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Correlation between mean arterial pressure (MAP) and length of stay (LoS) of heart failure in-patients with sacubitril/valsartan and ramipril at X Hospital Semarang

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ABSTRACT

Heart failure is a health problem with high morbidity and mortality rates globally and nationally, so optimal therapy is needed to improve clinical outcomes and efficiency. Sacubitril/valsartan (angiotensin receptor neprilysin inhibitor/ARNI) and ramipril (ACE inhibitor/ACEi) have become the therapeutic options in heart failure patients. However, the effectiveness of both therapies on length of stay (LoS) and changes in mean arterial pressure (MAP) in the Indonesian population has not much studied. This study used an observational retrospective design on the medical record data of heart failure inpatients at X Hospital, Semarang, during January to December 2024 period. All in-patients who received sacubitril/valsartan or ramipril therapy (in combination with beta blockers and aldosterone receptor antagonists) were included, and were differentiated based on changes in MAP (up, down and constant). Correlation statistical analysis was performed with normality test, Kruskal-Wallis, and Anova tests to correlate the LoS and MAP changes between therapy. A total of 131 patients were categorized by therapy and MAP changes. The average LoS on Sacubitril/valsartan and Ramipril therapy was approximately 5–6 d each for the entire MAP change group. Statistical tests showed no significant difference between the two therapies for LOS, as well as of MAP changes ($p > 0.05$). MAP changes (up, down, constant) in heart failure in-patients treated with sacubitril/valsartan and ramipril provided variation in LoS, but the differences were not statistically significant between the two therapies.

ABSTRAK

Gagal jantung merupakan masalah kesehatan dengan angka morbiditas dan mortalitas yang tinggi global maupun nasional, sehingga dibutuhkan terapi yang optimal untuk memperbaiki outcome klinis dan efisiensi pelayanan. Sacubitril/valsartan (ARNI) dan ramipril (ACE inhibitor/ACEi) telah menjadi pilihan terapi pada pasien gagal jantung. Namun, efektivitas kedua terapi terhadap lama rawat inap (*length of stay*/LoS) dan perubahan *mean arterial pressure* (MAP) pada populasi Indonesia secara statistik belum banyak dikaji. Studi ini menggunakan desain retrospektif observasional pada data rekam medis pasien rawat inap gagal jantung di RS X di Semarang periode Januari hingga Desember 2024. Seluruh pasien yang mendapat terapi sacubitril/valsartan atau ramipril (dikombinasikan dengan beta blocker dan antagonis reseptor aldosteron) diikutkan, dan dikelompokkan berdasarkan perubahan MAP (naik, turun, konstan). Analisis statistik komparatif dilakukan dengan uji normalitas, Kruskal-Wallis, dan Anova untuk membandingkan LoS antar kelompok terapi dan perubahan MAP. Total 131 pasien dikategorikan berdasarkan terapi dan perubahan MAP. Rata-rata LoS pada terapi sacubitril/valsartan dan ramipril masing-masing sekitar 5–6 hari untuk seluruh kelompok perubahan MAP. Uji statistik menunjukkan tidak terdapat perbedaan signifikan antara kedua terapi terhadap LoS, begitu pula antar berbagai kelompok perubahan MAP ($p > 0,05$). Perubahan MAP (naik, turun, konstan) pada pasien gagal jantung yang diterapi sacubitril/valsartan maupun ramipril memberikan variasi LoS, namun perbedaan signifikan secara statistik, tidak ditemukan, antara kedua terapi.

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INTRODUCTION

Heart failure is one of the major health problems in the world with high morbidity and mortality rates in the adult and elderly populations.[1–3] This condition is characterized by the inability of the heart to pump blood effectively, causing impaired organ perfusion and fluid retention which has an impact on decreasing quality of life and increasing the burden on the health system. Recent epidemiological data from Indonesia indicate an increasing prevalence of HF, primarily driven by an aging population, rapid urbanization, and a rise in cardiovascular risk factors, making HF a leading cause of hospitalization.[4,5] This presents considerable healthcare burdens.[1,6]

One of the important indicators used in the management of heart failure is mean arterial pressure (MAP), which plays a role in assessing organ perfusion and serves as a reference for therapeutic titration.[4,7] Length of stay (LoS) is also a relevant clinical outcome, as it is closely related to prognosis, healthcare efficiency, and cost of care for heart failure patients.[8] The combination of MAP and LoS measurements is widely used to evaluate the effectiveness of therapy and the quality of management of heart failure patients in various hospital settings.[4,7,9]

A fundamental aspect of HF management involves pharmacotherapy targeting the renin-angiotensin-aldosterone system (RAAS) and the neprilysin pathways.[3] Significant agents used include sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), and ramipril, an angiotensin-converting enzyme inhibitor (ACEi).[10] These pharmacological agents are effective in improving hemodynamics, reducing fluid retention, and enhancing organ perfusion.[11,12] Notably, ARNI has shown superior outcomes regarding mortality and rehospitalization rates, as evidenced by landmark trials such as PARADIGM-HF, when compared to traditional ACEi treatment.[13–15] Sacubitril/valsartan is a novel antihypertensive agent with potent antihypertensive effects, treatment with fixed-dose combination pills may improve patient's adherence and cardiovascular outcomes.[16] Additionally, both drug classes have exhibited direct influences on important clinical parameters such as MAP, a marker of organ perfusion and hospital LoS, reflecting clinical stability and resource utilization.[4,7]

Despite accumulating international data emphasizing the clinical significance of heart failure, local data from Indonesia regarding the comparative outcomes of ARNI and ACEi therapies are limited. While extensive studies from Western populations provide insights into the efficacy and safety of these treatments, the unique epidemiological context and patient characteristics in Indonesia necessitate tailored research.[5] Recent findings indicate a relatively high rate of HF hospitalizations in Indonesia, but they lack robust assessments of therapy impacts within diverse patient demographics, particularly from community healthcare settings like Semarang's X Hospital.[6] This gap underscores the need for guidelines that reflect Indonesia's specific health intricacies.

The upcoming research aims to provide empirical, real-world data concerning hospitalized patients with heart failure in Indonesia, focusing on a comparative analysis of sacubitril/valsartan and ramipril. By analyzing the dynamics of MAP changes and LoS associated with these regimens, this study seeks to address the current deficiency of local data that could inform therapy selection, adherence, and clinical.[11] The primary objective centers on examining the correlations

between changes in MAP and LoS, thus evaluating the practical impacts of these treatment regimens in a resource-limited healthcare environment, which is increasingly pertinent given the rising burden of heart failure.[4,8]

MATERIAL AND METHODS

Design and subjects

This study used a medical record-based observational retrospective design, which is commonly applied to cardiac failure therapy outcome evaluation studies to ensure external validity and clinical relevance. The target population is all inpatients with a primary diagnosis of heart failure at X Semarang Hospital during January-December 2024.

Protocol

The sampling technique was in the form of total sampling, namely all heart failure patients aged ≥18 years with BPJS financing guarantees, who received sacubitril/valsartan (Uperio) or ramipril therapy each in combination with beta blockers and aldosterone receptor antagonists according to the three-pillars guideline of heart failure therapy,[17] without blood pressure restrictions upon admission to the hospital. Patients with antihypertensive therapy other than the two main regimens during treatment, forced discharge, death, and incomplete medical records were excluded from the analysis.[6,9]

The independent variable in this study was the change in the MAP value during treatment (grouped into MAP up, down, or constant from the beginning of admission to hospital discharge). The main dependent variable is LoS measured in units of days. Other data collected included demographic characteristics, comorbidities, and drug use based on electronic medical record records.

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

Statistical analysis

The results of intergroup measurements were analyzed statistically according to the data distribution: Anova and Kruskal-Wallis to compare the LoS between therapy groups and MAP changes, after normality tests with Kolmogorov–Smirnov and Shapiro–Wilk.[4,7] In addition, Pearson product–moment correlation was performed between continuous MAP values and LoS to explore potential linear associations between hemodynamic status and hospitalization duration, complementing the categorical analysis of MAP changes. All analysis were performed using SPSS 25.

This methodology adapts the international protocol of the heart failure registry (such as PREFERS and PROVE/HF) that describes the details of the medical record data extraction stage, the selection of guideline-based inclusion-exclusion criteria, and data validation for the main outcomes of hospitalization and blood pressure parameters.[8,10]

RESULTS

Patient characteristics

This study involved 131 heart failure in-patients at X Hospital in Semarang, consisting of the sacubitril/valsartan (n=72) and ramipril (n=59) therapy groups. Both groups were similar in the distribution of age, sex, and NYHA class, resulting in comparisons can be said to be equivalent in basic characteristics. The complete data can be seen in TABLE 1.

The characteristics of heart failure patients who received ramipril and uperio (sacubitril/valsartan) therapy at X Hospital Semarang showed a similar age and sex distribution between the two groups. The mean age from the 2 groups were 54.47 ± 11.23 yr. The most dominant age in the Ramipril group was 51-60 yr (49.2%), while in the Uperio group, the largest distribution was also found in the elderly, 61-70 yr (27.8%). For gender, the majority of patients in both groups were male (62.7% in ramipril and 72.2% in uperio), while the proportion of women was relatively smaller. There is another research which conclude that sacubitril/valsartan was safe and well tolerated, irrespective of sex.[4,18]

MAP Distribution and LoS

The summary of the distribution of LoS by therapy group and changes in MAP is presented TABLE 2.

The results of this study showed that the average LoS in heart failure patients receiving sacubitril/valsartan and ramipril therapy did not differ significantly, both based on the category of changes in MAP (up, down, constant) and the type of therapy given, it can be seen in TABLE 3.

These findings are corroborated by the Pearson product moment correlation between changes in MAP, continuous variable and LoS in heart failure patients, which yielded a correlation coefficient (r) of -0.032 ($p = 0.358 > 0.05$), indicating no statistically significant association.

Comparable nonsignificant correlations were observed in the subgroup receiving sacubitril/valsartan therapy ($r = -0.049$; $p = 0.341 > 0.05$) and in those treated with ramipril ($r = -0.007$; $p = 0.478 > 0.05$). Detailed correlation results are presented in TABLE 4.

TABLE 1. Patient characteristics by therapy group

Characteristics	Ramipril [n (%)]	Uperio [n (%)]
Age (yr)		
21-30	0 (0.00)	7 (9.70)
31-40	3 (5.10)	2 (2.80)
41-50	13 (22.00)	18 (25.00)
51-60	29 (49.20)	17 (23.60
61-70	12 (20.30)	20 (27.80)
71-80	2 (3.40)	7 (9.70)
81-90	0 (0.00)	1 (1.40)
Total	59 (100.00)	72 (100.00)
Gender		
Male	37 (62.7)	52 (72.20)
Female	22 (37.3)	20 (27.80)
Total	59 (100.00)	72 (100.00)

TABLE 2. Distribution of LoS by therapy and MAP change

MAP changes after therapy	n	LoS (mean ± SD d)
Ramipril		
Constant	7	7.57 ± 10.89
Up	30	5.00 ± 2.97
Down	22	5.86 ± 4.16
Sacubitril/valsartan		
Constant	3	6.67 ± 3.21
Up	28	7.32 ± 5.70
Down	41	5.83 ± 3.07
Combination		
Constant	10	7.30 ± 9.03
Up	58	6.12 ± 4.61
Down	63	5.84 ± 3.46
Total	131	6.08 ± 4.56

TABLE 3. LoS average comparison chart

MAP changes	Ramipril	Sacubitril/valsartan	p
Constant	7.57	6.67	
Up	5.00	7.32	0.688
Down	5.86	5.83	

TABLE 4. Correlation of MAP changes with LoS.

Sample	n	r	p
Ramipril	59	-0.007	0.478
Sacubitril/valsartan	72	-0.049	0.341
Full sample	131	-0.032	0.358

DISCUSSION

Main findings

This study found no significant differences in LoS between the sacubitril/valsartan and ramipril treatment groups, with both averaging approximately 6 d. Furthermore, the correlation between changes in MAP and LoS was nonsignificant (r = -0.032; p >0.05). These findings, derived from a real-world Indonesian cohort, suggest that while MAP variations showed trends influencing LoS, they lacked statistical power to demonstrate a significant association, likely due to balanced baseline characteristics and the multifactorial nature of hospitalization outcomes.

Comparison with international literature

Our results align with some international studies that, despite demonstrating the superiority of ARNI in reducing heart failure hospitalizations and mortality, reported comparable acute LoS durations between ARNI and ACEi. For instance, the PARADIGM-HF trial, which compared sacubitril/valsartan to enalapril (similar to ramipril), showed ARNI's superiority in long-term cardiovascular outcomes but indicated comparable acute LoS in real-world extensions.[10,19] Similarly, the PARADISE-MI trial by Pfeffer *et al.*,[14] found no significant LoS disparities post-myocardial infarction between sacubitril/valsartan and ramipril, attributing outcomes to patient heterogeneity. While ARNI has shown excellence in reducing rehospitalization and improving long-term endpoint outcomes.[10,20,21] Its direct effect on acute episode LoS in Asian populations and Indonesian patients has not always been confirmed to be significant.[9,14] Some studies even suggest that sacubitril/valsartan did not result in a significantly lower rate of total hospitalizations for heart failure.[6] Regarding MAP, analyses by Gao *et al.*,[4] linked lower admission MAP to worse prognosis but not consistently to LoS in Asian HF cohorts, corroborating our observations of weak negative correlations. Early studies also noted that the combination of neprilysin inhibitors with ACEi could lead to increased synergistic efficacy for blood pressure lowering in hypertensive patients.[22]

Comparison with local studies

Local Indonesian data further support our findings. Hermawan *et al.*,[5] reported a similar median LoS of around 6 d for HF patients at Dr. Ramelan Hospital, Surabaya with demographic profiles (predominantly elderly males) consistent with our study. This demographic consistency may mask the specific effects of therapy. Marulin *et al.*,[23] cost-effectiveness analysis in Bandung also confirmed equivalent hemodynamic responses between ARNI and ACEi among patients with comorbid HF, reinforcing the nonsignificant MAP-LoS links in resource-limited settings. Research from other Indonesian hospitals suggests that clinical heterogeneity (e.g., varying NYHA classes, presence of pulmonary edema, and acute case management speed) can mask potential drug effects on LoS differences.[5]

Factors influencing LoS

The lack of significant differences in LoS between treatment groups and the weak MAP-LoS correlation can be attributed to several dominant external and internal factors. LoS in HF inpatients is strongly influenced by multifactorial elements beyond specific drug interventions, such as patient heterogeneity, treatment protocols, and local clinical characteristics.[18,24,25] Comorbidities like uncontrolled hypertension, chronic kidney disease, and diabetes significantly increase rehospitalization risk and prolong LoS, often overriding the direct impact of pharmacological interventions.[23,25] Our study population, predominantly aged 51-60 yr (72.8%), represents a late middle-age group where age-related physiological changes (e.g., stiffer blood vessels), lifestyle factors, and chronic conditions (diabetes, high cholesterol) inherently elevate heart disease risk.[26] This demographic profile, coupled with a male predominance, creates a homogeneous risk group where therapeutic interventions may not show significant LoS differences due to similar risk characteristics and clinical responses.[27] Internal study factors,

such as a relatively even distribution of baseline blood pressure, consistent patient functional status, and stable blood pressure during drug titration, also contributed to a uniform therapeutic response, diminishing the prominence of MAP's contribution to LoS variation.[21] Thus, the insignificance of our findings regarding LoS is likely due to the dominance of these external and internal patient-specific factors, rather than a failure of the drug's pharmacological effects.[23,25]

Strengths

This study offers valuable real-world insights through its total sampling of eligible HF inpatients at X Hospital Semarang, enhancing external validity for Indonesian BPJS settings, a contrast to the often-homogeneous populations in randomized controlled trials like PARADIGM-HF. The methodology, adhering to PERKI and registry protocols, ensures robustness. Our comprehensive analysis, incorporating both categorical MAP changes and continuous Pearson correlations, rigorously explored hemodynamic-LoS associations. The findings advocate for the concurrent monitoring of MAP alongside LoS to enhance therapy titration decisions, which is particularly pertinent as the burden of heart failure continues to escalate in Indonesia.[4,9] These insights may inform updates to the PERKI guidelines, further optimizing HF management practices amid growing healthcare demands.

Limitations

Key limitations include the retrospective, single-center design at X Hospital Semarang, which restricts the generalizability of findings beyond local demographics and protocols. The modest sample size (n=131) reduced statistical power for detailed subgroup analyses. Reliance on electronic medical records introduced potential measurement bias in MAP timing and completeness, and the use of complete-case analysis (excluding ~5% of cases) might have introduced selection effects. The absence of comprehensive multivariable adjustment for all potential confounders, such as granular NYHA class or detailed comorbidity severity, could mean that unmeasured factors influenced the outcomes. Furthermore, the lack of long-term follow-up precludes assessing the impact on rehospitalization or mortality, which are central to the established long-term benefits of ARNI in major trials.

Implications

These real-world findings suggest equivalent short-term efficacy of Sacubitril/Valsartan and Ramipril for Indonesian HF inpatients, guiding cost-conscious therapy selection in BPJS-funded settings. Despite weak LoS correlations, MAP remains an important indicator for therapy titration and monitoring in both Sacubitril/Valsartan and Ramipril recipients.[4,7,28] A controlled decrease in MAP can improve organ perfusion and speed recovery, although more research is needed to confirm its causal relationship with treatment duration.[8] The PARADIGM-HF trial noted a higher incidence of hypotension with sacubitril/valsartan,[29] reinforcing the need for careful MAP monitoring. Our results advocate for expanded local registries to power prospective comparisons and refine PERKI guidelines, incorporating Asian pharmacodynamics. Clinically, sustained hemodynamic monitoring alongside LoS optimization could enhance care efficiency amid rising HF prevalence. This study underscores the need for further research on the effectiveness of these therapies and their effect on main clinical outcomes, particularly in Indonesian hospitals.

CONCLUSION

In conclusion, changes in MAP both up, down, and constant in heart failure patients receiving sacubitril/valsartan and ramipril therapy does not associated with variations in LoS. The mean LoS for sacubitril/valsartan and ramipril therapy in this study is close to the findings of several national studies, which is about 5–6 d, with similar MAP-decreasing in both therapy groups.

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