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Review Article

Cost-Effectiveness of Sacubitril/Valsartan Compared with Enalapril in Patients with Heart Failure with Reduced Ejection Fraction: A Systematic Review

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Abstract

Background: *To assess the cost-effectiveness of sacubitril/valsartan compared with enalapril in patients with heart failure with reduced ejection (HFrEF).*

Methods: *A systematic literature search was conducted searching in major electronic databases from inception to January 1, 2021. All relevant full economic evaluation studies of sacubitril/valsartan versus enalapril for the treatment of patients with HFrEF were identified using ad hoc search strategies. Mortality, hospital admissions, quality-adjusted life years (QALYs), life-years (LYQs), annual drug costs, total lifetime costs, and incremental cost-effectiveness ratio (ICER) were considered as the outcomes. The quality of the included studies was assessed using the CHEERS checklist. This study was conducted and reported in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines.*

Results: *The initial search yielded a pool of 1026 articles, of which 703 unique articles were screened, 65 full-text articles were assessed for eligibility and 15 studies finally included in the qualitative synthesis. Studies show that sacubitril/valsartan reduces mortality and hospitalization rate. The mean of death risk ratio and hospitalization were computed at 0.843 and 0.844, respectively. Sacubitril/valsartan produced higher annual and total lifetime costs. The lowest and highest lifetime costs for sacubitril/valsartan were found in Thailand ($4,756) and Germany ($118,815), respectively. The lowest ICER was reported in Thailand ($4857/QALY) and the highest in the USA ($143,891/QALY).*

Conclusion: *Sacubitril/valsartan is associated with better outcomes and may be cost-effective compared to enalapril for the management of HFrEF. However, in developing countries such as Thailand, sacubitril-valsartan costs must be reduced to yield an ICER below the threshold.*

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Introduction

Heart failure (HF) is associated with notable mortality, morbidity and economic burden. Heart failure is the leading cause of admission in the United States with more than 1 million annual hospital admissions.[1] The prevalence is estimated to be 1 to 2%, and more than 50 percent of the patients have HF with reduced ejection fraction (HFrEF).[2] According to estimates, in 2010 15 million people in Europe and 6.6 million in the United States are expected to suffer from HF.[3,4] HF accounts for approximately 2% of the UK National Health Service (NHS) annual budget, however the cost will rise to 4%, if hospitalizations and nursing home visits costs are considered.[5]

Angiotensin-converting–enzyme (ACE) inhibitors have been used in the management of HFrEF for nearly 25 years.[6, 7] As evident in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial, long-term treatment with enalapril decreased the relative risk of death by 16% among patients with mild-to-moderate symptoms.[7] Sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI) previously known as LCZ696, is a novel oral agent, shown to reduce cardiovascular death (16%) and HF hospitalization (21%) in addition to improvement in quality of life (QOL) as reported in the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) compared with enalapril.[8, 9] As a result, in July 2015, sacubitril-valsartan was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for patients with New York Heart Association (NYHA) functional class II to IV HFrEF based on the results of the PARADIGM-HF trial.

Cost-effectiveness analyses (CEAs) and the resulting incremental cost-effectiveness ratio (ICERs), defined as cost per quality-adjusted life-year (QALY), have been commonly used to guide decisions on resource allocation in the health system and to compare the effectiveness of health interventions.[10] Since the current cornerstone of HFrEF pharmacotherapy revolves around low-cost generic medications such as ACEIs (Enalapril= $280 per year) and beta-blockers (BBs), it is unclear whether the cost of sacubitril-valsartan ($4,560 per year in the US) will influence its clinical utility.

Given the limited healthcare budgets, evidence-based cost-effectiveness studies need to support and inform healthcare decision and policy-makers. Within this context, this study aimed to systematically collect and synthesize economic evidence in terms of quality-adjusted life-years (QALYs) gained, deaths from cardiovascular causes and hospital admissions, the direct medical costs, and the cost-effectiveness of sacubitril/valsartan compared with enalapril in patients with HFrEF.

Methods

Identification of studies

A systematic literature search was conducted searching in PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase and NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database from inception to January 1, 2021. All relevant full economic evaluation studies of sacubitril/valsartan versus enalapril for the treatment of patients with HFrEF were identified using ad hoc search strategies. Separate search strategies were developed for each database (Supplementary data). The reference lists of eligible articles were hand searched to find additional relevant studies. The following search terms were included: Valsartan; "sacubitril-valsartan"; “hydrochlorothiazide plus valsartan”;”amlodipine plus valsartan”; cost*; economic*; “cost-benefit analysis”; “cost-effectiveness analysis”; and “cost-utility analysis”.

Eligibility Criteria

The “Patients, Intervention, Comparator, Outcomes and Study design” (PICOS) criteria are described below.

- Patients: HFrEF patients;
- Intervention: Sacubitril/valsartan;
- Comparator: Enalapril;
- Outcomes: Mortality, hospital admissions, Quality-Adjusted Life Years (QALYs), Life years gain (LYQs), annual drug costs, total lifetime costs, Incremental Cost-Effectiveness Ratio (ICER), costs per QALYs, costs per LYGs, and Net Monetary Benefit (NMB);
- Study design: Model-based or trial-based full economic

evaluations (Cost-Benefit Analysis (CBA), Cost-Effectiveness Analysis (CEA), and Cost-Utility Analysis (CUA).

Exclusion criteria

- Partial evaluation studies (cost-minimization analysis, cost-of-illness (CoI) studies, cost-analysis, cost outcome descriptions, and cost descriptions;
- Reviews, commentaries, letters to the editors, editorials, protocols, abstracts;
- Non-English language full-text studies.

Selection of Studies

After removing duplicates, titles and abstracts of studies were screened independently by two authors for inclusion. Full text of selected studies were assessed by one author against the eligibility criteria and checked in an independent manner by a second author. Any disagreements were resolved by discussion. The agreement was reached on all included studies. EndNote x9 software was used for management of search results and to remove duplications.

Data extraction and quality assessment of the studies

Two reviewers (SA and JA) independently extracted data using a predefined data extraction form. Disagreements were resolved by discussion at each step. Data extraction was performed in Microsoft Excel. The following data were extracted from each study included: study/publication year, country, funding, comparators, health outcomes, perspective, time horizon, number of patients, sensitivity analysis, discount rate, included costs, type of modelling, mortality, hospital admission, QALYs, LYQs, annual cost, total lifetime cost, ICER, Threshold and Base case analysis results.

The quality of the included studies was assessed by two independent reviewers (SA and JA) using the CHEERS checklist.[11, 12] Any disagreements were resolved through consensus. The CHEERS tool consisted of twenty-four items in six sections (i) title and abstract, ii) introduction, iii) methods, iv) results, v) discussion,[13] and vi) other) and were scored using 'Yes' (reported in full), 'No' (not reported), and 'Not Applicable'.

Synthesis of results

The key characteristics and results of included studies were summarized and synthesized qualitatively using tables and complemented by a narrative description and comparison of the results among studies. This study was conducted and reported in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines.[14] In order to aid in comparisons across studies, cost results were converted to $US, year 2019 values.

Results

The major findings of this systematic review and study selection are outlined in the PRISMA flow chart (Figure 1). The initial search yielded a pool of 1026 articles, of which 701 unique articles were screened, and 65 full-text articles were assessed for eligibility. Finally, 15 articles were included in the review to compare sacubitril/valsartan versus enalapril in the management of HFrEF. All studies retained have a minimum number of 15 items of the CHEERS checklist (Supplementary data).

Table 1 summarizes characteristics of each included study. The studies were conducted in USA (n=3),[15-17] Germany (n=2),[18, 19] Netherlands (n=2),[20, 21] Australia (n=2),[22, 23] Singapore (n=1),[24] UK (n=1),[25] Switzerland (n=1),[26] Thailand (n=1),[27] Portugal (n=1)[28] and South Korea (n=1).[29] The key health outcomes reported in the investigations were QALYs, LYQs, mortality and hospital admissions. The discount rate in the studies was between 1.5% to 5%. Eleven studies applied the results of the PARADIGM-HF trial for modelling. All studies included direct costs such as medications and hospitalization. Three studies applied modeling time horizon between 5 and 20 years and six studies considered time horizon between 30 and 40 years. One study did not clearly state the time horizon. All studies used Markov and decision-analytical model except Ramos studies. The remaining studies (n=5) applied "lifetime" horizon. Two studies used a societal perspective. Thirteen studies chose narrower perspectives such as third-party payer (n=6), health care system (n=5) and provider (n=1). One study did not clearly report the perspective. All studies performed a sensitivity analysis to assess the robustness of their results. Sources of funding for five studies were the industry.

Table 2 presents effectiveness and cost-effectiveness results. Included studies show that sacubitril/valsartan reduced mortality and hospitalization. Also, sacubitril/valsartan saved more life years and QALY in HFrEF patients. Studies showed that sacubitril/valsartan generated higher total lifetime costs. The lowest and highest lifetime costs for enalapril in comparison with sacubitril/valsartan were reported in Thailand ($529, $4,756) and Germany ($84,407, $118,815), respectively. Reports showed a different cost per QALY among various countries. The lowest ICER value was found in Thailand ($4857/QALY) and the highest in the US ($143,891 /QALY). As demonstrated, there was a wide range for annual costs of sacubitril/valsartan in different countries with the lowest cost in Thailand ($171 per year) and the highest in the US ($5,025 per year). Figure 2 shows the mean of death and hospitalization risk ratios (0.843 and 0.844, respectively).

Table 1. Characteristics of included studies in the review

Study/ Publication year	Country	Funding	Comparators	Health Outcomes	Perspective	Time Horizon	Number of patients	Mean age	Sensitivity analysis	Discount rate	Included Costs
Gaziano et al, 2016	USA	-	Sacubitril/valsartan vs enalapril	QALYs, Mortality, hospital admissions	-	30-year	PARADIGM-HF trial	63.8	Yes	3%	Direct cost
King et al, 2016	USA	-	Sacubitril/valsartan vs enalapril	QALYs, Mortality, hospital admissions	Third-party payer perspective	Lifetime (40 years)	PARADIGM-HF trial	60 years	Yes	3%	Direct cost
Van der Pol et al, 2017	Netherlands	-	Sacubitril/valsartan vs enalapril	QALYs, Mortality, hospital admissions	Payer's perspective	30-year	-	-	Yes	Costs = 4% per year health outcomes= 1.5%	Direct cost
Lin et al, 2017	Singapore	-	Sacubitril/valsartan vs enalapril	QALYs, Mortality, hospital admissions	Singapore healthcare payer perspective	10 years	1,000 66-year-old patients with HF	66	Yes	3%	Direct costs
McMurray et al, 2017	UK	Novartis ag	Sacubitril/valsartan vs enalapril	QALYs, Mortality, hospital admissions	Healthcare providers in the UK, Denmark and colombia	Lifetime horizon	-	-	Yes	3.5%, 3% and 5% for the UK, Danish and Colombian	Direct cost
Ramos et al, 2017	Netherlands	-	Sacubitril/valsartan vs enalapril	QALYs, hospital admissions	Societal perspective	Lifetime time horizon	PARADIGM-HF trial	63.80	Yes	4% for costs and a discount rate of 1.5% for effects	Direct cost
Ademi et al, 2017	Switzerland	Novartis AG	Sacubitril/valsartan vs enalapril	QALYs, hospital admissions	Swiss health care system	Lifetime time horizon	PARADIGM-HF trials: Enalapril 10 mg twice daily=4212 Sac/Val 200 mg twice daily=4187	63.80	Yes	3%	
Gandjour et al, 2018	Germany	Novartis Deutschland GmbH	Sacubitril/valsartan vs enalapril	QALYs, LYQs	German social health insurance (SHI)	36 years in the base case	PARADIGM-HF trials	64 years	Yes	3%	Direct cost
Krittayaphong et al, 2018	Thailand	-	Sacubitril/valsartan vs enalapril	QALYs, LYQs, Mortality, hospital admissions	Healthcare perspective	-	PARADIGM-HF trial	63.80	Yes	3%	Direct cost
Zueger et al, 2018	USA	-	Sacubitril/valsartan vs enalapril	QALYs	US payer perspective	5-year time horizon	PARADIGM-HF trial	63.80	Yes	3%	Direct costs
Borges et al, 2019	Portugal	Novartis Farma, Produtos Farmacêuticos SA	Sacubitril/valsartan vs enalapril	QALYs, LYQs	societal perspective	A time horizon of 30-years	PARADIGM-HF trial	63.80	Yes	5%	Direct costs
Chin et al, 2019	Australia	-	Sacubitril/valsartan vs enalapril	QALYs, LYQs, Mortality, hospital admissions	Australian health care perspective	20 years	PARADIGM-HF trial	63	Yes	5%	Direct costs
Park et al, 2019	South Korea	Novartis Korea Ltd.	Sacubitril/valsartan vs enalapril	QALYs, LYQs, Mortality, hospital admissions	Health care sector perspective	Lifetime horizon	PARADIGM-HF trial	63.8	Yes	5%	Direct costs
Perera et al, 2019	Australia	-	Sacubitril/valsartan vs enalapril	QALYs, LYQs	Australian healthcare perspective	Lifetime time horizon	PIONEER-HF trial	61 years	Yes	5.0%	Direct costs
Van der Pol et al, 2019	Germany	-	Sacubitril/valsartan vs enalapril	QALYs, LYQs, Mortality, hospital admissions	Perspective of the German Statutory Health Insurance	30 years	PARADIGM-HF trial	64 years	Yes	3%	Direct costs

QALY, Quality-adjusted life-year; HF, Heart failure; LYQ, Life-years gained; Y, Yes

Table 2. Summary results of cost effectiveness parameters

Study/ year	Patient population	Model	Mortality	Heart failure Hospitalization	LYQs	QALYs	Annual drug cost	Total Lifetime Cost	ICER	Threshold	Base case results
Gaziano et al, 2016	Patients with HFrEF	Markov model	Mortality (Sacubitril/ valsartan) vs enalapril= HR, 0.84	Heart failure hospitalization (Sacubitril/valsartan) vs enalapril= HR, 0.79	-	Enalapril= 6.02 Sacubitril/valsartan = 6.80 Incremental= 0.78	Enalapril= 96$ Sacubitril/ valsartan =4500$	Enalapril= 83,303 $ per life Sacubitril/valsartan = 118,815 $ Incremental= 35,512	45,017$ per QALY	$150 000 per QALY	Sacubitril/valsartan is cost-effective and could lead to the prevention of thousands of premature deaths and hospitalizations for patients with heart failure.
King et al, 2016	Patients with HFrEF	Markov model	Risk of CV mortality: Enalapril =1.87 Sacubitril/valsartan = 1.49 (1.49/1.87=0.79)	Risk of HF hospitalization: Enalapril=3.44 Sacubitril-valsartan=2.62 HR=0.76	Enalapril= 8.4 Sacubitril/ valsartan = 9.48 Incremental =1.08	Sacubitril/valsartan = 6.49 Enalapril=5.74 Incremental=0.75	Enalapril=$280 Sacubitril/ valsartan =$ 4,560	Enalapril= $21,758 Sacubitril/valsartan= $60,391 Incremental=$38,633	35,879$, Per LYQs and 50,959$ per QALY	$100,000 per QALY	Sacubitril-valsartan is a cost-effective treatment option depending on the willingness-to-pay threshold.
van der Pol et al, 2016	Patients with HFrEF	Markov model	Death Risk ratio (Sacubitril/valsartan compared with enalapril) =0.84	Hospitalization Risk ratio (Sacubitril/ valsartan compared with enalapril) = 0.77	Enalapril=6.87 Sacubitril/ valsartan =7.28 Incremental =0.40	Enalapril= 4.93 Sacubitril/valsartan = 5.22 Incremental = 0.29	Sacubitril/ valsartan = $1,890	Enalapril= €12,358 (13,747$) Sacubitril/valsartan = €17,918 (19,889$) Incremental= €5,560	€19,113 (21,215$)	€20,000(22,000$) and €50,000(55,000$) per QALY	Sacubitril/valsartan can be considered a cost-effective treatment at a daily price of €5.25.
Lin et al, 2017	Patients with HFrEF	Markov model	CV deaths 10 years: Enalapril=426 Sacubitril/valsartan =361 Difference=-65 (361/426= 0.84)	Hospitalisation for HF in 1000 patients: Enalapril=306 Sacubitril/valsartan =269 Difference=-37 HR==0.88	-	Enalapril=3.29 Sacubitril/valsartan =3.50 Incremental QALYs=0.21	Enalapril= $54 Sac/Val = $2,397	Enalapril= 2,197 (SGD (1,625$)) Sacubitril/valsartan = 17,857(SGD (13,214$)) Incremental cost=15,660	74,592(SGD/ QALY gained) (55,198$)	SGD 20,000(14800$) and SGD 100,000(74,000$) per QALY	Sacubitril/valsartan may not represent good value for limited health care dollars at its current price of SGD 9.00/day.
McMurray et al, 2017	Patients with HFrEF	A decision-analytic model	All-cause mortality (%) at year 5 UK: Enalapril =38% Sacubitril/valsartan =33% Difference =-0.05 (33%/38%=0.86) Denmark: Enalapril =44% Sacubitril/valsartan =40% Difference =-0.04 (40%/44%=0.90.9) Colombia: Enalapril =40% Sacubitril/valsartan =36% Difference =-0.04 (36%/40%=0.9)	Number of HF hospitalizations per patient UK: Enalapril=0.89 Sacubitril/valsartan =0.84 Difference=-0.05 HR= 0.94) Denmark: Enalapril=0.82 Sacubitril/valsartan =0.76 Difference=-0.05 HR= 0.92 Colombia: Enalapril=0.85 Sacubitril/valsartan =0.79 Difference=-0.05 HR= 0.93	-	UK: Enalapril=5.06 Sacubitril/valsartan = 5.58 Incremental= 0.52 Denmark: Enalapril=4.81 Sacubitril/valsartan = 5.27 Incremental=0.47 Colombia: Enalapril=4.52 Sacubitril/valsartan = 4.95 Incremental=0.42	-	UK(GBP): Enalapril= 14,814 (19,110$) Sacubitril/valsartan = 23,720 (30,598$) Incremental= 8906 Denmark (DKK): Enalapril= 145,346 (21,511$) Sacubitril/valsartan = 226 330 (33,496$) Incremental= 80 984 Colombia (COP): Enalapril= 29,284, 724 (8,785$) Sacubitril/valsartan = 4, 008 231(13,360) Incremental= 16 723 507	UK (GBP)= 17, 134(22,103$) Denmark (DKK)= 173, 994(25,751$) Colombia (COP)= 39, 522, 754(11,856$)	UK: £20, 000 (EUR 23,862) £30 000 (EUR 35, 793) Denmark: Kr250, 000 (EUR 33, 624) Colombian: OP$52.4 million (EUR 15 975)	in all three countries, sacubitril/valsartan is likely to be cost-effective compared with an ACEI (the current standard of care) in patients with HFrEF.
Ramos et al, 2017	Chronic Heart Failure and Reduced Ejection Fraction	-	-	Heart failure hospitalizations hazard ratio: Enalapril=0.88 Sacubitril/valsartan =0.85 Difference= -0.03 HR= 0.96	Enalapril=5.28 Sacubitril/ valsartan= 5.67 Incremental =0.39	Enalapril=4.06 Sacubitril/valsartan =4.39 Incremental=0.33	Enalapril= €368 Sacubitril/ valsartan =€1440	Enalapril= €16,001 (17,761$) Sacubitril/valsartan = €21,840 (24,242$) Incremental= €5,839	€17,600	€50,000 per QALY	Sacubitril/valsartan is cost effective compared with enalapril.
Ademi et al, 2017	Patients with HFrEF	Markov model	-	Enalapril= 35 797 Sacubitril/valsartan = 32 857 Difference= −2940 HR= 0.91	Enalapril=6.17 Sacubitril/ Valsartan=6.67 Incremental =0.50	Enalapril=4.56 Sacubitril/valsartan =4.99 Incremental=0.42	Sac/Val = $2,126	Enalapril= 53,479 CHF (54,548$) Sacubitril/valsartan = 69,683 CHF (71,076$) Incremental= 10 926	25 684 CHF	50,000 CHF per QALY	The treatment of HFrEF patients with Sacubitril/valsartan versus enalapril is cost effective.
Gandjour et al, 2018	Patients with HFrEF	Markov model	-	-	Enalapril=7.18 Sacubitril/ valsartan =8.04 Incremental =0.86	Enalapril=5.40 Sac/Val = 6.16 Incremental=0.76	sacubitril/ valsartan= $2,110	Total lifetime costs (€): Enalapril= 76,043 (84,407$) Sacubitril/valsartan = 96,194 (106,775$) Incremental=20,151	cost (€) per QALY. 26,278, cost (€) per life-year gained 23,401	€30,000 per QALY	The treatment of HFrEF patients with Sacubitril/valsartan versus enalapril is cost effective.
Krittayaphong et al, 2018	Patients with HFrEF	An analytical decision model	Death (per cohort of 1000 per year). Cardiovascular death: Enalapril=687 Sacubitril/valsartan =618 Incremental= -69 HR= 0.89	Number of events (per cohort of 1000 per year): Enalapril=101 Sacubitril/valsartan =69 Incremental= -51 HR= 0.68	Enalapril= 8.36 Sacubitril/ valsartan = 9.21 Incremental =0.85	Enalapril= 6.90 Sacubitril/valsartan = 7.69 Incremental=0.79	Enalapril= $0.75 Sacubitril/ valsartan = $171	Total cost (THB): Enalapril= 16,048 ($529) Sacubitril/valsartan = 144,146 ($4,756) Incremental= $4,227	162,276 THB/QALY (4857.11$US/ QALY). 151,233 THB/life-year (4526.57 $US/life-year)	160,000 THB per QALY (4,789$) or about 1.2 times per capita gross national income	At its current price in Thailand, Sacubitril/ valsartan may not represent good value for the ntions's limited healthcare resources. The cost of sacubitril-valsartan needs to reduce by approximately 2% to yield an ICER below the threshold.
Zueger et al, 2018	Patients with HFrEF	Markov model	-	-	-	Enalapril= 2.546 Sacubitril/valsartan = 2.647 Incremental=0.10	Enalapril= $714 Sacubitril/ valsartan = $5,025	Enalapril= $67,287 Sacubitril/valsartan = $81,943 Incremental= $14,655	$143,891 $/QALY	$100,000/QALY	Sacubitril/ Valsartan is not cost effective compared with enalapril.

Borges et al, 2019	Patients with HFrEF	Markov model	-	-	Enalapril= 6.19 Sacubitril/ valsartan = 6.71 Incremental = 0.52	Enalapril= 4.65 Sacubitril/valsartan = 5.09 Incremental= 0.44	-	Enalapril= 9,928 € (11,020$) Sacubitril/valsartan = 19,949 € (22,143$) Incremental= 10,021 €	22,702 €/QALY	30,000 €/QALY	Sacubitril/valsartan is a cost-effective therapeutic option in the treatment of Portuguese patients with HFrEF and translate into significant health gains and increased life expectancy versus the current standard of care.
Chin et al, 2019	Patients with HFrEF	Markov model	CV deaths Enalapril= 7.3% Sac/Val = 5.9% HR= 0.8	HF hospitalization Enalapril= 6.9% Sac/Val = 5.7% HR= 0.82	Enalapril=5.81 Sacubitril/ valsartan =6.42 Incremental =0.61	Enalapril=4.01 Sacubitril/valsartan =4.43 Incremental=0.42	Enalapril = $252 Sacubitril/ valsartan = $1,873	Enalapril= $10,056 Sacubitril/valsartan = $24,909 Incremental= $14,852	$27,954 per YoLS, $40,513 per QALY	A$50,000 per QALY	Sacubitril/ Valsartan is cost effective compared with enalapril.
Park et al, 2019	Chronic Heart Failure and Reduced Ejection Fraction	Markov model	HR=0.77	Monthly probability of hospitalization: Enalapril=3.53% Sac/Val = 2.96% HR= 0.83	Enalapril= 6.02 Sacubitril/ valsartan = 6.70 Incremental =0.68	Enalapril= 5.15 Sacubitril/valsartan = 5.74 Incremental=0.59	Enalapril= $323 Sacubitril/ valsartan = $1,446	Enalapril= $18,295 Sacubitril/valsartan = $25,831 Incremental= 7,536.4	11,130.1 $ Per life year gained. 12,721.9 Per QALY gained	$20,000	Sacubitril/valsartan is a cost-effective treatment for HFrEF compared with enalapril.
Perera et al, 2019	Acute decompensated heart failure	Markov model	-	-	Enalapril= 3.34 Sacubitril/ valsartan = 3.47 Incremental =0.12	Enalapril= 2.49 Sacubitril/ Valsartan= 2.58 Incremental=0.09	Enalapril= $250 Sacubitril/ valsartan = $1,809	Enalapril= $17,589 Sacubitril/valsartan =$25,053 Incremental= $7,464	$58,629 per life year gained, $77,889 per QALY	AU$50,000 per QALY	At its current acquisition price, sacubitril-valsartan in comparison to enalapril is not likely to be cost effective in the management of acute decompensated heart failure in Australia. A price reduction of more than 25% would confer cost-effectiveness.
Van der Pol et al, 2019	Patients with HFrEF	Markov model	-	Hospitalizations per 10 000 patients: Enalapril= 10 192 Sacubitril/valsartan = 8121 Incremental=2071 HR= 0.79	Enalapril= 6.30 Sacubitril/ valsartan = 7.24 Incremental =0.94	Enalapril=4.90 Sacubitril/valsartan =5.71 Incremental=0.81	Sacubitril/ valsartan = $2,613	Enalapril= €7,329 (8,136$) Sacubitril/valsartan = €23,114 (25,657$) Incremental= €14,978	€19 300 per QALY	€18,250 per QALY	Sacubitril/valsartan can be considered cost-effective at current price in Germany.

HFrEF, Heart Failure reduced Ejection Fraction; HR, Hazard ratio; LYQ, Life-years gained; QALY, Quality-adjusted life-year; ICER, Incremental cost-effectiveness ratio

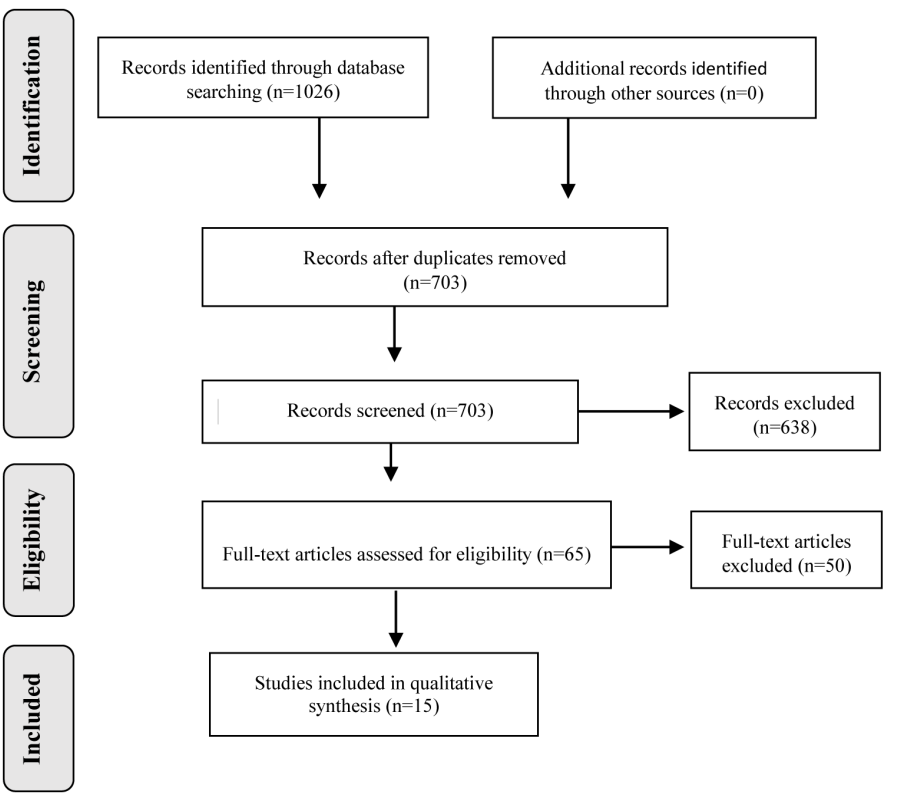

Figure1. Process of the systematic literature search, according to the Preferred Reporting Items for Systematic Reviews and Mete-Analyses

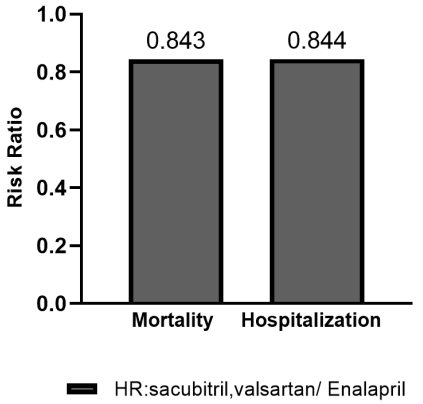

Figure 2. Mean of death and hospitalization Risk ratio

Discussion

Our systematic review and economic evaluation have identified four important findings, as follows:

1. Risk of mortality and hospitalization in Sacubitril/valsartan and Enalapril;
2. QALYs and LYQs in Sacubitril/valsartan vs Enalapril;
3. Annual and total lifetime costs;
4. ICER and Threshold to evaluate the cost-effectiveness of Sacubitril/valsartan.

Risk of mortality and hospitalization in Sacubitril/valsartan and Enalapril

All 15 studies included demonstrated that Sacubitril/valsartan reduces cardiovascular death and HF hospitalization. Figure 2 showed that mean values of mortality and hospitalization risk in Sacubitril-valsartan /Enalapril were 0.843 and 0.844, respectively. The most significant reduction in mortality was demonstrated in Park et al study[29] (hazard ratio or HR=0.77) and the least one in McMurray et al study[25] (Denmark, HR=0.90. 9). These results are in line with the PARADIGM-HF trial, which has randomized 8,399 patients with HFrEF and NYHA class II-IV symptoms to the ARNI LCZ696 (sacubitril) 200 mg or enalapril 10 mg. The PARADIGM-HF trial showed that the HRs of cardiovascular death and hospitalization were 0.80 and 0.79, respectively.[8] Altogether, this suggests that the sacubitril/valsartan could lead to the prevention of thousands of premature deaths and hospitalizations for patients with HFrEF globally. For this reason, the FDA fast-tracked the Sacubitril/valsartan combination pill for approval in July 2015.

QALYs and LYQs in Sacubitril/valsartan vs Enalapril

QALY and LYQs are effectiveness measures commonly utilized in economic evaluation studies. Table 2 shows that Sacubitril/valsartan generated more QALY and LYQs than enalapril, in all studies. The decline in mortality and hospitalization rates in Sacubitril/valsartan versus enalapril, probably is one of the reasons for the increase in LYQs and QALYs. Figure 3 shows the mean values of the QALY for Sacubitril/valsartan and enalapril were 5.12 and 4.64, respectively. Moreover, LYQs were 6.97 and 6.35 in Sacubitril/valsartan and enalapril, respectively. The low QALY and LYQ in Perera et al[30] study could be explained by different patient's population compared with other studies (acute HF versus chronic HF).

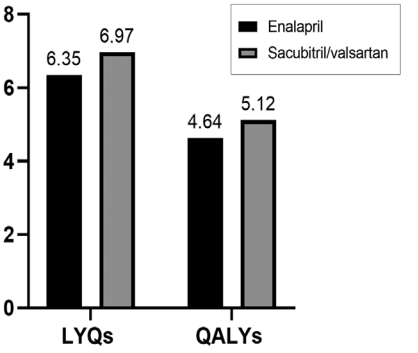

Figure 3. Mean of LYQs and QALYs in studies

Annual and total lifetime costs

The highest annual price ratio (cost of Sacubitril-valsartan / enalapril) was reported in Thailand (228 times) and the lowest price ratio in Netherlands and Korea (4 times). Studies show that the new drug was far more expensive than the old one. The mean values of annual costs for Sacubitril-valsartan and enalapril were $2460 and $259, respectively (annual price ratio in Sacubitril-valsartan /enalapril= 9.5 times). As demonstrated in figure 4, the highest lifetime cost was reported in the US ($129,746 for Sacubitril/valsartan and $91,027 for enalapril) and the least in Thailand ($4,898 for Sacubitril/valsartan and $545 for enalapril). The mean values of lifetime cost in studies for Sacubitril/valsartan and enalapril were $43,498 and $28,467, respectively (total lifetime price ratio in Sacubitril-valsartan /enalapril= 1.5 times). These results showed that, despite the large differences in the annual cost of Sacubitril/valsartan vs enalapril, there is much less difference in lifetime costs, which can be explained by reduced hospitalization and mortality for Sacubitril/valsartan.

ICER and Threshold to evaluate the cost-effectiveness of Sacubitril/valsartan

An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of the 'extra cost per extra unit of health

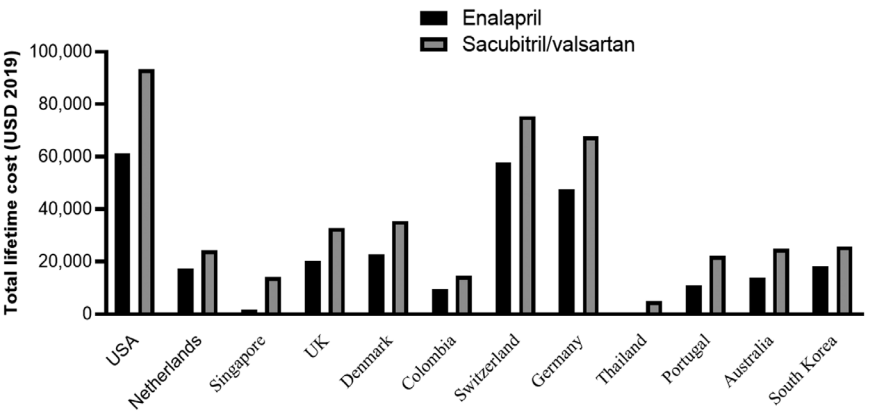

Figure 4. Total lifetıme cost Sacubıtrıl/valsartan and enalaprıl ın studıes

effect' – for the most expensive therapy vs its alternative/competitor.[31] The cost-effectiveness threshold is the maximum amount a decision-maker is willing to pay for a unit of health outcome. If the cost-effectiveness (ICER) of a new therapy (compared with a relevant alternative) is estimated to be below the threshold, then (other things being equal) it is likely that the decision-maker will recommend the new therapy.[32]

The threshold spectrum in US in three studies ranged from $100,000 to $150,000. In Gaziano et al and King et al studies threshold was more than ICER (ICER:45,017$ and $50,959 per QALY, in threshold $150,000 and $100,000, respectively) and in Zueger et al study ICER was more than threshold ($143,891 vs $100,000 per QALY). This difference in ICER could be due to different incremental QALY in these studies. Incremental QALY in Gaziano et al and King et al studies were 0.78 and 0.75 respectively and in Zueger was 0.10. Maximum threshold, i.e., $150,000 could increase the chance of being cost-effective option for Sacubitril/valsartan. In studies conducted in the Netherlands, the ICER was lower than threshold (threshold was €20,000 and €50,000, and the ICER was €17,600 € and 19,113). Accordingly, Sacubitril/valsartan is cost effectiveness in the Netherlands and threshold of €50,000 could probably be more cost effective.

In Singapore, ICER is $54,700 / QALY and threshold is $14,600 and $73,300; data shows that in current price (SGD 9.00/day or $6.6/day) lower QALY and high annual and total lifetime cost probably make Sac/Val being not cost effective in Singapore. Studies done in Germany had diversity in results, in Gandjour et al study, ICER was lower than threshold (€26,278 vs €30,000 per QALY) and in Van der Pol study, ICER was more than threshold (€19 300 vs 18,250 per QALY). The higher ICER to threshold in Van der Pol et al study could explain the higher cost of Sacubitril/valsartan comparing to Gandjour et al study (€6.66 vs €5.33). However, since ICER values were near the threshold, Sacubitril/valsartan can be considered cost effective at current price in Germany. Chin and Perera et al study results were opposed to each other. The reason for this difference could be explained by lower QALY in acute (Perera et al) vs chronic (Chin et al) HF for Sacubitril/valsartan.

As demonstrated in Krittayaphong et al study in Thailand,[33] the ICER was higher than threshold (162,276 vs 160,000 THB/QALY) and at its current price, Sacubitril/valsartan may not be cost-effective. Low threshold and limited healthcare resources in developing countries such as Thailand can make it not cost-effective. However, to make sacubitril/valsartan cost-effective, a reduction in cost to yield an ICER below the threshold is needed.

Studies conducted in UK, Denmark, Colombia, Portugal and South Korea[25] showed that in all five countries, threshold was upper than ICER and sacubitril/valsartan was likely to be cost-effective compared with the current standard of care in patients with HFrEF, which could be attributed to higher threshold compared to developing countries such as Thailand. As a result, a high threshold is an important factor to make sacubitril/valsartan cost-effective.

Compared to the previous two review studies[34] (Proudfoot C, Gautam R, Cristino J, Agrawal R, Thakur L, Tolley K. Model parameters influencing the cost-effectiveness of sacubitril/valsartan in heart failure: evidence from a systematic literature review. Eur J Health Econ. 2022 Jul 5.), the present study included 30% more articles compared to the study by Liu et al. and compared to the study by Proudfoot et al., included only full economic evaluation and model-based studies; Partial economic evaluations studies, conference abstracts have been excluded.

This study has some limitations. Effectiveness data of the majority studies was drawn from a single trial (PARADIGM-HF). It seems that the effectiveness measures and the results of the studies in the included studies are influenced by the trial data. We also excluded abstracts because there was not enough information. Our study compared findings from studies conducted in a variety of countries with different health systems. Theses difference are likely to have affected results of the included analyses. Health system characteristics such as reimbursement policies, prescribing

patterns, and country-specific cost-effectiveness thresholds should be considered when interpreting and generalizing the findings.

Conclusion

Our study shows that in current acquisition price sacubitril-valsartan in western countries compared to enalapril is likely to be cost-effective for the management of HFrEF. However, in Asian countries such as Singapore and Thailand, the cost of sacubitril-valsartan needs to be reduced to yield an ICER below the threshold.

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Supplements

Table 3. Supplementary data
A. Search strategies and results for selected databases

Database	Date conducted	Search strategy	#Results
PubMed	January 1, 2020	("Valsartan"[Mesh] OR "sacubitril-valsartan" [Supplementary Concept] OR sacubitril [tiab] OR valsartan [tiab]) AND (“cost-benefit analysis” [MeSH] OR ”cost-utility analysis” OR “cost-effectiveness analysis” OR economics [mesh] OR Cost* [tiab] OR Economic*[tiab])	151
Embase	January 1, 2020	('sacubitril'/exp OR sacubitril OR 'sacubitrilat'/exp OR sacubitrilat OR 'sacubitril plus valsartan'/exp OR 'hydrochloro-thiazide plus valsartan'/exp OR 'hydrochlorothiazide plus valsartan' OR 'amlodipine plus valsartan'/exp OR 'am-lodipine plus valsartan' OR 'valsartan'/exp OR valsartan) AND ('cost benefit analysis'/exp OR 'cost benefit analysis' OR 'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'cost utility analysis'/exp OR 'cost utility analysis' OR economic*:ab,ti)	530
Web of Science	January 1, 2020	TS=((sacubitril OR “sacubitril-valsartan” OR “sacubitril/valsartan” OR valsartan) AND (cost* OR Economic* OR "cost-benefit analysis" OR "cost benefit analysis" OR “cost effectiveness analysis” OR "cost-effectiveness analysis" OR “cost utility analysis” OR "cost-utility analysis"))	229
Scopus	January 1, 2020	Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.	103
NHS Economic Evaluation Database(NHS EED) and the health technology assessment	January 1, 2020	TITLE-ABS-KEY (sacubitril OR “sacubitril-valsartan” OR valsartan) AND TITLE-ABS-KEY ("cost benefit analy-sis" OR "cost-benefit analysis" OR "cost-effectiveness analysis" OR "cost effectiveness analysis" OR "cost utility analysis" OR "cost-utility analysis" OR cost*OR economic*)	13
Total		MeSH DESCRIPTOR valsartan EXPLODE ALL TREES IN NHSEED,HTA	1026
Total with duplicates removed			703

Table 4. Supplementary data
B. Quality of reporting of included studies using CHEERS checklist

Section/item	Item No	Gaziano, 2016	King, 2016	van der Pol, 2016	Lin, 2017	McMurray,2017	Ramos,2017	Ademi, 2017	Gandjour, 2018	Krittayaphong,2018	Zueger, 2018	Borges, 2019	Chin, 2019	Park, 2019	Perera,2 019	van der Pol, 2019
Title and abstract																
Title	1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Introduction																
Background and objectives	3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods																
Target population and subgroups	4	Y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	5	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study perspective	6	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Comparators	7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	8	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Discount rate	9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	11a	Y	Y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	11b	-	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement and valuation of preference based outcomes	12	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Estimating resources and costs	13a	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	13b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Currency, price date, and conversion	14	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of model	15	Y	-	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assumptions	16	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	
Analytical methods	17	Y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results																
Study parameters	18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Incremental costs and outcomes	19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Characterising uncertainty	20a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	20b	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y
Characterising heterogeneity	21	N	N	N	Y	-	N	Y	N	N	Y	Y	N	N	N	N
Discussion																
Study findings, limitations, generalisability, and current knowledge	22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Other																
Source of funding	23	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Conflicts of interest	24	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y

CHEERS Consolidated Health Economic Evaluation Reporting Standards,
NA not applicable, N not reported, Part partially reported, Y reported