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Cost-Effectiveness of Sacubitril–Valsartan in Patients With Heart Failure With Reduced Ejection Fraction

Alexander T. Sandhu, MD, MS; Daniel A. Ollendorf, PhD; Richard H. Chapman, PhD; Steven D. Pearson, MD, MSc; and Paul A. Heidenreich, MD, MS

Background: Sacubitril–valsartan therapy reduces cardiovascular mortality compared with enalapril therapy in patients with heart failure with reduced ejection fraction.

Objective: To evaluate the cost-effectiveness of sacubitril–valsartan versus angiotensin-converting enzyme inhibitor therapy in patients with chronic heart failure.

Design: Markov decision model.

Data Sources: Clinical trials, observational analyses, reimbursement data from the Centers for Medicare & Medicaid Services, drug pricing databases, and Centers for Disease Control and Prevention life tables.

Target Population: Patients at an average age of 64 years, New York Heart Association (NYHA) class II to IV heart failure, and left ventricular ejection fraction of 0.40 or less.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Treatment with sacubitril–valsartan or lisinopril.

Outcome Measures: Life-years, quality-adjusted life-years (QALYs), costs, heart failure hospitalizations, and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: The sacubitril–valsartan group experienced 0.08 fewer heart failure hospitalization, 0.69 additional life-year, 0.62 additional QALY, and $29 203 in incremental costs, equating to a cost per QALY gained of $47 053. The cost per QALY gained was $44 531 in patients with NYHA class II heart failure and $58 194 in those with class III or IV heart failure.

Results of Sensitivity Analysis: Sacubitril–valsartan treatment was most sensitive to the duration of improved outcomes, with a cost per QALY gained of $120 623 if the duration was limited to the length of the trial (median, 27 months). No variations in other parameters caused the cost to exceed $100 000 per QALY gained.

Limitation: The benefit of sacubitril–valsartan is based on a single clinical trial.

Conclusion: Treatment with sacubitril–valsartan provides reasonable value in reducing cardiovascular mortality and morbidity in patients with NYHA class II to IV heart failure.

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For author affiliations, see end of text.
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Heart failure continues to cause substantial morbidity despite therapeutic advances over the past 3 decades (1). One of the cornerstones of therapy for heart failure with reduced ejection fraction is treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB) to inhibit the renin–angiotensin–aldosterone system, a neurohormonal system that plays a large role in disease progression (2, 3). The natriuretic peptide system is a distinct neurohormonal system that induces positive hemodynamic effects in patients with heart failure. Sacubitril–valsartan (Entresto [Novartis]) is a novel medication consisting of the ARB valsartan and sacubitril, a neprilysin inhibitor that decreases the degradation of natriuretic peptides.

The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial was a randomized, double-blind trial that compared twice-daily treatment with sacubitril–valsartan (200 mg) or enalapril (10 mg) in patients with chronic heart failure and reduced ejection fraction who were tolerating therapy with an ACEI or an ARB (4). It included a sequential run-in period before randomization, during which 10.5% of enrolled patients dropped out during the enalapril phase followed by 10.4% in the sacubitril–valsartan phase. The trial randomly assigned 8442 patients and was stopped after a median follow-up of 27 months due to an overwhelming survival benefit. The study found that treatment with sacubitril–valsartan reduced cardiovascular mortality, decreased hospitalizations and emergency department (ED) visits for heart failure, and improved quality of life compared with enalapril therapy (4, 5). However, at $12.50 per day, sacubitril–valsartan represents a substantial price increase compared with generic ACEIs that can cost less than 10 cents per day (6).

We performed an independent analysis of the cost-effectiveness of sacubitril–valsartan compared with usual care in a cohort of patients with New York Heart Association (NYHA) class II to IV heart failure based on the PARADIGM-HF trial population, as well as in subgroups defined by NYHA class.

See also:

Editorial comment 735

Web-Only

Supplement

METHODS

Decision Model

We developed a Markov model to evaluate the cost-effectiveness of sacubitril–valsartan compared with lisinopril in patients at a mean age of 64 years, NYHA class II to IV heart failure, and reduced ejection fraction (<0.40), with a subgroup composition based on that of the PARADIGM-HF trial (72.9% with class II heart failure, 26.2% with class III, and 0.9% with class IV) (4, 7). We excluded patients with class I heart failure (4.7% of the trial population), who were unintentionally enrolled because they were more ill during screening and improved during the run-in phase; we included these patients in a sensitivity analysis (4, 7). We analyzed cost-effectiveness in the subgroups of patients with class II or class III/IV heart failure.

We modeled a cohort of patients based on the PARADIGM-HF trial, which excluded patients with systolic blood pressure less than 95 to 100 mm Hg, chronic kidney disease (glomerular filtration rate <30 mL/min/1.73 m^2), or inability to tolerate therapy during the run-in phase (4). Patients initially received sacubitril–valsartan, 200 mg twice daily, or lisinopril, 20 mg daily (the target dose for heart failure). We modeled lisinopril instead of enalapril (the comparator in PARADIGM-HF) because it is less expensive, is more widely used, and has demonstrated functionally equivalent benefits compared with enalapril (6, 8, 9). In the model, patients incurred a monthly risk for heart failure hospitalization, non–heart failure hospitalization, ED visit for heart failure, treatment intolerance, and cardiovascular or noncardiovascular death (**Appendix Figure 1**, available at www.annals.org). In addition, those with severe angioedema experienced a hospitalization. Patients with treatment intolerance during receipt of sacubitril–valsartan were switched to lisinopril, and those with intolerance while receiving lisinopril were switched to the ARB losartan (100 mg/d). We used losartan as the alternative ARB therapy because it has effects similar to those of valsartan but lower cost (6, 8). We assumed that no patients would have intolerance of losartan or would discontinue its use.

The model followed patients over their lifetime with a monthly time cycle. We used a series of willingness-to-pay thresholds based on the cost-effectiveness guidelines of the American Heart Association and the World Health Organization, with less than $50 000 per quality-adjusted life-year (QALY) (approximately the U.S. gross domestic product per capita) considered very cost-effective, $50 000 to $100 000 per QALY representing intermediate value, and greater than $150 000 per QALY (approximately 3 times the U.S. gross domestic product per capita) considered not cost-effective (10, 11). All costs and effects were discounted at 3% annually (12). We used a societal perspective, with inclusion of all health care costs regardless of payer, and adhered to best practices (12, 13).

Event Probabilities

Event probabilities, excluding therapy intolerance, were assumed to be the same in patients receiving lisinopril and those receiving losartan, given the absence of evidence for differences in effectiveness (14). We estimated event probabilities for the lisinopril and losartan groups from the event rates for the enalapril group in the PARADIGM-HF trial (**Table 1**) (4–7, 15–20). Rates were adjusted to account for exclusion of the NYHA class I patients by using subgroup-specific estimates of events and follow-up. Alternative estimates of follow-up were tested in sensitivity analyses (see the **Supplement**, available at www.annals.org, for details). We adjusted cardiovascular and noncardiovascular mortality to increase with age and calibrated to mortality rates over the trial duration (21, 22).

The probabilities of cardiovascular death, heart failure hospitalization, and ED visits for patients receiving sacubitril–valsartan were based on the event rate in the lisinopril group and calculated rate ratios between groups. The trial's subgroup-specific hazard ratio (HR) was used for cardiovascular death (see the **Supplement** for details).

Non–heart failure hospitalization and noncardiovascular mortality probabilities for all patients were based on the trial event rates in both groups combined. The probabilities of treatment intolerance and severe angioedema were based on the rates from each group of the trial. We assumed that losartan therapy had no associated intolerance or angioedema.

Costs

Costs of all 3 treatments were estimated using wholesale acquisition costs from the *Red Book* (6). The wholesale acquisition cost is the manufacturer's national list price, subject to both discounts and dispensing premiums (23). The range of prices tested in deterministic sensitivity analyses was based on the minimum and maximum observed wholesale acquisition prices of a package of 90 pills for both lisinopril and losartan (**Table 2**).

For sacubitril–valsartan, the range was set to ±50% of the base case ($12.50 per day) due to the lack of variation in listed wholesale acquisition cost and the uncertainty about discounts and markups. We also tested estimates for specific payer groups whose average price varies (see the **Supplement** for details) (23).

The cost of heart failure hospitalization was derived from the Agency for Healthcare Research and Quality's National Inpatient Sample along with 2015 Medicare professional fees (17, 20). The costs of medication intolerance and severe angioedema were set to the Medicare reimbursements for a primary care appointment (17) and an anaphylaxis hospitalization (24), respectively. Additional health care costs were adjusted for age and NYHA class (25). Further details are provided in the **Supplement**.

Utilities

The baseline utility was based on the average EuroQol-5D baseline measurement for the enalapril group in the PARADIGM-HF trial (18). The incremental utility of patients receiving sacubitril–valsartan was based on the average least-squares mean of the difference between the changes from baseline in the 2

Table 1. Selected Model Inputs

Input Parameter	Point Estimate (Range)	Reference
Monthly event probabilities, %*		
Lisinopril		
Heart failure hospitalization	0.99 (0.75 to 1.23)	4, 5, 7†‡
Cardiovascular mortality§	0.61 (0.43 to 0.80)	4, 7, 15†‡
Therapy intolerance	0.51 (0.47 to 0.56)	4, 7
Severe angioedema‖	0.001 (0 to 0.003)	4, 7
Sacubitril–valsartan		
Therapy intolerance	0.43 (0.39 to 0.48)	4, 7
Severe angioedema‖	0.003 (0 to 0.006)	4, 7
Rate ratios¶		
Heart failure hospitalization with sacubitril–valsartan	0.77 (0.70 to 0.84)	4, 5, 7‡
Cardiovascular mortality with sacubitril–valsartan	0.77 (0.69 to 0.86)	4, 7, 15‡
Monthly costs, *2015 U.S. dollars*		
Sacubitril–valsartan	380.21 (190.11 to 570.32)	6
Lisinopril	1.87 (0.73 to 3.01)	6
Losartan	6.93 (2.87 to 10.99)	6
Heart failure hospitalization	11 829 (11 541 to 12 117)**	17, 20
Utilities		
Baseline utility	0.822 (0.706 to 0.938)	18
Utility increment for sacubitril–valsartan	0.009 (0.005 to 0.013)	18, 19
Heart failure hospitalization and non–heart failure hospitalization	−0.0066†† (0 to −0.0135)	16

NYHA = New York Heart Association.
* Identical with lisinopril and losartan therapy except for therapy intolerance and severe angioedema. We assumed no therapy intolerance or severe angioedema with losartan therapy.
† The baseline event rates in the model were calibrated to the rate seen in the trial period. See the "Calibration of Baseline Event Rates and Rate Ratios" section of the Supplement.
‡ Event probabilities and rate ratios of the cohort were adjusted to exclude patients with NYHA class I heart failure. See the "Estimating Events by NYHA Class" and "Estimating Follow-up by NYHA Class" sections of the Supplement.
§ Increased by 2.58% per year to adjust for the lifetime horizon and the effect of aging (see the Supplement).
‖ Angioedema requiring hospitalization.
¶ For sacubitril–valsartan versus lisinopril or losartan. Monthly probabilities of cardiovascular mortality and heart failure hospitalization in the sacubitril–valsartan group were based on the rates in the lisinopril group and the rate ratios. The point estimate and 95% CI of the rate ratio for heart failure hospitalization were estimated from reported events. The trial's reported hazard ratio and 95% CI were used for cardiovascular mortality. Ranges were defined as the 95% CIs. Both ratios were adjusted to exclude patients with NYHA class I heart failure. See the "Efficacy of Sacubitril–Valsartan" section of the Supplement.
** In 1- and 2-way sensitivity analyses, we tested the average cost of heart failure hospitalization in high- and low-cost settings. In the probabilistic sensitivity analysis, the distribution was based on the 95% CI of the national mean cost, which is shown here.
†† 3 days.

groups (18, 19). Disutilities were applied for heart failure hospitalization and non–heart failure hospitalization, which were approximately equivalent to 3 days (16). In an alternative scenario analysis, we modeled long-term disutility secondary to heart failure hospitalizations (26). Additional disutilities are described in the Supplement.

Additional Sensitivity Analysis

We evaluated the uncertainty of all parameters using 1-way sensitivity analyses in the entire cohort along with NYHA subgroups. We also performed 2-way sensitivity analyses on potentially correlated variables, including baseline event probabilities and effectiveness of sacubitril–valsartan.

We conducted 2 additional scenario analyses. First, we modeled treatment initiation and initial intolerance based on data from the run-in period of PARADIGM-HF. The cost of starting therapy was assumed to be equivalent to a clinic visit and 1 month of therapy. Second, in an exploratory analysis, we determined the necessary reduction in cardiovascular mortality to achieve given value thresholds ($50 000 and $100 000 per QALY) in the context of varied cardiovascular mortality rates.

We performed probabilistic sensitivity analyses of the cost-effectiveness estimates to further explore model uncertainty. Distributions were developed for each parameter (see the Supplement for details). We performed 10 000 simulations while sampling all input parameters across their distributions simultaneously.

Role of the Funding Source

The U.S. Department of Veterans Affairs had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication. The Institute for Clinical and Economic Review helped to design the study and analyze results and suggested edits to the final manuscript.

RESULTS

On a discounted basis, our model predicted an average of 6.98 years of survival and 0.83 heart failure hospitalization in the lisinopril group (Table 2). In the sacubitril–valsartan group, it predicted an average of 7.67 years of survival with 0.75 heart failure hospitalization. The lisinopril group had an average of 5.71 QALYs and lifetime costs of $131 581. The sacubitril–valsartan group had an additional 0.62 QALY and $29 203 in

Table 2. Health and Economic Outcomes of Sacubitril–Valsartan Versus Lisinopril Therapy

Group, by NYHA Class	Heart Failure Hospitalizations, *n*	Survival, *y*	QALYs	Cost, $	Cost per Life-Year, $	Incremental Cost-Effectiveness Ratio, *$/QALY*
II–IV						
Lisinopril	0.83	6.98	5.71	131 581	–	–
Sacubitril–valsartan	0.75	7.67	6.33	160 785	42 397	47 053
II						
Lisinopril	0.86	7.39	6.23	132 367	–	–
Sacubitril–valsartan	0.71	8.10	6.89	161 860	41 300	44 531
III/IV						
Lisinopril	0.77	6.04	4.53	129 908	–	–
Sacubitril–valsartan	0.87	6.62	5.01	158 136	48 610	58 194

NYHA = New York Heart Association; QALY = quality-adjusted life-year.

costs; this included an increase of $26 275 in outpatient medication costs and a savings of $967 from reduction in heart failure hospitalizations and ED visits. The cost per QALY gained with sacubitril–valsartan was $47 053.

Subgroup Analysis

In patients with NYHA class II heart failure, sacubitril–valsartan treatment was associated with an increase of 0.66 QALY and $29 494 in costs, with a cost per QALY gained of $44 531. For those with class III or IV heart failure, it was associated with an additional 0.49 QALY and $28 228 in costs, with a cost per QALY gained of $58 194.

In NYHA class I patients, the risk for cardiovascular death was greater in the sacubitril–valsartan group. It was associated with a decrease in average survival of 0.84 year or 0.57 QALY and a cost increase of $21 029.

Sensitivity Analysis

Treatment Efficacy

We performed 1-way sensitivity analyses on all input parameters (Figure 1). The model was most sensitive to the duration of effectiveness of the treatment. If the treatment was effective only for the median duration of follow-up (27 months), with no subsequent reduction in event risks or improvement in quality of life but continued costs and therapy intolerance, the cost per QALY increased to $120 623. The cost per QALY was less than $100 000 if the treatment was effective for at least 36 months.

When the HR for cardiovascular mortality with sacubitril–valsartan was varied from 0.86 to 0.69 (the estimated 95% confidence bounds), the cost-effectiveness of therapy ranged from $67 626 to $37 939 per QALY gained. In patients with NYHA class III or IV heart failure, the cost per QALY ranged from $253 974 (at an HR of 0.98) to $39 263 (at an HR of 0.66). Changes to the effectiveness in reducing heart failure hospitalizations or ED visits or varying the change in quality of life had much smaller effects on the cost-effectiveness of the therapy (Supplement).

Cost of Treatment

The daily cost of sacubitril–valsartan was set to $12.50 in the base case. The cost of the treatment would increase above $50 000 per QALY with a 6.9% increase in price (to $13.36). The drug price would have to more than double (to $28.01) for the treatment to cost more than $100 000 per QALY. However, in the subgroup of patients with NYHA class III or IV heart failure (in whom sacubitril–valsartan was less effective), the daily cost would need to be less than $10.39 for the treatment to cost less than $50 000 per QALY and greater than $23.27 for the treatment to cost more than $100 000 per QALY. Differences in price between payers also affected the cost-effectiveness (Figure 2).

The cost per QALY gained did not change substantially with changes to the cost of heart failure hospitalizations, ED visits not requiring hospitalization, treatment intolerance costs, or the cost of angioedema hospitalizations (Supplement).

Utilities

The baseline utility of 0.822 had a 95% CI of 0.706 to 0.938. Varying the baseline utility across this range led to costs per QALY gained of $54 012 to $41 682, respectively. In patients with NYHA class III or IV heart failure, the baseline utility of 0.754 had a 95% CI of 0.648 to 0.860; with these lower and upper estimates, the cost per QALY ranged between $66 674 and $51 628, respectively. The effect of varying baseline utility was less substantial in class II patients.

In an alternative scenario analysis in which we incorporated long-term disutility secondary to heart failure hospitalizations, the treatment had a cost per QALY gained of $48 408. Adjusting the disutilities of adverse events did not substantially change the cost per QALY (Supplement).

Heart Failure Morbidity

The cost of the treatment per QALY gained increased with lower baseline risk for cardiovascular death and heart failure hospitalization but did not exceed $100 000 in 1- or 2-way sensitivity analyses assuming unchanged treatment effect (Supplement). With decreased monthly probabilities of cardiovascular death (0.43%) and heart failure hospitalization (0.75%) and decreased treatment benefit (the lower-limit effect

on cardiovascular death, heart failure hospitalization, and improvement in quality of life with sacubitril–valsartan), the cost per QALY gained would be $85 546. In an exploratory threshold analysis, with cardiovascular mortality reduced to lead to an average survival of 9 years in the lisinopril group, the reduction in cardiovascular mortality with sacubitril–valsartan would need to be 29% for the treatment to cost less than $50 000 per QALY and 10% for it to cost less than $100 000 per QALY (Appendix Figure 2, available at www.annals.org).

Varying the age at treatment initiation between 54 and 74 years (with subsequent changes to baseline mortality and health care costs) did not affect the cost-effectiveness substantially when we assumed unchanged treatment benefit (Supplement).

A cohort of patients with NYHA class II heart failure may unintentionally include class I patients due to misclassification. If the risk for misclassification matched the relative patient proportions in the PARADIGM-HF trial, nearly 7% of patients in a class II cohort would actually have class I disease. Although this would only increase the cost per QALY in this combined cohort to $51 176, misclassified class I patients would experience a decrease in average survival with sacubitril–valsartan therapy.

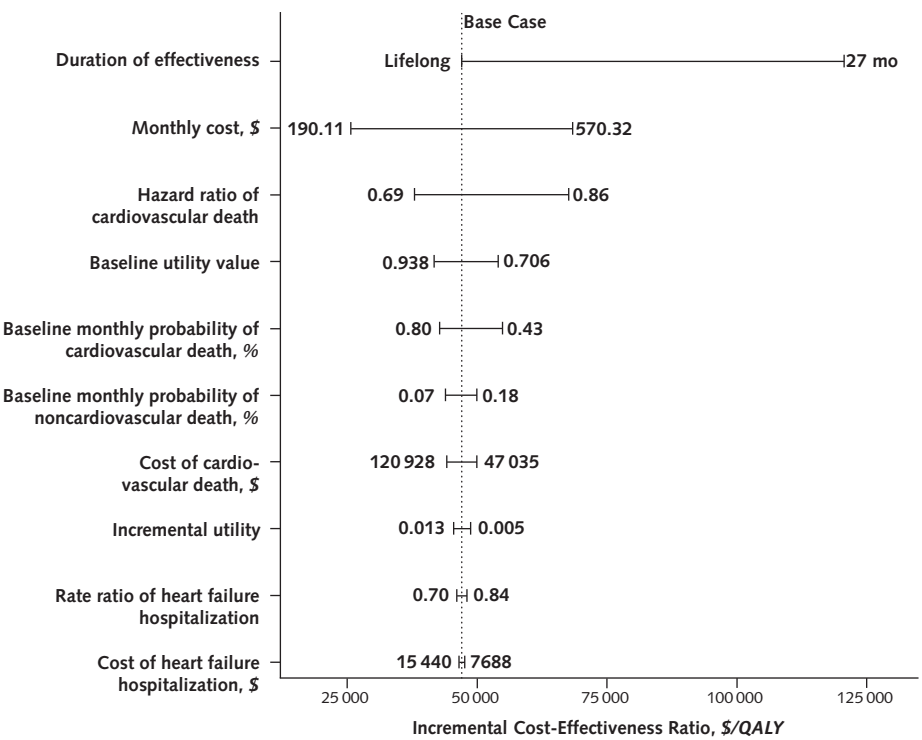
Therapy Tolerance

In the base case, we used angioedema probability and treatment intolerance based on the randomized data. If sacubitril–valsartan carried an increased risk for angioedema requiring hospitalization (0.006% monthly risk) and an increase in the cost ($3112) and disutility (−0.009) of an angioedema event, the cost per QALY gained would increase only slightly, to $47 064. Similar variation in therapy intolerance parameters also only marginally affected the cost-effectiveness (Supplement). In an alternative scenario analysis in which we modeled initiation of the therapy and included the run-in data, the incremental QALYs decreased to 0.59 and the incremental cost decreased to $27 915. The cost per QALY gained was $47 674.

Probabilistic Sensitivity Analysis

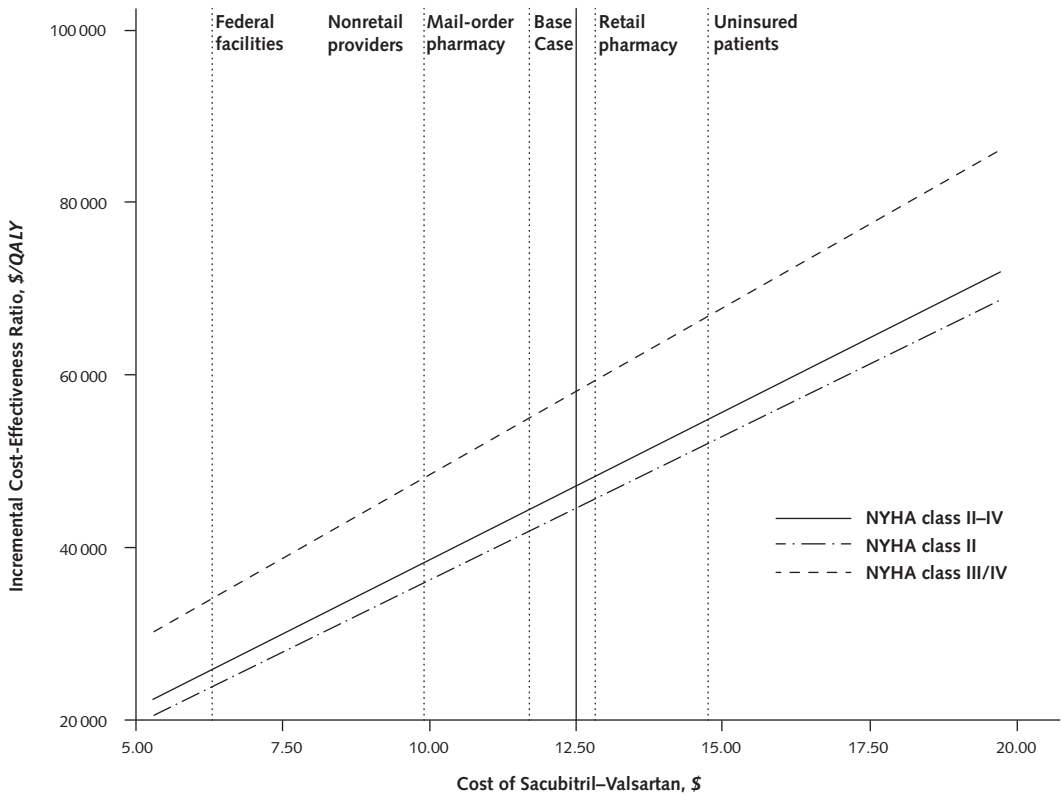
We performed 10 000 simulations while simultaneously varying all input parameters in the model. In the entire cohort, the cost per QALY gained was less than $50 000 in 57.5% of the simulations and less than $100 000 in 99.4% of the simulations (Figure 3). Additional sensitivity analyses are included in the Supplement.

Figure 1. One-way sensitivity analysis of the parameters that led to the largest change in the cost per QALY gained with sacubitril–valsartan (incremental cost-effectiveness ratio) when tested across the range of possible values.



The parameters are listed on the *y*-axis in descending order of the difference between the maximum and minimum incremental cost-effectiveness ratios. The upper and lower limits of each parameter are listed to the left and right of the bars. The dotted vertical line is the incremental cost-effectiveness ratio in the base-case analysis. QALY = quality-adjusted life-year.

Figure 2. Sensitivity analysis of the price of sacubitril–valsartan.



The figure shows the cost per QALY gained of sacubitril–valsartan, with variation in its price in the entire cohort of patients with NYHA class II to IV heart failure and both subgroups: class II and class III/IV. The solid vertical line represents the daily cost of sacubitril–valsartan in the base case ($12.50). Dotted vertical lines indicate price estimates for alternate payers: $6.30 for federal facilities, $9.90 for nonretail providers (hospitals or HMOs), $11.70 for mail-order pharmacies, $12.82 for retail pharmacies with pharmacy benefits managers (with manufacturer rebates excluded), and $14.74 for uninsured patients at a retail pharmacy. Details on the calculation of these price estimates are provided in the "Treatment Costs" section of the **Supplement**. NYHA = New York Heart Association; QALY = quality-adjusted life-year.

DISCUSSION

Our analysis indicates that sacubitril–valsartan is a cost-effective therapy for patients with NYHA class II to IV heart failure and reduced ejection fraction. We found a cost of $47 053 per QALY gained in a cohort derived from the PARADIGM-HF trial. The evidence of efficacy is based on a single trial, but our findings were robust in sensitivity analyses across model parameters. The improved outcomes with sacubitril–valsartan would need to be sustained for at least 36 months for the cost per QALY to remain less than $100 000.

Our model projected undiscounted survival of 8.4 and 9.4 years in the control and sacubitril–valsartan groups, respectively, compared with 10.2 and 11.5 years (difference, 1.3 years [95% CI, 0.2 to 2.4 years]) in the trialists' modeled survival analysis (27). Their analysis estimated long-term mortality based on observed trial mortality as a function of age and treatment group. This was under the assumption that the long-term increase in mortality was the same as the observed difference in short-term mortality between trial patients of different ages, discounting effects of patient selection and exclusion criteria (28). Our analysis explicitly increased mortality as the cohort aged, which may account for the differences.

The PARADIGM-HF findings have been heralded as a breakthrough for heart failure therapy, but treatment adoption has been slow (29, 30). Concerns have centered on the cost of therapy, potentially overstated efficacy, therapy tolerance during the run-in period, and the generalizability of the trial (28, 31–34). Our analysis evaluated the effects of the first 3 of these concerns on the value of sacubitril–valsartan.

Sacubitril–valsartan treatment would cost less than $100 000 per QALY unless the price was more than 2-fold higher than the wholesale acquisition cost of $12.50 per day. At the estimated retail pharmacy price, sacubitril–valsartan provided intermediate value. However, many providers will likely obtain the drug at a price below the wholesale acquisition cost, with a subsequent cost per QALY less than $50 000.

Concerns about overstatement of the effectiveness of the treatment versus usual care are due to the reliance on a single clinical trial (which was stopped prematurely), its use of an ACEI comparison group, and the questionable bioequivalence of renin–angiotensin–aldosterone system inhibition in the 2 groups (31–34). However, PARADIGM-HF used a mean enalapril dose of 18.9 mg/d, which was greater than the dose used in 2 major trials that demonstrated the survival benefit of

ACEI therapy for heart failure (35, 36). Furthermore, there is limited evidence of dose-responsiveness between moderate and high doses of ACEIs or a comparative benefit of ARBs, suggesting that the comparator group was appropriate (14, 37, 38). Therefore, we did not directly compare sacubitril–valsartan therapy with primary ARB therapy or estimate the efficacy of alternate doses. In addition, in a trial-based population, sacubitril–valsartan still provided intermediate value with a substantial reduction in estimated effectiveness.

Finally, there are concerns about initial therapy tolerance secondary to a high dropout rate during the run-in phase due to adverse events. In a scenario analysis, we showed that including therapy initiation data decreased the population effect of the treatment because many potential patients would be unable to tolerate therapy. However, it did not affect the cost-effectiveness substantially because the costs of initiating treatment and managing intolerance events are marginal compared with those of long-term therapy. Our analysis may have underestimated the effect of therapy intolerance in patients who are naive to ACEI or ARB therapy, in whom starting treatment with an ACEI alone can cause hypotension (30).

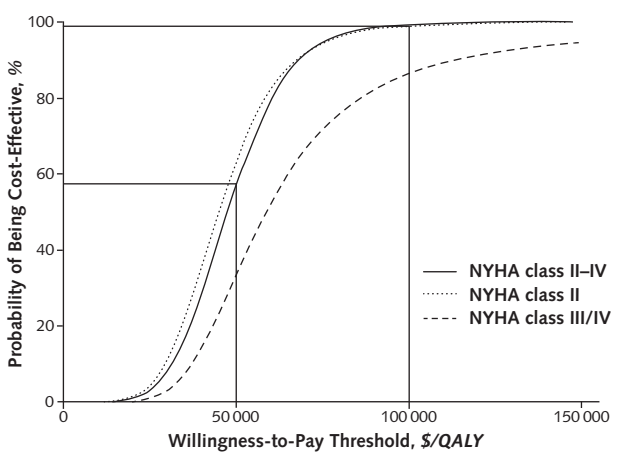
Our results suggest that the incremental health benefits—largely driven by an increased average survival of 0.69 year due to decreased cardiovascular mortality—may justify the increase in treatment costs, depending on the societal willingness to pay. However, in selecting patients for treatment, remembering the trial's exclusion criteria and the composition of the trial population will be important. Fewer than 1% of trial participants (and <3% of those in our NYHA class III and IV subgroup) had class IV heart failure. The effectiveness and value in these patients remain unclear. In addition, misclassification and unintentional treatment of class I patients could cause clinical harm while increasing lifetime costs.

Two previous cost-effectiveness analyses of sacubitril–valsartan therapy, by Gaziano and colleagues (39) and King and associates (40), found similar incremental cost-effectiveness ratios ($45 017 and $50 959 per QALY, respectively). These analyses modeled the treatment effect across all patients in the PARADIGM-HF trial, whereas we estimated the treatment effect by NYHA class, adjusted for the exclusion of class I patients (for whom therapy is not approved), and included NYHA class subgroup analyses. The analysis by King and associates found greater uncertainty in sensitivity analyses than our analysis and that of Gaziano and colleagues. This discrepancy may be due to differences in modeling cardiovascular mortality and heart failure hospitalization. We used event rates from the enalapril group in PARADIGM-HF and the rate ratio between groups, whereas their analysis modeled the event rates in each group independently, which potentially overestimated the uncertainty in the treatment effect. On the basis of their sensitivity analysis of cardiovascular mortality, they suggested the value may be greater in higher-risk patients. In contrast, we found that treatment value is greater in patients with class II heart failure than in those with class III or IV disease because treatment leads to a larger increase in survival. This suggests that we should prioritize therapy in class II patients rather than class III or IV patients, which contradicts previous recommendations to prioritize patients with worse disease (40, 41). Our findings are supported by a secondary analysis of PARADIGM-HF that showed greater treatment effect in clinically stable patients (class II disease without a previous heart failure hospitalization [42]).

Our model was used to analyze the cost-effectiveness and budgetary impact of sacubitril–valsartan for a public meeting of the California Technology Assessment Forum (18, 41). This article adds to the previous reports by focusing on the uncertainty of the value of sacubitril–valsartan from the clinician's perspective. It includes updated model parameters, probabilistic sensitivity analyses, additional subgroup analyses, and analyses that specifically evaluate clinical concerns about therapy adoption.

Our analysis has several limitations. First, treatment efficacy was derived from a single trial with limited subgroup data available. Given a lack of patient-level data, we estimated follow-up and event rates by NYHA class and tested alternative estimates in sensitivity analyses. Second, there are no data on long-term treatment effectiveness. The effectiveness must be sustained for at least 9 months after the trial period for the treatment to cost less than $100 000 per QALY. Although longer-term experience with neurohormonal modulation therapy with β-blockers and ACEIs suggests continued effectiveness, postmarketing surveillance should monitor the long-term treatment effect (43, 44). Third, we did not model transition between NYHA classes due to lim-

Figure 3. Probabilistic sensitivity analysis: cost-effectiveness acceptability curves, by NYHA class.



The curves show the proportion of the 10 000 simulations at which sacubitril–valsartan was cost-effective at a given threshold for the entire cohort of patients with NYHA class II to IV heart failure and both subgroups: class II and class III/IV. The analyses were performed by independently sampling each model input parameter from its distribution for each simulation. NYHA = New York Heart Association; QALY = quality-adjusted life-year.

ited data, but we did include changes in quality of life. Fourth, drug transaction costs were not available, so we estimated costs based on wholesale acquisition costs and included threshold analyses. Finally, we did not evaluate potential concerns about neurocognitive function with neprilysin inhibition, which is being studied in a follow-up trial (45).

In conclusion, this analysis showed that treatment with sacubitril–valsartan seems to be a cost-effective mechanism to reduce the cardiovascular mortality and morbidity associated with chronic heart failure in patients with NYHA class II to IV heart failure and reduced ejection fraction. The value of the treatment was highest in class II patients, who had greater treatment benefit in the PARADIGM-HF trial. These results were robust to sensitivity analyses that addressed concerns about treatment and support the adoption of sacubitril–valsartan therapy.

From Veterans Affairs Palo Alto Health Care System, Palo Alto, California; Center for Health Policy and Center for Primary Care and Outcomes Research, Stanford University, and Stanford University School of Medicine, Stanford, California; and Institute for Clinical and Economic Review, Boston, Massachusetts.

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Reproducible Research Statement: *Study protocol:* See the Supplement. *Statistical code:* The model is available from Dr. Sandhu (e-mail, ats114@stanford.edu). *Data set:* No additional data are available.

Requests for Single Reprints: Alexander T. Sandhu, MD, MS, Stanford University Center for Primary Care and Outcomes Research, 117 Encina Commons, Stanford, CA 94305; e-mail, ats114@stanford.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Sandhu: Stanford University Center for Primary Care and Outcomes Research, 117 Encina Commons, Stanford, CA 94305.
Drs. Ollendorf, Chapman, and Pearson: Institute for Clinical and Economic Review, Two Liberty Square, 9th Floor, Boston, MA 02109.
Dr. Heidenreich: Palo Alto VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

Author Contributions: Conception and design: A.T. Sandhu, D.A. Ollendorf, S.D. Pearson, P.A. Heidenreich.
Analysis and interpretation of the data: A.T. Sandhu, D.A. Ollendorf, S.D. Pearson, P.A. Heidenreich.
Drafting of the article: A.T. Sandhu.
Critical revision of the article for important intellectual content: A.T. Sandhu, D.A. Ollendorf, R.H. Chapman, S.D. Pearson, P.A. Heidenreich.
Final approval of the article: A.T. Sandhu, D.A. Ollendorf, R.H. Chapman, S.D. Pearson, P.A. Heidenreich.
Provision of study materials or patients: A.T. Sandhu.
Statistical expertise: A.T. Sandhu.
Obtaining of funding: D.A. Ollendorf, S.D. Pearson.
Administrative, technical, or logistic support: A.T. Sandhu, D.A. Ollendorf, R.H. Chapman.
Collection and assembly of data: A.T. Sandhu.

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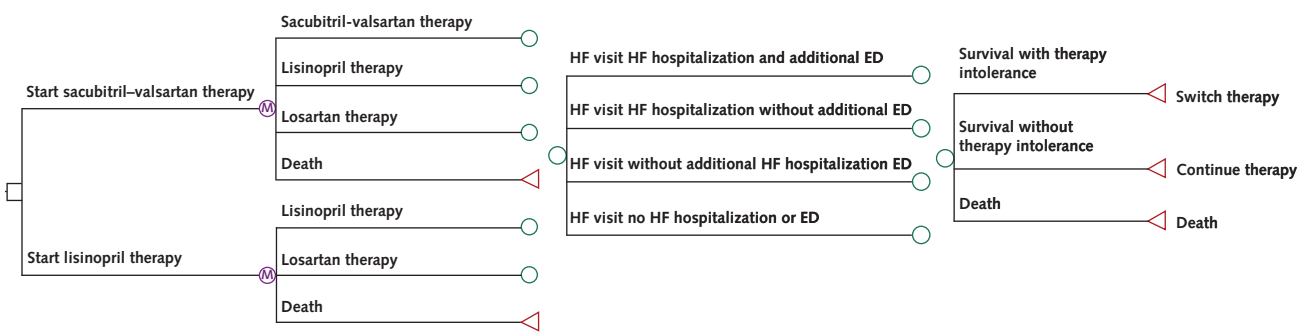
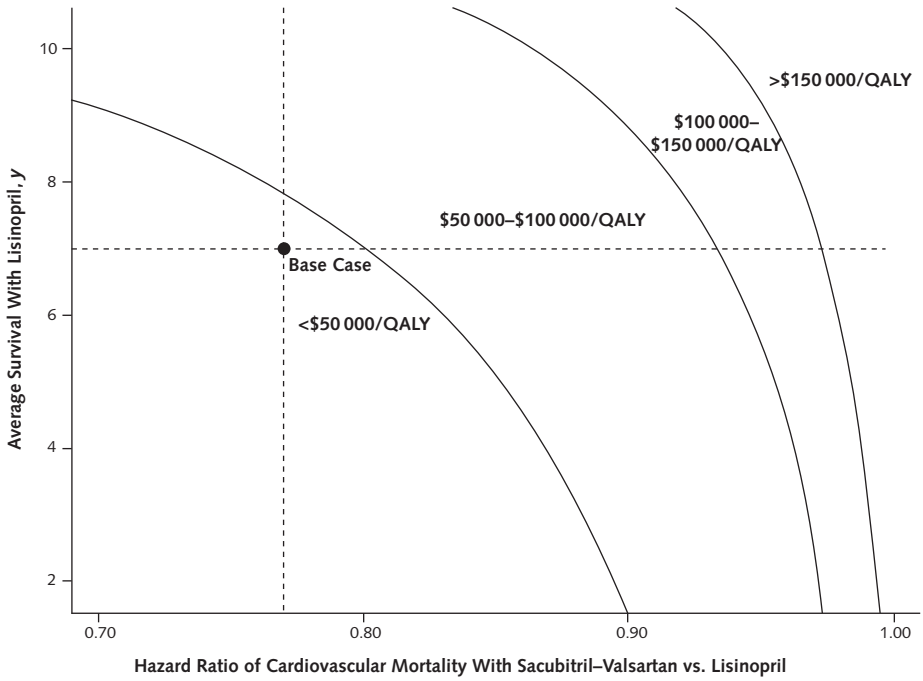
Appendix Figure 1. Model schema.



The square is the treatment decision to start therapy with sacubitril–valsartan or lisinopril (angiotensin-converting enzyme inhibitor). The M's represent monthly models during which surviving patients are at risk for multiple events at chance nodes (*circles*): HF hospitalization, ED visits for HF without subsequent hospitalization, non-HF hospitalization (not shown), and death. Patients are also at risk for therapy intolerance, including angioedema, and death. The triangles signify the end of a monthly cycle and the initial state of the subsequent cycle. Surviving patients receiving sacubitril–valsartan who have therapy intolerance switch to lisinopril the following month. Those receiving lisinopril with intolerance switch to losartan. ED = emergency department; HF = heart failure.

Appendix Figure 2. Two-way sensitivity analysis of baseline risk for cardiovascular death and hazard ratio of cardiovascular death with sacubitril–valsartan relative to lisinopril.



The baseline probability of cardiovascular death was varied, with the resulting average survival with lisinopril therapy displayed on the *y*-axis. No change in the noncardiovascular mortality rate was assumed. The *x*-axis shows the hazard ratio of cardiovascular death during receipt of sacubitril–valsartan therapy relative to lisinopril therapy. The 3 curved lines represent the incremental cost-effectiveness ratios (cost per QALY gained) with sacubitril–valsartan at $50 000, $100 000, and $150 000; the incremental cost-effectiveness ratio between the lines is displayed. The dashed vertical and horizontal lines represent the hazard ratio and average survival in the base case. QALY = quality-adjusted life-year.