Cost-Effectiveness of Sacubitril/Valsartan Compared to Enalapril in Patients with Heart Failure and Reduced Ejection Fraction (HFrEF): a Systematic Review of Model Based Economic Evaluations

Ina Kusuma Diana[1], Sri Rukayah[1], Puspitaningrum Inpastiarini[1], Nor Hamidah[1], Tugiyanti Tugiyanti[1], Dwi Endarti[2*], Tuangrat Phodha[3]

[1] Master Program in Pharmacy Management, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2] Deparment of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3]Faculty of Pharmacy, Thammasat University, Bangkok, Thailand
endarti_apt@ugm.ac.id

Abstract. Heart failure with reduced ejection fraction (HFrEF) is a major global health and economic challenge. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated superior clinical efficacy compared to enalapril, but its cost-effectiveness across different economic settings remains uncertain. This study aimed to systematically review and synthesize full cost-utility evaluations comparing sacubitril/valsartan with enalapril in HFrEF patients, focusing on incremental cost-effectiveness ratios (ICERs) and country-specific willingness-to-pay (WTP) thresholds. A systematic search from 2015 to 2025 across five databases identified studies using Markov models and reporting cost per quality-adjusted life year (QALY) gained. All costs were standardized to June 2025 US dollars, and reporting quality was assessed using the CHEERS 2022 checklist. Twelve studies were included, representing high-, upper-middle-, and lower-middle-income countries. All reported ICERs were below or within national WTP thresholds, ranging from $2,214/QALY in Indonesia to $103,416/QALY in Qatar. Sacubitril/valsartan was consistently found to be cost-effective across all settings, despite heterogeneity in methodologies. However, most studies lacked considerations for equity, stakeholder involvement, and model transparency. Overall, sacubitril/valsartan represents a cost-effective option for managing HFrEF globally, and its wider adoption is supported. Future research should address equity issues, utilize real-world data, and promote open access to economic models.

Keywords: Sacubitril/Valsartan; Cost-Effectiveness; ICER; Hfref; Markov Model; QALY; Economic Evaluation.

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1 Introduction

Heart failure with reduced ejection fraction (HFrEF) is a progressive clinical syndrome characterized by impaired ventricular contraction, leading to significant morbidity, reduced quality of life, recurrent hospitalizations, and high mortality globally. According to [1], HFrEF affects millions worldwide and accounts for substantial healthcare expenditures, particularly due to frequent admissions and long-term pharmacological management. Angiotensin-converting enzyme inhibitors (ACEi), such as enalapril, have long been the cornerstone of HFrEF therapy. However, advances in neurohormonal blockade led to the development of angiotensin receptor–neprilysin inhibitor (ARNI) therapy, notably sacubitril/valsartan, which offers a dual mechanism by inhibiting the renin-angiotensin system and enhancing natriuretic peptide activity [2].

The landmark PARADIGM-HF trial demonstrated that sacubitril/valsartan significantly reduced the composite endpoint of cardiovascular death or heart failure hospitalization by 20 % compared to enalapril [3], findings that were later supported by real-world evidence across multiple settings [4–6]. Consequently, both European and American heart failure guidelines now recommend sacubitril/valsartan as first-line therapy for patients with HFrEF, including newly hospitalized patients [7,8]. Despite its proven clinical benefit, the higher acquisition cost of sacubitril/valsartan compared to generic ACE inhibitors has raised concerns regarding affordability and cost-effectiveness, particularly in low- and middle-income countries (LMICs) where national health insurance systems operate under stringent fiscal constraints. In Indonesia, for example, the national willingness-to-pay (WTP) threshold is estimated at approximately USD 4,135 per quality-adjusted life year (QALY), whereas in Thailand it is around USD 5,089 per QALY. In such contexts, the clinical relevance of sacubitril/valsartan must be interpreted alongside economic viability: a drug that saves lives but exceeds a country's ability to pay may not be adopted, regardless of efficacy.

Recent systematic reviews have assessed the economic value of sacubitril/valsartan, concluding that it is cost-effective in most high-income countries but not consistently so in lower-income settings without price adjustments [6,9]. However, these reviews have several limitations: they include both full and partial economic evaluations, use heterogeneous quality criteria, and lack recent studies from emerging economies such as Indonesia and Argentina. Moreover, they do not incorporate updated economic conditions, inflation adjustments, or recent guideline expansions recommending early ARNI initiation.

Given these gaps, there is a need for a contemporary, methodologically consistent synthesis focused solely on full cost-utility analyses across diverse global settings. This study aims to systematically review and critically evaluate the cost-effectiveness of sacubitril/valsartan compared to enalapril in patients with HFrEF, using updated ICER data standardized to June 2025 USD values. It incorporates the latest clinical and economic evidence, applies the CHEERS 2022 reporting standard, and includes recent evaluations from both high-income and middle-income countries.

The novelty of this research lies in its integration of cost-effectiveness findings with updated economic metrics, standardized cross-country comparisons, and incorporation of guideline-aligned clinical insights. This contributes to the scientific discourse by

bridging economic modeling with practical health policy considerations, supporting the rational and equitable adoption of sacubitril/valsartan in diverse health systems.

2 Methods

2.1 Search Strategy and Inclusion Criteria

This systematic review was conducted in accordance with the 2020 PRISMA guidelines to ensure a rigorous and transparent process [10]. A comprehensive literature search was performed across multiple electronic databases, including PubMed, Scopus, ScienceDirect and SpringerLink June 2025. The search strategy combined keywords and Boolean operators as follows: ("Sacubitril/Valsartan" OR "ARNI") AND ("Enalapril" OR "ACE inhibitor") AND ("Heart Failure with Reduced Ejection Fraction" OR "HFrEF") AND ("Cost-Effectiveness" OR "Economic Evaluation" OR "Cost-Utility" OR "ICER").

The search was limited to studies published in English or Bahasa Indonesia between 2015 and 2025 to capture recent and relevant economic evaluations. Eligible studies were required to be full economic evaluations, specifically cost-utility analyses (CUAs) employing Markov models to simulate long-term outcomes in adult patients with HFrEF. Studies had to directly compare sacubitril/valsartan with enalapril or ACE inhibitor-based standard care and report key economic outcomes such as incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALYs), life years (LY), or cost-saving analysis. Model transparency, including clear descriptions of Markov states, transition probabilities, time horizons, discount rates, and assumptions, was a prerequisite for inclusion.

This search strategy and inclusion criteria were developed and agreed upon by all authors to ensure a comprehensive and focused review of the cost-utility of sacubitril/valsartan versus enalapril in the management of HfrEF.

2.2 Data Extraction and Quality Assesment

Data extraction was performed systematically to capture key information relevant to study design, methodological characteristics, and economic outcomes of the included cost-utility analyses. Extracted data items included the target population (adult patients with HFrEF), study setting and country, intervention (sacubitril/valsartan) and comparator (enalapril or ACE inhibitor-based standard care), study perspective (e.g., healthcare system, societal), time horizon, and discount rates applied for costs and outcomes. Details of the Markov model structure were recorded, including health states, cycle length, transition probabilities, and assumptions underpinning the model. Additionally, economic outcomes such as incremental cost-effectiveness ratios (ICERs), quality-adjusted life years (QALYs), life years gained (LY), total costs, and cost-effectiveness thresholds were extracted to enable consistent comparison across studies.

Further contextual information was collected, including the year of publication, funding sources, and author affiliations, to assess potential conflicts of interest and study context. This comprehensive data extraction process aimed to synthesize the cost-

effectiveness evidence of sacubitril/valsartan versus enalapril in HFrEF patients in a transparent and structured manner.

Quality assessment of the included studies was conducted using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist, which comprises 28 items designed to evaluate the completeness and transparency of health economic evaluations[11].The CHEERS checklist covers key domains such as clear identification of the economic evaluation type, detailed description of interventions and comparators, analytic methods including model rationale and assumptions, measurement and valuation of outcomes and costs, handling of heterogeneity and uncertainty, and reporting of funding sources and conflicts of interest. Each study was critically appraised against these criteria to identify strengths and limitations in reporting quality, ensuring that the synthesis of cost-effectiveness results was based on robust and transparent evidence.

2.3 Data Analysis

The cost-effectiveness results of sacubitril/valsartan compared to enalapril in patients with heart failure with reduced ejection fraction (HFrEF) were synthesized across included studies. To ensure comparability, all reported incremental cost-effectiveness ratios (ICERs) were standardized to 2025 US Dollar (USD) values. For studies reporting costs in other currencies, original costs were first converted to USD using the average exchange rate for the respective base year. Subsequently, these USD values were adjusted for inflation to 2025 values using the Consumer Price Index (CPI) calculator provided by the United States Bureau of Labor Statistics.

This standardization process allowed for consistent comparison of cost-effectiveness outcomes across different countries and time periods. Key drivers of cost-effectiveness, such as drug acquisition costs, mortality benefits, hospitalization rates, and model assumptions, were analyzed qualitatively. Sensitivity analyses reported in the included studies, including deterministic and probabilistic approaches, were reviewed to assess the robustness of the findings and the impact of parameter uncertainty.

The synthesis focused on the incremental cost per quality-adjusted life year (QALY) gained, life years (LY) gained, and whether sacubitril/valsartan met commonly accepted willingness-to-pay (WTP) thresholds in the respective healthcare settings. This approach provides a comprehensive overview of the economic value of sacubitril/valsartan compared to enalapril in managing HFrEF, supporting evidence-based healthcare decision-making.

2.4 Population

Most of the included studies evaluated adult patients with heart failure with reduced ejection fraction (HFrEF), consistent with the population enrolled in the PARADIGM-HF trial, which served as the main clinical input source across nearly all models. The typical patient profile involved a mean age ranging from 60 to 65 years, with left ventricular ejection fraction (LVEF) ≤40 %, reflecting real-world clinical demographics for HFrEF.

Some studies restricted the population to stable chronic HFrEF patients on optimized guideline-directed medical therapy prior to initiating sacubitril/valsartan, mirroring the strict inclusion criteria of PARADIGM-HF (e.g., Zakiyah et al., 2021; Wu et al., 2020). Others extended their scope to include hospitalized patients with acute decompensated HFrEF, particularly in the Thai context (Krittayaphong & Permsuwan, 2021), leveraging efficacy inputs from both the PIONEER-HF and PARADIGM-HF trials.

Several studies explicitly compared sacubitril/valsartan at 97/103 mg twice daily versus enalapril at 10 mg twice daily, aligning with standard trial-based regimens [12–14]. In other studies, while the exact dosage was not always stated, the modeled effectiveness and cost inputs were derived from clinical trials employing these standard doses, maintaining methodological consistency across evaluations [15–17].

3 Results

3.1 Search Results

The systematic search identified a total of 150 records from five electronic databases: PubMed (n = 18), Scopus (n = 47), ScienceDirect (n = 83), and Handsearch (n=2). After removing 18 duplicate records, 132 records remained for screening. During the screening process, 111 articles were excluded for the following reasons: abstract only (n = 12), author reply (n = 1), congress proceedings (n = 1), guidelines (n = 2), consensus statements (n = 1), book sections (n = 15), unrelated topics (n = 65), review articles (n = 11), research letters (n = 2), and panel meeting summaries (n = 1). Twenty-one reports were sought for full-text retrieval; however, six reports could not be retrieved due to limited access, broken links, technical errors, or administrative issues such as unsupported access requests1. Fifteen full-text articles were assessed for eligibility, of which five were subsequently excluded: three studies were not published in English or Bahasa Indonesia, and two studies did not include the relevant comparator (enalapril or ACE inhibitor-based standard care). Ultimately, 12 studies met the inclusion criteria and were included in this systematic review. The detailed study selection process and reasons for exclusion are presented in the PRISMA 2020 flow diagram (Fig. 1). All included studies were cost-utility analyses employing Markov models to evaluate the cost-effectiveness of sacubitril/valsartan compared to enalapril in adult patients with heart failure with reduced ejection fraction.

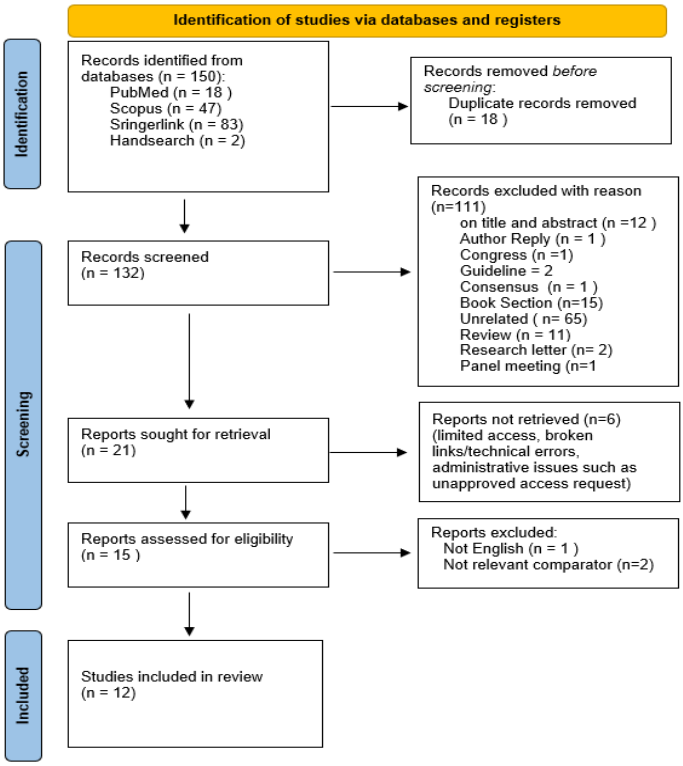


Fig. 1. PRISMA flow diagram.

Table 1. Summary characteristics of included studies

Characteristic	Number of Studies	%
Study Setting		
High-income countries	8	66,7
Lower-Middle-Income Country (LMIC)	1	8,3
Upper-middle income countries	3	25
First Author Affiliation		
Academe	9	75
Hospital	3	25
Funding Source		
Research agencies/grants	1	8,3

Characteristic	Number of Studies	%
Pharmaceutical industry	6	50
Declared no funding	5	41,7
Type of Model		
Markov model	12	100
Intervention		
Sacubitril Valsartan vs Enalapril	12	100
Study Perspective		
Healthcare payer	9	75
Healthcare providers	2	16,7
Societal	1	8,3
Time Horizon		
10 years	2	17
20 years	1	8
30 years	2	17
Lifetime	7	58
Cycle Length		
1-month cycle length	9	75
3-month cycle length	2	17
Yearly cycle	1	8
Discounting for Outcomes		
3%	7	58
3.5%, 3% and 5% for the UK, Danish and Colombian	1	8
4.5%	1	8
5%	3	25
Publication Year		
2016-2020	8	67
2021-2023	4	33

3.2 Study Characteristics

This systematic review included twelve cost-utility analyses that evaluated the cost-effectiveness of sacubitril/valsartan in comparison to enalapril for patients with heart failure with reduced ejection fraction (HFrEF). The characteristics of the included studies are described in detail as shown in Table 1, synthesizing aspects related to study setting, methodological design, perspectives, and reporting standards.

Most studies (n = 8; 66.7 %) were conducted in high-income countries, such as Portugal, the United States, Australia, Qatar, South Korea, and Switzerland [13,14,16,18–22]. Three studies (25 %) were conducted in upper-middle-income countries, including Thailand, Argentina, and China [12,15,17], while one study (8.3 %) was conducted in a lower-middle-income country, namely Indonesia [23].

With respect to author affiliation, the majority of first authors were affiliated with academic institutions (n = 9; 75 %) [13,14,16–19,21–23], while the remaining three studies (25 %) were led by hospital-affiliated researchers [12–14].

Regarding funding sources, six studies (41.7 %) received sponsorship from the pharmaceutical industry [13,16–19,21], while five studies (41.7 %) reported no external funding [12,14,15,20,22], and one study (8.3 %) was funded by a research agency [23].

All included studies employed a Markov model (100 %) for economic simulation [12–23], and all assessed the same intervention: sacubitril/valsartan compared to enalapril.

In terms of analytical perspective, most studies (n = 9; 75 %) used the healthcare payer perspective [12–17,21–23]. Two studies (16.7 %) applied the healthcare provider perspective [19,20], while only one study (8.3 %) adopted a societal perspective [18].

Time horizons varied across studies: seven studies (58 %) used a lifetime horizon [12,16,17,19–22], two studies (17 %) used a 10-[15,23], two studies (17%) used a 30-year horizon [13,18], and one study (8 %) used a 20-year horizon [14].

With regard to model cycle length, the majority (n = 9; 75 %) applied a 1-month cycle [12,13,15–21], while two studies (17 %) used a 3-month cycle [14,23]), and one study (8 %) applied a yearly cycle [14].

In terms of discounting rates for outcomes, seven studies (58 %) used a 3 % rate [12,13,15,20–23], one study (8 %) used differentiated rates for multiple countries (3 %, 3.5 %, and 5 %) [19], one study (8 %) applied a 4.5 % rate [16], and three studies (25 %) used a 5 % rate [14,17,18]

Finally, regarding year of publication, two-thirds of the studies (n = 8; 67 %) were published between 2016 and 2020 [13–16,18,19,21,22]), while the remaining four studies (3 3%) were published between 2021 and 2023 [12,17,20,23].

Overall, these studies demonstrated consistency in methodological approaches, particularly in model choice and comparator intervention, while showing variation in setting, perspective, and economic assumptions, which may influence comparability and generalizability of cost-effectiveness results across health systems.

3.3 Quality of Economic Analyses

In total, 12 studies were critically appraised using the CHEERS 2022 checklist to assess the quality of health economic evaluations. As shown in Table 2, the checklist consists of 28 items grouped into seven categories, including title/abstract, introduction, methods, results, discussion, and other relevant information [11]. Overall, the reporting quality of the included studies was moderate to good, with some domains consistently well reported, while others were frequently neglected. All studies (12/12, 100 %) explicitly identified themselves as economic evaluations in the title and provided a structured abstract containing core components of the study. Likewise, the background and objectives were clearly described in all articles (12/12, 100%), providing a strong foundation for understanding the rationale of each analysis. The comparators or interventions and the time horizon were fully reported in every study (12/12, 100 %). The perspective of analysis was stated in 11 of 12 studies (92 %), and discount rates were described in all articles (12/12, 100 %), though with varying depth of justification. Importantly, all studies (12/12, 100 %) also reported having a health economic analysis plan, demonstrating adherence to pre-specified planning principles and strengthening transparency in methodological design. Modeling was described in seven studies (58 %), although none provided public access to the model for replication. Stakeholder engagement was not reported in any study (0 %), and distributional effects or equity considerations were also entirely absent (0 %). Nonetheless, all studies (12/12, 100 %) conducted some form of uncertainty analysis, indicating widespread recognition of the importance of sensitivity or scenario analysis in health economic modeling. In terms of transparency, funding sources and conflict of interest declarations were clearly disclosed in all 12 studies (100 %).

Table 2. Quality assessment of included studies.

Item	Number of studies		
	Yes	Partial	No
Title			
Title	12		
Abstract			
Abstract	12		
Introduction			
Background and objectives	12		
Methods			
Health economic analysis plan	12		
Study population	12		
Setting and location	12		
Comparators	12		
Perspective	11	1	
Time horizon	12		
Discount rate	12		

Item	Number of studies		
	Yes	Partial	No
Selection of outcomes	12		
Measurement of outcomes	12		
Valuation of outcomes	12		
Measurement and valuation of resources and costs	12		
Currency, price date, and conversion	11	1	
Rationale and description of model	7	5	
Analytics and assumptions	12		
Characterizing heterogeneity		2	10
Characterizing distributional effects			12
Characterizing uncertainty	12		
Approach to engagement with patients and others affected by the study			12
RESULTS			
Study parameters	12		
Summary of main results	12		
Effect of uncertainty	12		
Effect of engagement with patients and others affected by the study			12
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	12		
OTHER RELEVANT INFORMATION			
Source of funding	12		
Conflicts of interest	12		

3.4 Cost-utility Analysis Results

This review identified 12 full cost-utility analyses assessing the economic value of sacubitril/valsartan compared to enalapril in patients with heart failure with reduced ejection fraction (HFrEF) as shown in Table 3. These studies spanned diverse economic settings, including high-income countries (United States, UK, Denmark, Switzerland, Australia, Qatar, and Portugal), upper-middle-income countries (Argentina, China, Colombia, Thailand), and lower-middle-income country (Indonesia). All evaluations employed Markov models and reported ICERs in cost per QALY gained, standardized to June 2025 USD.

Table 3. Summary of cost-utility analysis results

Country	Baseline Year	Incremental QALY	Incremental Cost	Incremental Cost in USD (June 2025)	ICER (Baseline/ QALY)	ICER baseline year (USD)/ QALY	Threshold/ QALY (Baseline)	Threshold/ QALY Baseline (USD)	ICER as % of WTP Threshold	ICER/ QALY in USD (June 2025)	Sac-Val Cost-Effective
Portugal	2016	0.44	$10,020	$13,441	€22,702	$25,200	€30,000	$33,300	75.67%	$33,790	Yes
UK	2015	0.52	£8,906	$18,412	£17,134	$26,252	£20,000 – £30,000	$30,600 – $45,900	85.67% of lower – 57.11% of upper	$35,500	Yes
Denmark	2015	0.47	Kr 80,984	$18,167	Kr 173,994	$26,099	Kr 250,000	$37,500	69.60%	$35,306	Yes
Colombia	2015	0.42	COP$16,723,507	$9,037	COP 39,500,000	$15,800	COP 52,400,000	$20,960	75.38%	$21,387	Yes
Thailand	2020	0.21	$738.12	$916	$3,451	$3,451	$5,089	$5,089	67.81%	$4,282	Yes
Indonesia	2020	0.88	$1,673.87	$2,078	$1,890	$1,890	$4,135	$4,135	45.71%	$2,345	Yes
Australia	2018	0.3	A$2,284	$2,159	A$40,513	$29,979	A$42,000 – A$76,000	$31,080 – $56,240	96.46% of lower – 53.31% of upper	$38,266	Yes
USA	2014	0.78	$35,512	$47,226	$45,017	$45,017	$50,000 – $100,000	$50,000 – $100,000	90.03% of lower – 45.02% of upper	$59,857	Yes

Country	Baseline Year	Incremental QALY	Incremental Cost	Incremental Cost in USD (June 2025)	ICER (Baseline/ QALY)	ICER baseline year (USD)/ QALY	Threshold/ QALY (Baseline)	Threshold/ QALY Baseline (USD)	ICER as % of WTP Threshold	ICER/ QALY in USD (June 2025)	Sac-Val Cost-Effective
Qatar	2022	0.04	$3,832	$4,179	$93,687	$93,687	$150,000	$150,000	62.46%	$103,146	Yes
Argentina	2020	0.36	ARS 37,666	$561	ARS 2,326,312	$27,915	ARS 2,337,402	$28,048	99.53%	$34,622	Yes
China	2019	0.27	$579.78	$725	$2,480.67	$2,779	$10,276	$10,276	24.14%	$3,481	Yes
South Korea	2017	0.59	$7,537	$9,915	$12,722	$12,722	$20,000	$20,000	63.61%	$16,726	Yes
Switzerland	2014	0.43	CHF 10,926	$15,839	CHF 25,684	$28,996	$50,000	$50,000	51.37%	$38,526	Yes
USA	2015	0.75	$38,633	$52,242	$50,959	$50,959	$50,000 – $150,000	$50,000 – $150,000	101.92 % of lower – 33.97% of upper	$68,853	Yes

Note: All cost data originally reported in historical USD or local currencies have been converted to constant USD as of June 2025. For values not originally reported in USD, historical exchange rates for the respective baseline year were applied to convert costs into USD. Subsequently, inflation adjustment was performed using the U.S. Consumer Price Index (CPI) as published by the Bureau of Labor Statistics (BLS). The CPI values used correspond to the baseline year of each study and to June 2025 (CPI = 321.465). This method ensures consistency and comparability across studies by applying standardized inflation correction rather than using average annual inflation rates or local price indices [24].

In Indonesia, the ICER was $2,345/QALY, with sacubitril/valsartan costing only 45.71 % of the national willingness-to-pay (WTP) threshold [23]. Similarly, in China, the ICER was $3,481/QALY, representing 24.14 % of the WTP threshold [15]. Thailand reported an ICER of $4,282/QALY (67.81 % of WTP), also demonstrating strong cost-effectiveness [12].

Among upper-middle-income settings, Colombia recorded an ICER of $21,387/QALY (75.38 % of threshold), confirming economic favorability [19]. Argentina reported an ICER of $34,622/QALY, equating to 99.53 % of its national WTP limit [17], suggesting borderline cost-effectiveness.

In high-income countries, Portugal reported an ICER of $33,790/QALY (75.67 % of WTP), confirming cost-effectivenes [18]. The UK and Denmark, analyzed in the same study, reported ICERs of $35,500/QALY and $35,306/QALY, consuming 85.67 % – 57.11 % and 69.60 % of their national WTP thresholds, respectively [19]. Switzerland reported an ICER of $38,526/QALY (51.37 % of WTP), reflecting favorable value [21].

In Australia, the ICER was $38,266/QALY, which represented between 96.46 % (lower threshold) and 53.31 % (upper threshold) of the acceptable cost-effectiveness range [14].

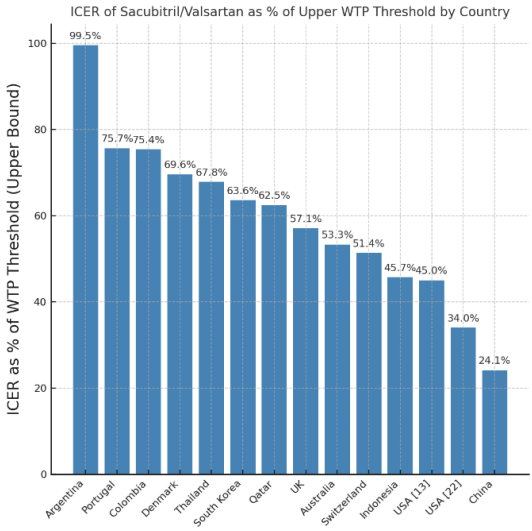
Two studies from the United States presented different estimates: Gaziano et al. (2016) reported an ICER of $59,857/QALY (90.03% – 45.02 % of the WTP threshold), while King et al. (2016) reported $68,853/QALY, which slightly exceeded the $50,000 lower bound but remained within the $150,000 upper limit (101.92 % – 33.97 %). Despite higher absolute costs, both studies concluded that sacubitril/valsartan remained cost-effective.

Qatar, representing another high-income setting, reported the highest ICER at $103,146/QALY, equivalent to 62.46 % of its national threshold of $150,000, thereby meeting cost-effectiveness criteria [20].

Fig. 2 illustrates the ICER of sacubitril/valsartan as a percentage of each country's upper-bound WTP threshold. The most favorable cost-effectiveness profiles were seen in China (24.14 %) [15], Indonesia (45.71 %) [23] and Switzerland (51.37 %) [21], indicating substantial value. In contrast, Argentina (99.53%) [17] and USA [22] (101.92% of lower bound) [22] approached or slightly exceeded conservative thresholds, though still within acceptable limits.

Fig. 3 presents the absolute ICERs in June 2025 USD. High-income countries like Qatar ($103,146) [20] and USA [22] ($68,853) had the highest ICERs, reflecting higher healthcare costs. In contrast, Indonesia ($2,345), China ($3,481), and Thailand ($4,282) showed the lowest ICERs, confirming cost-effectiveness in lower-income settings.

Overall, sacubitril/valsartan demonstrated cost-effectiveness across all settings, with notable affordability in low- and middle-income countries and acceptable economic value in high-income contexts.



ICER: Incremental Cost-Effectiveness Ratio; WTP: Willingness to Pay

Fig. 2. Relative Cost-Effectiveness of Sacubitril/Valsartan Compared to National WTP Thresholds.

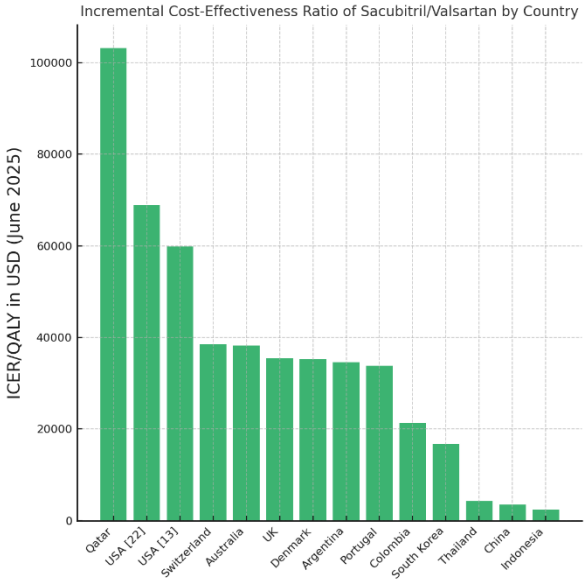


Fig. 3. Incremental Cost-Effectiveness Ratio of Sacubitril/Valsartan by Country.

4 Discussion

4.1 Cost-Effectiveness Across Countries and Economic Settings

The cross-country consistency in cost-effectiveness outcomes for sacubitril/valsartan highlights its robustness as a high-value intervention for HFrEF across a wide range of economic and healthcare settings. Despite substantial variation in local pricing, healthcare resource utilization, and modeling methods, all included studies reported incremental cost-effectiveness ratios (ICERs) below or within their respective willingness-to-pay (WTP) thresholds.

In lower- and middle-income countries, sacubitril/valsartan not only showed low ICERs but also demonstrated favorable incremental QALY gains relative to cost. For instance, Indonesia [23] reported the highest incremental QALY (0.88) with a modest incremental cost of $2,078, resulting in the lowest ICER ($2,345/QALY; 45.71 %). Similarly, China [15] achieved a moderate QALY gain (0.27) at a very low incremental cost ($725), yielding a low ICER ($3,481/QALY; 24.14 %). These findings indicate not only affordability but also meaningful health gains at low cost, which supports the argument for expanded access in resource-limited settings.

In Thailand [12], the QALY gain was more modest (0.21), yet the total incremental cost remained below $1,000, producing an ICER of $4,282/QALY (67.81 %), which is still well within national cost-effectiveness thresholds. Colombia [19] reported a QALY gain of 0.42 with moderate cost ($9,037), also resulting in a favorable ICER of $21,387/QALY (75.38 %).

In Argentina [17], the ICER of $34,622 was nearly identical to the national threshold, with a QALY gain of 0.36 and cost of $561 (converted from ARS). This borderline finding suggests that even small fluctuations in price or model parameters could shift the cost-effectiveness conclusion, and supports the use of local sensitivity analysis or outcome-based reimbursement strategies.

In high-income countries, ICERs tended to be higher in absolute terms due to greater healthcare costs, yet still remained under WTP thresholds. Portugal [18] reported an ICER of $33,790 (75.67 %) based on a QALY gain of 0.44 and cost of $13,441. UK and Denmark [19] reported similar cost-effectiveness, with ICERs of $35,500 and $35,306, respectively, driven by QALY gains of 0.52 and 0.47. Switzerland [21] had an ICER of $38,526 based on a gain of 0.43 QALY and a cost of $15,839, placing it among the more efficient high-income settings (51.37 % of WTP).

In Australia [14], sacubitril/valsartan gained 0.30 QALY with $2,159 in incremental cost, resulting in an ICER of $38,266—close to the lower WTP limit (96.46 %) but still cost-effective.

The United States had the highest incremental costs ($47,226 in Gaziano et al., 2016 and $52,242 in King et al., 2016) and also some of the highest QALY gains (0.78 and 0.75, respectively). The resulting ICERs were $59,857 and $68,853, still well within the broad U.S. WTP range of $50,000–$150,000, though with narrower margins compared to other countries. These findings highlight how high costs can be offset by large clinical benefits in maintaining favorable cost-effectiveness.

Qatar [20] reported the lowest incremental QALY (0.04) but also the highest ICER ($103,146), due to a relatively high cost ($4,179). Despite this, the ICER was still only 62.46 % of the $150,000 WTP threshold, confirming cost-effectiveness. This case illustrates how even minimal health gains may be economically justifiable when thresholds are generous.

In summary, the relationship between incremental cost and QALY gain critically shapes ICER values and cost-effectiveness conclusions. Countries with low costs and moderate QALY gains, such as Indonesia and China, offer compelling examples of value-for-money. Meanwhile, high-income settings often require larger clinical benefits to justify higher costs. These findings support the broad economic appeal of sacubitril/valsartan and underscore the importance of contextualizing cost and outcome data in local decision-making processes.

4.2 Clinical Evidence Supporting Economic Value

The favorable economic profile of sacubitril/valsartan is underpinned by its well-established clinical efficacy. The PARADIGM-HF trial demonstrated that sacubitril/valsartan reduced the risk of cardiovascular death or heart failure hospitalization by 20 % compared to enalapril [19]. The dual mechanism, angiotensin receptor blockade and neprilysin inhibition, offers improved neurohormonal modulation, promoting natriuresis and cardiac remodeling [2,19]. Real-world studies have confirmed these benefits: Chen et al. (2021) and Liu et al. (2020) reported improvements in LVEF, NT-proBNP, and NYHA class, while Romano et al. (2019) demonstrated enhanced symptom control and reduced diuretic use.

However, nearly all studies included in this review relied on PARADIGM-HF as the sole or dominant source of clinical inputs. While the trial is robust, dependence on a single RCT may introduce structural bias and limit the generalizability of cost-effectiveness estimates to real-world populations, particularly in LMICs with different demographics or comorbidities. Utility estimates were also often derived from Western sources, raising concerns about applicability in non-Western settings.

4.3 Budget Impact and Health Policy Implications

Beyond individual cost-effectiveness, national-level budget impact analyses emphasize the wider value of sacubitril/valsartan. In the Philippines, projections show that more than 8,000 hospitalizations could be prevented, along with ₱4 billion in societal savings over five years [25]. Similarly, in Indonesia, the prevention of 1,300 deaths and 3,500 hospitalizations is estimated with only a 5 % increase in national health expenditure. These findings demonstrate the population-level efficiency of ARNI adoption. Since heart failure is a significant cost driver for public insurance systems, incorporating sacubitril/valsartan into formularies provides not only clinical but also fiscal advantages [26].

These findings have been endorsed by major clinical guidelines. The European Society of Cardiology [1] and American College of Cardiology [7] both recommend sacubitril/valsartan as a first-line agent, with the 2024 ACC consensus [8] supporting early initiation, including for hospitalized patients.

For low- and middle-income countries, the findings of this review are particularly important in informing pricing negotiations and reimbursement decisions. Differential pricing, managed entry agreements, or tiered formularies may be necessary to ensure both access and affordability in these settings.

4.4 Implications of Methodological Heterogeneity

While the direction of cost-effectiveness was consistent across all studies, important methodological differences may influence the magnitude of ICERs and their comparability. Time horizons ranged from 10 years to lifetime, with longer horizons typically yielding more favorable ICERs due to cumulative benefits. Similarly, cycle lengths (monthly, quarterly, or annual) may impact how transitions and costs are accrued over time.

Discount rates for both costs and outcomes varied from 3 % to 5 % [14,18], (Giorgi et al., 2023) and even within multi-country studies (e.g., McMurray et al., 2018), differential discounting was applied based on local economic evaluation guidelines. Such variability introduces analytical heterogeneity that complicates direct cross-country comparison.

Another key source of variation is the perspective of the analysis. While most studies adopted a healthcare payer perspective, two used a provider perspective, and one applied a societal lens. This affects the scope of included costs (e.g., indirect costs such as productivity loss) and thus the resulting ICER.

Although all studies applied Markov modeling, assumptions regarding state transition probabilities, hospitalization costs, and baseline risk varied, reflecting differences in local clinical practice, unit costs, and healthcare system structure. While standardizing ICERs to 2025 USD improved comparability, these methodological nuances must still be considered when interpreting and applying results across jurisdictions.

Based on the CHEERS 2022 assessment, the overall reporting quality of the included studies ranged from moderate to good. While most studies clearly reported key methodological elements such as the perspective, time horizon, and discounting, only 7 out of 12 provided a comprehensive rationale and description of the model structure. Furthermore, none of the studies made their models publicly accessible, limiting transparency and reproducibility. Notably, equity considerations and stakeholder engagement were entirely absent across all studies. These consistent omissions underscore the need for future economic evaluations to improve reporting transparency, incorporate distributional impact analysis, and actively involve relevant stakeholders to enhance the real-world applicability and policy relevance of their findings.

4.5 Risk of Bias, Equity, and Stakeholder Engagement

An important methodological concern is the potential influence of industry funding. As shown in the study characteristics, six out of twelve studies (50 %) were sponsored by the pharmaceutical industry [13,16–19,21]. While funding disclosures were made, none of the studies explicitly described how sponsor influence was mitigated, nor were analytic assumptions independently validated. This omission raises concerns of publication and design bias, warranting cautious interpretation of results. Future studies should in-

corporate third-party model validation, disclose funding-related safeguards, and consider journal-led methodological audits.

Equally important is the notable absence of equity-focused analyses and stakeholder engagement across all included studies. None of the evaluations accounted for distributional impacts—such as differential cost-effectiveness across age, gender, income, or rural/urban populations—nor did they engage patients, clinicians, or policymakers in model development or interpretation. This omission limits the real-world applicability and credibility of economic evaluations, particularly in low- and middle-income countries (LMICs) where health inequities are more pronounced.

Studies have emphasized that including equity considerations can alter funding priorities and increase societal acceptability of new interventions [27,28]. Likewise, stakeholder engagement is crucial in contextualizing model assumptions, improving transparency, and fostering policy uptake [29,30]. For instance, Cookson et al. (2021) demonstrated how equity weighting could shift funding toward interventions benefiting disadvantaged groups. Similarly, Tsoi et al. (2013) found that involving patients and decision-makers in the modeling process improved trust and increased alignment with policy needs. Without these elements, model outputs may be seen as technically sound but socially disconnected—limiting their influence in resource allocation debates in LMICs.

Future economic evaluations should integrate methods such as distributional cost-effectiveness analysis (DCEA) and adopt participatory modeling approaches. Doing so will enhance both the ethical robustness and policy relevance of findings, ensuring that value-for-money assessments reflect the pluralistic goals of health systems beyond efficiency alone.

4.6 Comparison with Previous Systematic Reviews

The present findings are consistent with and built upon earlier systematic reviews by Rezapour et al. (2022) and Liu et al. (2021). Rezapour et al. synthesized 15 studies and reported cost-effectiveness of sacubitril/valsartan mainly in high-income countries, identifying Thailand and Singapore as borderline cases due to tighter WTP constraints. Liu et al. (2021) analyzed 11 studies and found a mean ICER of $44,305/QALY, noting that cost-effectiveness was not achieved in Singapore or Thailand without price reduction.

Compared to these prior reviews, the current synthesis applied stricter methodological inclusion, limiting to full model-based cost-utility evaluations, and employed the updated CHEERS 2022 guidelines. Additionally, this review expanded geographic coverage by including Indonesia and captured more recent data (2021–2023), thereby increasing its relevance for current decision-making.

4.7 Strengths and Limitations

This review has several notable strengths. It applied a focused and rigorous inclusion strategy, incorporated the most recent literature (up to 2023), and evaluated quality based on CHEERS 2022 standards. Furthermore, it provided updated ICER values con-

verted to June 2025 USD to allow direct comparability across countries, enhancing its utility for policy stakeholders.

However, several limitations should be acknowledged. Most included studies derived clinical inputs from a single source, the PARADIGM-HF trial, limiting applicability to broader populations. Utility estimates were often based on European or American populations, potentially reducing transferability to other regions. Furthermore, none of the included studies conducted equity analyses, involved stakeholder input, or made their economic models accessible for review or replication. Lastly, there remains a paucity of data from low-income countries, which limits the generalizability of these findings to the most resource-constrained environments.

4.8 Future Research Directions

Future research on the cost-effectiveness of sacubitril/valsartan should incorporate real-world effectiveness, local utility values, and cost data to improve contextual relevance. Greater transparency through protocol registration and open-access models is also needed to facilitate replication. Additionally, integrating equity considerations and engaging stakeholders in model development would enhance the credibility and applicability of findings for health policy and reimbursement decisions

5 Conclusion

This systematic review concludes that sacubitril/valsartan is a cost-effective therapy for heart failure with reduced ejection fraction (HFrEF) across various countries, with all studies reporting ICERs below national willingness-to-pay thresholds as of June 2025. Supported by strong clinical trial outcomes, real-world benefits, and favorable budget impact projections, sacubitril/valsartan offers substantial health and economic value despite higher upfront costs. Its inclusion in national formularies and reimbursement schemes is justified, particularly in settings with high heart failure burdens. Future research should enhance contextual relevance by incorporating local data, equity considerations, and stakeholder engagement to support equitable and evidence-informed policymaking.

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Statement Of Ethics. This study is a systematic review of previously published literature and does not involve the recruitment or participation of human subjects or animals. Therefore, ethical approval and informed consent were not required. All data used in this review were obtained from publicly accessible peer-reviewed sources. The authors affirm that all relevant ethical guidelines for the conduct and reporting of research have been followed.

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