs.

CONCLUSION

This cost-minimization analysis demonstrates that sacubitril/valsartan is economically comparable to ramipril from hospital perspective in the treatment of hospitalized heart failure patients, despite its substantially higher drug acquisition cost. Under the assumption of equivalent clinical effectiveness (supported by comparable length of stay), sacubitril/valsartan offers a modest economic advantage, particularly from the national insurance payer perspective. These findings support the inclusion of sacubitril/valsartan in clinical protocols and formulary policies as an economically viable therapeutic option for heart failure management in Indonesian healthcare settings, while acknowledging the need for further studies with longer follow-up periods and expanded outcome measures.

FUNDING

This research received no external funding and the authors declare no financial conflicts of interest related to this study.

ACKNOWLEDGMENTS

We would like to thank all individuals and institutions who provided technical support and administrative assistance during this research. Special thanks to those who contributed to data collection and management. All acknowledged parties have given their consent to be mentioned in this section.

AUTHOR CONTRIBUTION STATEMENT

HD: Data curation, Writing—Original draft preparation; **MC**: Writing-Reviewing and Editing; **FR**: Conceptualization, Methodology; **YS**: administration, Investigation.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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