Original Investigation

Cost-effectiveness Analysis of Sacubitril/Valsartan vs Enalapril in Patients With Heart Failure and Reduced Ejection Fraction

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IMPORTANCE The angiotensin receptor neprilysin inhibitor sacubitril/valsartan was associated with a reduction in cardiovascular mortality, all-cause mortality, and hospitalizations compared with enalapril. Sacubitril/valsartan has been approved for use in heart failure (HF) with reduced ejection fraction in the United States and cost has been suggested as 1 factor that will influence the use of this agent.

OBJECTIVE To estimate the cost-effectiveness of sacubitril/valsartan vs enalapril in the United States.

DESIGN, SETTING, AND PARTICIPANTS Data from US adults (mean [SD] age, 63.8 [11.5] years) with HF with reduced ejection fraction and characteristics similar to those in the PARADIGM-HF trial were used as inputs for a 2-state Markov model simulated HF. Risks of all-cause mortality and hospitalization from HF or other reasons were estimated with a 30-year time horizon. Quality of life was based on trial EQ-5D scores. Hospital costs combined Medicare and private insurance reimbursement rates; medication costs included the wholesale acquisition cost for sacubitril/valsartan and enalapril. A discount rate of 3% was used. Sensitivity analyses were performed on key inputs including: hospital costs, mortality benefit, hazard ratio for hospitalization reduction, drug costs, and quality-of-life estimates.

MAIN OUTCOMES AND MEASURES Hospitalizations, quality-adjusted life-years (QALYs), costs, and incremental costs per QALY gained.

RESULTS The 2-state Markov model of US adult patients (mean age, 63.8 years) calculated that there would be 220 fewer hospital admissions per 1000 patients with HF treated with sacubitril/valsartan vs enalapril over 30 years. The incremental costs and QALYs gained with sacubitril/valsartan treatment were estimated at $35 512 and 0.78, respectively, compared with enalapril, equating to an incremental cost-effectiveness ratio (ICER) of $45 017 per QALY for the base-case. Sensitivity analyses demonstrated ICERs ranging from $35 357 to $75 301 per QALY.

CONCLUSIONS AND RELEVANCE For eligible patients with HF with reduced ejection fraction, the Markov model calculated that sacubitril/valsartan would increase life expectancy at an ICER consistent with other high-value accepted cardiovascular interventions. Sensitivity analyses demonstrated sacubitril/valsartan would remain cost-effective vs enalapril.

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Heart failure (HF) is associated with considerable mortality, morbidity, and financial costs. Heart failure is the leading cause of admission to hospital in the United States, with more than 1 million annual admissions.[1] Total costs for HF are estimated to be between $24 and $47 billion per year.[2] Heart failure progression is aggravated by several detrimental neurohormonal pathways. Over the last 3 decades, therapies that inhibit or alter these pathways, including the use of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid receptor antagonists, have improved mortality and morbidity of patients with HF with reduced ejection fraction.

Sacubitril/valsartan (LCZ696), an angiotensin receptor neprilysin inhibitor, has been shown to reduce cardiovascular death and HF hospitalization in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial compared with enalapril.[3] Sacubitril/valsartan has been approved for use for HF with reduced ejection fraction in the United States, and cost has been suggested as a factor that could influence use of this agent. We estimated the cost-effectiveness of this new medication relative to enalapril in the United States.

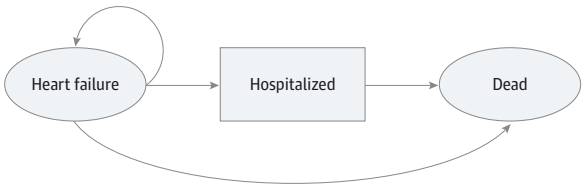
Key Points

Question Is sacubitril/valsartan cost-effective in patients with heart failure with reduced ejection fraction?

Findings When compared with enalapril, sacubitril/valsartan extends life, reduces hospitalizations, and has an incremental cost-effectiveness ratio of US $45 017 per quality-adjusted life-year gained in the United States.

Meaning Sacubitril/valsartan is cost-effective and could lead to the prevention of thousands of premature deaths and hospitalizations for patients with heart failure.

Figure 1. Markov Model Diagram



Patients occupy health states, shown in ovals. Patients transition from different health states represented as arrows based on transition probabilities.

Methods

HF Disease Simulation Model Strategies

A 2-state Markov model simulating HF was developed for the US population using data derived from patients involved in the PARADIGM-HF trial, which compared 10 mg of enalapril twice daily with 97 mg of sacubitril/103 mg of valsartan mg twice daily.[3,4] Using the results of the trial, we simulated a population with equivalent characteristics as the trial population and then modeled additionally the costs and health consequences for the duration of the trial and beyond for 30 years. The model follows a standard structure of HF,[5-7] in which a patient with HF each month has a risk of either surviving without further complication, becoming hospitalized, or dying (**Figure 1**).

Patient Population

We modeled a population that was similar to that in the PARADIGM-HF trial, a double-blind, randomized, active clinical trial that assessed the effect of the angiotensin receptor neprilysin inhibitor sacubitril/valsartan compared with enalapril on cardiovascular mortality and HF hospitalizations in patients with left ventricular ejection fraction (LVEF) of 40% or less and a New York Heart Association functional class II through IV HF. The details of inclusion and exclusion and the study design have been previously reported.[8] Patients were followed up for a median of 27 months. The primary outcome was death from cardiovascular causes or HF hospitalization. Data from all hospitalizations were recorded.

Intervention Effects and Model Assumptions

Separate hazard ratios (HRs) for all-cause mortality, HF hospitalizations, non-HF hospitalizations, and absolute risk of dying and being admitted were calculated and are reported in **Table 1**. All-cause mortality for the patients with HF follows a hazard function based on the PARADIGM-HF trial data. We further compared our model's life expectancy results with an analysis using age-based Kaplan-Meier methods that was used to project long-term survival rates[15] and was validated with data from the Studies of Left Ventricular Dysfunction (SOLVD)–Treatment trial, which also used enalapril. This baseline function approximates a monthly mortality probability of 0.008 for those in the enalapril group with a mean (SD) age of 63.8 (11.5) years. The HR of 0.84 for all-cause mortality in the patients who receive sacubitril/valsartan was then applied to the baseline rate. As a sensitivity analysis, we also applied a Gompertz function based on the trial data to see if this had an effect on the overall results. The monthly probability of both non-HF and HF hospitalizations were based on the US subset of the trial data and were approximately 0.049 and 0.022, respectively, for those in the enalapril group. The HR for reductions in hospitalizations for those receiving sacubitril/valsartan was 0.79 for HF admissions and 0.92 for non-HF admissions, which was taken from the overall trial results.

Costs and Utilities

Costs included both cost of the medications as well as the downstream costs of hospitalizations that occurred in each group of simulated patients. Medication costs were based on the wholesale acquisition cost for sacubitril/valsartan (trade name Entresto) and enalapril. The monthly cost for sacubitril/valsartan was $375 and $0.96 for enalapril.[13] Hospital costs combined Medicare and private insurance rates.[9,16] The mean cost of hospitalizations for HF was $18 158; for non-HF, $10 467.

Table 1. Model Inputs

Input	Value (Range)	Source
Health		
Probability, median (IQR), mo		
Hospitalization		
Other causes	0.0487 (0.040-0.058)	Trial[3,4]
Heart failure	0.0216 (0.018-0.026)	Trial
All-cause mortality	0.0081 (0.0072-0.0091)	Trial
Sacubitril/valsartan vs enalapril, HR (95% CI)		
Mortality	0.84 (0.76-0.93)	Trial
Hospitalization		
Heart failure	0.79 (0.71-0.89)	Trial
Other causes	0.92 (0.85-0.99)	Trial
Costs, (median range), $		
Hospitalization		
Heart failure	18 158 (12 148-26 595)	Medicare fee schedule/ private payers[9,10]
Other causes	10 467 (7200-12 300)	AHRQ,[11] Pfunter[12]
Annual treatment		
Enalapril	96 (48-1080)	Red Book[13]
Sacubitril/valsartan	4500 (3375-5675)	Red Book[13]
Utilities[a]		
Heart failure		
Sacubitril/valsartan	0.838 (0.833-0.843)	Trial
Enalapril	0.829 (0.824-0.834)	Trial
Discount rate, median (IQR), %	3 (0-5)	Gold et al[14]

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; HR, hazard ratio.

[a] Utilities were calculated based on a mixed-effects model based on EQ-5D scores reported at baseline and over time during the trial. Model utilities were a function of baseline EQ-5D scores, age, time, hospitalization, and treatment status. Values reported in table are utilities for an average age patient in the first year of the model. Further details are available in the eAppendix in the Supplement.

Quality of life or utility decrements were applied for each month that a person spent in the HF state and were based on EQ-5D scores from the trial. Determination of the utility for each strategy was determined following a mixed model based on baseline EQ-5D responses, follow-up responses, hospitalizations, baseline age, and time from the start of the trial. Values in Table 1 represent utilities for a person with the mean age at the beginning of the trial. Further details of the EQ-5D model are provided in the eAppendix in the Supplement.

Base-Case Cost-effectiveness Analysis

We projected the lifetime discounted HF-related health care costs and quality-adjusted life-years (QALYs) accrued under the 2 treatment options. Incremental cost-effectiveness ratios (ICERs) were calculated per conventional cost-effectiveness analysis guidelines.[17] Costs and QALYs were each discounted at 3% as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.[18] We applied commonly accepted cost-effectiveness thresholds of $50 000 per QALY, $100 000 per QALY, and $150 000 per QALY to determine the optimal strategy in base-case and sensitivity analyses.[19]

Sensitivity Analysis

We varied values for all variables (or groups of related variables) through plausible ranges or used alternative values to assess the robustness of our cost-effectiveness analysis results to changes in these input parameters. Sensitivity analyses were performed on key inputs including: hospital cost, mortality benefit, use of a Gompertz function for mortality, HF hospitalization reduction, drug costs, and quality of life. The model was run using DATA TreeAge Pro version 2015. Finally, we conducted a second order probabilistic sensitivity analysis based on 1000 iterations using distributions appropriate to the variable,[20] beta distributions for health probabilities bounded by 0 and 1, log-normal distributions for the HRs, and gamma distributions for the costs.

Results

Model Validation and Clinical Results

The mean (SD) age of our population was 63.8 (11.5) years. At the end of the PARADIGM-HF trial, with a mean follow-up of 27 months, 17% of the sacubitril/valsartan and 19.8% of the enalapril group had died. In our model, at 29 months, we predicted that 17.1% of the sacubitril/valsartan population and 19.9% of the enalapril population would die. The average survival time without discounting in the model was estimated to be 9.65 years in the enalapril group and 11.08 years in the sacubitril/valsartan group. In a separate analysis using actuarial methods, PARADIGM-HF investigators estimated the survival times of a 65-year-old to be similar at 10.2 years for those taking enalapril and 11.5 years for those taking sacubitril/valsartan.[15]

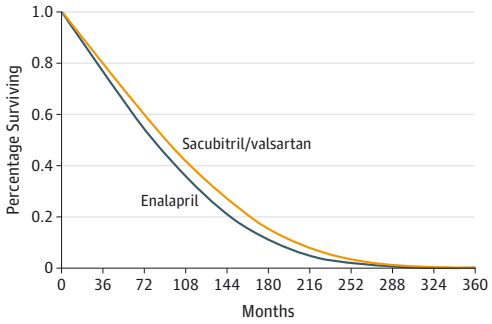
At the end of the 30 years of simulation, more than 95% of the model population was deceased in each group making it essentially a life-time horizon analysis.

For every 1000 patients with HF treated with sacubitril/valsartan, approximately 220 admissions were averted over the course of their lifetimes. However, given that the population declined more rapidly with the enalapril strategy (**Figure 2**) due to increased total mortality, the potential for HF admissions savings in the latter years diminished. When adjusted for time alive in the model, there were 59.7 HF admissions averted for each year alive per 1000 patients in the sacubitril/valsartan strategy compared with those in the enalapril strategy.

Cost-effectiveness Analysis

In a given year, 1000 patients receiving sacubitril/valsartan would cost approximately $4.4 million more in differential drug costs. In the same year, the reductions in hospitalizations would lead to a savings of $1.3 million compared with patients receiving enalapril. The cost per patient over the average life expectancy would be approximately $83 300 per patient treated with the enalapril and $118 500 for each patient treated with sacubitril/valsartan. After adjustments for quality of life, the difference in health effects is 0.78 QALYs (**Table 2**). Compared with enalapril, the strategy of using sacubitril/valsartan has an ICER of $45 017 per QALY gained.

Figure 2. Survival Curves, According to Treatment Strategy



No. at risk

Sacubitril/valsartan	1000	795	598	420	270	156	79	34	12	3
Enalapril	1000	762	544	357	212	111	50	18	5	1

Shown are estimates of the probability of being alive at any given time over 360 months.

Sensitivity Analyses

In all the sensitivity analyses presented in the tornado diagram (**Figure 3**), the ICER remained less than $100 000 per QALY. When the mortality hazard was tested over the 95% CI from the trial, the ICER ranged from as low as $35 357 per QALY to as high as $75 301 per QALY gained. The HF hospitalization hazard benefit was tested across the 95% CI seen in the trial and showed a lower range of sensitivity results with ICERs ranging only from $40 874 per QALY to $50 212 per QALY gained. When we applied the Gompertz mortality function instead of the Kaplan-Meier–based function the ICER changed minimally to $48 322 per QALY.

The results were not very sensitive to the cost of either drug. When we tested the cost of sacubitril/valsartan across an annual cost of $3375 to $5675, the ICER ranged from $35 696 per QALY to $56 805 per QALY. When we tested the cost of enalapril from its highest ($1000) to lowest ($48) annual cost, the ICER ranged from $35 403 per QALY to $45 481 per QALY gained. When the cost of HF hospitalization was tested from an average of $12 000 to approximately $27 000 per hospitalizations, there was little effect on the ICER, ranging from a low of $42 618 per QALY to $46 726 per QALY. Finally, when we assessed the quality-of-life benefit across its 95% CI from the trial, the ICER ranged from $42 869 to $47 480 per QALY. When we assumed no utility benefit, the ICER was $49 603 per QALY. All of these results are considered a "very good value" (<$50 000 per QALY) to a "good value" (<$150 000 per QALY), using both American College of

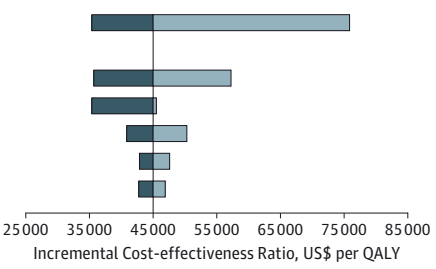
Table 2. Total Costs, Health Effects, and Incremental Cost-effectiveness Ratio

	Costs, $		QALYs		
	Total	Incremental	Total	Incremental	ICER, $
Enalapril	83 303		6.02		
Sacubitril/valsartan	118 815	35 512	6.80	0.78	45 017

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYS, quality-adjusted life-years.

Figure 3. Tornado Diagram

	Base Case Value	Sensitivity Analysis Range
Mortality (sacubitril/valsartan) vs enalapril	HR, 0.84	95% CI, 0.76-0.93
Annual drug cost		
Sacubitril/valsartan	$4500	$3375-$5675
Enalapril	$96	$1080-$48
Heart failure hospitalization (sacubitril/valsartan) vs enalapril	HR, 0.79	95% CI, 0.71-0.89
Quality of life benefit	0.0084	0.013-0.0037
Heart failure hospitalization cost	$18 158	$26 595-$12 148



Univariate sensitivity analyses evaluating the effect of each variable's uncertainty on an overall cost-effectiveness ratio. The central black line represents the base-case analysis. None of the analyses lead to an incremental cost-effectiveness ratio greater than $150 000 per quality-adjusted life-year (QALY). HR indicates hazard ratio.

Cardiology/American Heart Association (ACC/AHA) and World Health Organization standards. The probabilistic sensitivity analysis revealed a mean value of $47 519 per QALY with 95% of the values between $34 751 and $71 039 per QALY. Furthermore, we tested the assumption that the medication benefit persists with the same relative risk reduction beyond the trial. In one case we assume a linear decay of treatment to where it has no effect at the end of 30 years and one in which the linear decay is to half of its effectiveness at 30 years. In the scenario of linear decay to no benefit, the ICER is $53 970 per QALY. In the scenario when the decay is to the level of half of the reported trial benefit the, ICER is $49 232 per QALY. When we modeled the extreme case of the benefit only lasting 27 months as opposed to 360 months, the ICER for sacubitril/valsartan compared with enalapril was $135 964 per QALY, which remained below the willingness to pay threshold of $150 000 per QALY.

Discussion

Our model-based analyses suggest that the health benefits associated with the use of sacubitril/valsartan in patients with New York Heart Association class II through IV HF with reduced ejection fraction is cost-effective when compared with the use of enalapril at commonly accepted willingness-to-pay thresholds of $50 000 per QALY gained. Furthermore, use of sacubitril/valsartan could lead to more than a year of life gained per patient using the medication and significant cost savings through avoided hospitalizations. Because of this additional life expectancy with 5.7 million individuals in the United States with HF,[1] the benefits of expanded use of sacubitril/valsartan could be large. Given that up to half of patients with HF have HF with reduced ejection fraction, a considerable number would be potentially eligible for the medication based on the trial criteria.[21-23] For every 100 000 people receiving sacubitril/valsartan, this strategy could potentially reduce hospitalizations by 3000 and reduce deaths by nearly the same number over a 2-year period. Medical savings from reduced HF admissions would be more than $27 million.

The ICER of $45 017 per QALY is not only below standard-accepted levels for evaluations of new therapies and interventions, its value also compares well with other accepted cardiovascular therapies when they were first adopted or approved. For example, the ICER for pravastatin before it became generic was $54 000 to $1.4 million per QALY gained,[24] with similar results for other statins.[25,26] In addition, ICERs for implantable cardioverter defibrillators with and without cardiac resynchronization therapy range from $35 000 to $108 000 per QALY,[27,28] whereas the ICERs for percutaneous coronary interventions are approximately $36 000 per QALY[29] and the ICER for left ventricular assist devices range from $120 000 to more than $300 000 per QALY gained.[30]

With the exception of one extreme case, all of the sensitivity analyses revealed ICERs lower than $76 000 per QALY. The results are robust over a range of varying assumptions in the sensitivity analyses for several reasons. First, HF is a condition with significant mortality with a median survival of less than 5 years of those receiving optimized treatment in previous assessments.[31-33] Any treatment that can reduce this mortality by 15% to 20% is likely to be cost-effective across a reasonable price range. Second, patients with HF along with their other frequent comorbidities are at risk of multiple admissions. In the PARADIGM-HF trial, patients with optimized treatment were still admitted an average of once every 2 years for HF or other cardiovascular causes. A 15% to 20% reduction in those admissions likely contributes to the relative improvements in overall quality of life as decrements in quality of life were associated with admissions. Third, the cost of cardiovascular care including admissions is relatively expensive at $10 000 to $27 000 per admission, and reductions in these will also be relatively robust to changes in price of the intervention. Even with conservative estimates around the parameters used in the model for sensitivity analyses, the findings remain cost-effective across a range of estimates in the model assumptions at the threshold of $150 000 per QALY. This threshold has been justified, in part, by empirical evidence from surveys investigating patient and insurance company's willingness to pay for health, by revealed preference studies, and by general increases on health care spending, in addition to the World Health Organization recognizing 3 times the gross domestic product per capita as an upper threshold.[19] Furthermore, the ACC/AHA have set a similar target equivalent to $150 000 per QALY gained as of at least intermediate value.[34] Finally, we did not make any adjustment for the possibility that the cost of sacubitril/valsartan may decrease in 2023 after its patent expiration date. Although we are unable to estimate what the cost would change to, any decrease in the cost would make the cost-effectiveness ratio for sacubitril/valsartan more favorable.

Other evaluations of sacubitril/valsartan also found the medication to be cost-effective with ICERs of approximately $50 000 per QALY gained.[23,35] The Institute for Clinical and Economic Review obtained an ICER of $50 915 per QALY that was very similar to our result. One key difference is its use of the lowest-cost ACE inhibitor at $3 per month whereas we use the reported costs of enalapril at $8 per month. When we performed a sensitivity analysis using the lower-cost, we still found sacubitril/valsartan to be cost-effective. Another difference is that we modeled the event rates for hospitalization based on the US subset of the trial, which has a higher hospitalization rate than the other countries participating in the trial. This would lead to reductions in the ICER given the greater opportunity for cost reductions. Furthermore, our mortality function reflected the trial experience and did not rely on creating estimates using life tables from the National Vital Statistics System for noncardiovascular disease deaths. King et al[35] found similar results but their analysis included patients with New York Heart Association functional class I in their model. These patients were excluded from the PARADIGM-HF trial. King et al used utility values from another trial as opposed to those from the PARADIGM-HF trial that was used in our analysis. They also did not include non-HF admissions.

Among the limitations of our study is the active run-in of the trial. Therefore, our results assume that patients can tolerate the recommended dose of each medication without an

adverse event. However, only 12% of patients did not complete the run-in phase, and the rates of adverse advents were higher for those receiving enalapril during the run-in. Another limitation is that we did not model changes in adverse events directly in the model. In the PARADIGM-HF trial, the most common adverse events included hypotension, cardiac failure, hyperkalemia, renal impairment, and cough. However, discontinuing study medications due to these events was lower among patients taking sacubitril/valsartan (10.7%) than among patients taking enalapril (12.3%), further highlighting that the results from our analysis may be conservative. Only episodes of symptomatic hypotension (14% vs 9.2%) were higher in the sacubitril/valsartan group (14%) than the enalapril group (9.2%). Although we did not model reductions in emergency department visits, the sacubitril/valsartan group had fewer emergency department visits for HF than did the enalapril group. The risk of angioedema was not statistically significantly elevated in the trial, and hospitalizations for angioedema were rare (0.1%). Also, there were no cases of angioedema requiring intubation for sacubitril/valsartan.

This study only evaluated the cost-effectiveness of sacubitril/valsartan in the United States. Although the HRs for reductions in hospitalizations and mortality were trial-wide, the baseline rate of each is different with the highest rates in the United States. Further costs for hospitalizations are different in each country so that individual analyses need to be conducted in other countries.

Conclusion

We found that for eligible patients, sacubitril/valsartan was cost-effective at an ICER consistent with other high-value accepted cardiovascular interventions, such as implantable cardioverter-defibrillators and cholesterol-lowering medications, at a commonly accepted willingness to pay.

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Author Contributions: Dr Gaziano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gaziano, Fonarow, Chan, Deschaseaux-Voinet, Turner, Zile, McMurray, Solomon.
Acquisition, analysis, or interpretation of data: Gaziano, Fonarow, Claggett, Chan, Turner, Rouleau, McMurray.
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