Cost-Effectiveness of Sacubitril-Valsartan Combination Therapy Compared With Enalapril for the Treatment of Heart Failure With Reduced Ejection Fraction

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CME Objective for This Article: After reading this article, the reader should be able to discuss: 1) the improvement in outcomes observed with sacubitril-valsartan compared to enalapril in the PARADIGM-HF trial; 2) the estimated cost of an initial heart failure hospitalization; and 3) understand how costs to payers per quality-adjusted-life-year gained may change with duration of therapy of sacubitril-valsartan.

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ABSTRACT

OBJECTIVES The objective of this study was to determine the cost-effectiveness and cost per quality-adjusted life year (QALY) gained of sacubitril-valsartan relative to enalapril for treatment of heart failure with reduced ejection fraction (HFrEF).

BACKGROUND Compared with enalapril, combination angiotensin receptor-neprilysin inhibition (ARNI), as is found in sacubitril-valsartan, reduces cardiovascular death and heart failure hospitalization rates in patients with HFrEF.

METHODS Using a Markov model, costs, effects, and cost-effectiveness were estimated for sacubitril-valsartan and enalapril therapies for the treatment of HFrEF. Patients were 60 years of age at model entry and were modeled over a lifetime (40 years) from a third-party payer perspective. Clinical probabilities were derived predominantly from PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). All costs and effects were discounted at a 3% rate annually and are presented in 2015 U.S. dollars.

RESULTS In the base case, sacubitril-valsartan, compared with enalapril, was more costly ($60,391 vs. $21,758) and more effective (6.49 vs. 5.74 QALYs) over a lifetime. The cost-effectiveness of sacubitril-valsartan was highly dependent on duration of treatment, ranging from $249,411 per QALY at 3 years to $50,959 per QALY gained over a lifetime.

CONCLUSIONS Sacubitril-valsartan may be a cost-effective treatment option depending on the willingness-to-pay threshold. Future investigations should incorporate real-world evidence with sacubitril-valsartan to further inform decision making. (J Am Coll Cardiol HF 2016;4:392–402) © 2016 by the American College of Cardiology Foundation.

Between the late 1980s and early 2000s, the development and use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), beta-blockers (BBs), and aldosterone receptor antagonists have decreased morbidity and mortality and improved quality of life among patients with heart failure (HF) and a reduced ejection fraction (HFrEF) (1–9). The most recent pharmacotherapy to demonstrate a mortality benefit in HFrEF is the dual-acting angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan. In July 2015, sacubitril-valsartan was approved by the U.S. Food and Drug Administration for use in patients with New York Heart Association (NYHA) functional class II to IV HFrEF based on the results of the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (10). Sacubitril-valsartan treatment resulted in a significant 20% reduction in the primary outcome of a composite of death of cardiovascular causes or hospitalization for HF. The approval of sacubitril-valsartan marked the first new medication with a demonstrated mortality benefit in HFrEF in more than 10 years. Because the current cornerstone of HFrEF pharmacotherapy revolves around low-cost generic medications such as ACEIs and BBs, it is unclear how the cost of sacubitril-valsartan ($4,560 per year) will influence its clinical utility (11).

One of several considerations in medical decision making is value (12). Cost-effectiveness analysis (CEA) is one approach to determining medication value by quantifying the benefits and costs of different treatment options. The basic conduct and interpretation of CEs have been described previously (13). With the goal of aiding decision making, we estimated the incremental costs and cost-effectiveness of sacubitril-valsartan relative to ACEIs for the treatment of HFrEF.

METHODS

SIMULATION MODEL DESCRIPTION. We used a Markov model to perform a decision analysis...
comparing 2 treatment strategies for patients with HFrEF: 1) ARNI with sacubitril-valsartan and 2) ACEI with enalapril (Figure 1). Our base case was a hypothetical cohort based on the characteristics observed in the PARADIGM-HF trial (10). The treatment effect, which included cardiovascular mortality and HF hospitalization rates, was derived from the PARADIGM-HF trial, and additional model inputs were derived from published reports (Tables 1-3). We assumed that event rates and associated costs for non-HFrEF-related conditions were similar across both treatments. The health states included in the model were NYHA functional classification I, II, III, and IV and death. Patients accrued quality-adjusted life-years (QALYs) and costs based on events experienced in each health state in the model and were allowed to transition between states once every 3 months. We calculated all-cause and cardiovascular mortality, QALYs, HF hospitalizations and 30-day readmissions, and net costs over 40 years or until death, with the assumption that all patients remained in their treatment group over their lifetime. A third-party payer perspective (private insurance for those <65 years old or Medicare for those ≥65 years old) was used, and thus, only direct costs (e.g., inpatient medical care, prescription drugs) were accounted for in the model. In the base-case scenario, the duration of follow-up was a lifetime. Costs were inflated to 2015 U.S. dollars using the general Consumer Price Index (22). Future costs and QALYs were discounted at a 3% rate annually. The performance of the model was validated by comparing results in the base case to the results observed in PARADIGM-HF for both mortality and HF hospitalizations. Model creation and analyses were performed with TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts).

**MODEL INPUTS. PARADIGM-HF.** Cardiovascular mortality risk. The risk of cardiovascular mortality was derived from the results of the PARADIGM-HF trial (10). During the trial follow-up, 13.3% of patients receiving sacubitril-valsartan, and 16.5% of patients receiving enalapril experienced cardiovascular mortality. In the base case, these were converted to 3-month probabilities, and the probability of dying of cardiovascular causes during each 3-month model cycle was 1.49% in the sacubitril-valsartan group and 1.87% in the enalapril group (Table 1). An assumption of the model is that the cardiovascular mortality rate observed in PARADIGM-HF trial remained constant throughout the model time horizon.

**HF hospitalization risk.** The cumulative rate of HF hospitalizations was lower in the sacubitril-valsartan group than in the enalapril group in PARADIGM-HF (rate ratio: 0.77; 95% confidence interval: 0.67 to 0.89) (15). Careful graphical measurement of the cumulative number of hospitalizations for HF in

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**FIGURE 1 Markov Model Structure**

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Health States</th>
<th>Clinical Events During 3-month cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>sacubitril 93mg / valsartan 103mg BID</td>
<td>NYHA Class I</td>
<td>No event</td>
</tr>
<tr>
<td></td>
<td>NYHA Class II</td>
<td>HF hospitalization</td>
</tr>
<tr>
<td></td>
<td>NYHA Class III</td>
<td>30-day readmission</td>
</tr>
<tr>
<td></td>
<td>NYHA Class IV</td>
<td>No readmission</td>
</tr>
<tr>
<td></td>
<td>Death*</td>
<td>Death*</td>
</tr>
<tr>
<td>enalapril 10mg BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients enter the model and are placed on either sacubitril-valsartan or enalapril. Patients who experience clinical events are transitioned through the health states of New York Heart Association (NYHA) functional class I, II, III, IV, or death once every 3 months. *Death was subgrouped by all-cause or cardiovascular specific causes for model validation. BID = twice a day; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.
the 2 study groups in PARADIGM-HF was used to estimate hospitalization rates. These rates were converted to 3-month probabilities and input into the model. These probabilities were 2.62% and 3.44% for sacubitril-valsartan and enalapril, respectively (Table 1).

Other input sources. Noncardiovascular mortality risk. The age-dependent risk of death that occurred because of noncardiovascular causes was derived from the Centers for Disease Control and Prevention life tables, with major cardiovascular death removed as a cause of death (Table 1) (14). No estimates are available for patients >100 years old. In the model, those patients who survived to 100 years were assumed to die during the next cycle. No differences were observed in noncardiovascular death between groups in PARADIGM-HF (23).

All-cause readmission. A readmission was defined as a hospitalization for any cause that occurred within 30 days of discharge. The probability of experiencing a readmission after an HF hospitalization was 24.65% (16). We used a conservative assumption in the base case of no difference in risk for the sacubitril-valsartan and enalapril groups. A recent post hoc analysis of PARADIGM-HF provides the first evidence that sacubitril-valsartan may be associated with a lower risk of readmission after an HF hospitalization (24). We explored this association in sensitivity analysis by reducing the risks of all-cause readmission by 36% in the sacubitril-valsartan group relative to the enalapril group.

Quality-of-life estimates. NYHA functional classification was used as a marker of health status, and NYHA specific-utility weights were derived from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial (Table 2) (20). A 1-time disutility of –0.1 was applied to the 3-month cycle for any cycle in which an HF hospitalization occurred (17,18,25). Utility weights are a measure of a patient’s preference for their health state and are used as a quality-of-life estimate. These weights are measured between 0 and 1, with 0 reflecting death and 1, perfect health. The utilities are then multiplied by the time in the health state to generate QALYs.

NYHA functional class transitions. Published reports regarding transition probabilities for movement between NYHA functional classes of HF are scarce. For this analysis, we utilized an established transition matrix in CEAs that was derived from the SENIORS study (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) (17-19). We made the conservative assumption that the probability of disease progression between the health states was the same for both treatment groups, because it is unclear how sacubitril-valsartan alters NYHA progression relative to enalapril. We also assumed that transition probabilities were fixed over time. The starting NYHA functional class was based on the distribution of patients from the PARADIGM-HF trial (class I: 4.6%; class II: 70.6%; class III: 24.1%; and class IV: 0.7%). The transition matrix for each 3-month period is provided in Table 4.

Drug costs. Medication costs in the base case were determined by the average wholesale acquisition cost (WAC) listed in the Red Book online database for 20 mg of enalapril and 97 to 103 mg of sacubitril-valsartan.
valsartan (Table 3) (21). The high and low WACs in the Red Book for enalapril were used in sensitivity analysis. Sacubitril-valsartan was varied ±25% because no range exists in the Red Book. The costs of additional HF medications were assumed to be equivalent between groups, because these medications were well balanced between groups in PARADIGM-HF (10). In sensitivity analysis, medication costs were derived from National Average Drug Acquisition Cost data available from the Centers for Medicare and Medicaid Services (26).

Many ACEIs, including enalapril, appear on $4 per 30-day ($0.13 per day) or $10 per 90-day ($0.11 per day) retail prescription drug lists (27). To account for this, we conducted a sensitivity scenario in which enalapril costs were based on $10 for a 3-month supply of medication.

Prices of new medications decrease over time as patents expire and generic versions enter markets; however, this is often not addressed in CEA. Additionally, no clear guidelines exist and there is a lack of expert consensus on how to handle future price changes, which complicated how to incorporate this concept into our model (28). For the base-case evaluation, we made the assumption that medication prices were fixed over time. We then performed a 2-way sensitivity analysis in which we explored both timing of generic medication market entry and the potential cost of a generic ARNI.

Cost of hospitalizations. The average costs for an HF hospitalization or a 30-day all-cause readmission were based on an analysis by Bress et al. (16). Charges in this analysis were converted to costs using the Centers for Medicare and Medicaid cost-to-charge ratio (29). Cost of a readmission was found to be $11,361, and the cost of an initial HF hospitalization was $10,698.

SENSITIVITY ANALYSES. We used 1-way, 2-way, and probabilistic sensitivity analyses (PSAs) to determine the impact of model parameter uncertainty and variability on model outcomes. In 1-way sensitivity analyses (SAs), model inputs were varied 1 at a time across a plausible range of estimates, while all other variables were held constant. This determined the relative impact each variable had on model outcomes. For the base-case evaluation, we conducted a sensitivity analysis to vary model inputs, we also varied model duration from 3 years (median follow-up in PARADIGM-HF was 27 months) to a lifetime. We conducted a PSA allowing all variables to simultaneously vary stochastically. A second-order Monte Carlo simulation was performed (n = 10,000) based on the variable specific distributions. Results of the PSA are presented graphically as scatterplots and cost-effectiveness acceptability curves.

RESULTS

BASE CASE. The discounted costs, benefits, and cost-effectiveness of the 2 treatment strategies over a 40-year time horizon, which was considered a lifetime perspective, are presented in Table 5. Average medication and HF hospitalization costs for patients in the sacubitril-valsartan and enalapril groups were $60,391 and $21,758, respectively. The use of sacubitril-valsartan yielded 6.59 QALYs (9.48 life-years), and enalapril yielded 5.83 QALYs.

<table>
<thead>
<tr>
<th>TABLE 3 Cost Inputs</th>
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<tbody>
<tr>
<td>Input Variable</td>
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<tr>
<td>Medications, 3 months (21)</td>
</tr>
<tr>
<td>Enalapril</td>
</tr>
<tr>
<td>Sacubitril-valsartan</td>
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<tr>
<td>Hospitalizations, per event (16)</td>
</tr>
<tr>
<td>HF hospitalization</td>
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<tr>
<td>30-Day all-cause readmission</td>
</tr>
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Values are in 2015 U.S. dollars.
HF = heart failure.

<table>
<thead>
<tr>
<th>TABLE 4 NYHA Transition Probabilities per 3-Month Cycle</th>
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<tr>
<td>From NYHA</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td>Class IV</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association.

<table>
<thead>
<tr>
<th>TABLE 5 Base-Case Estimates From the Simulation Model</th>
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<tbody>
<tr>
<td>Life years</td>
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<tr>
<td>Incremental life years</td>
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<tr>
<td>QALYs</td>
</tr>
<tr>
<td>Incremental QALYs</td>
</tr>
<tr>
<td>Costs</td>
</tr>
<tr>
<td>Incremental costs</td>
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<tr>
<td>ICER</td>
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</tbody>
</table>

All costs (in U.S. dollars), life years, and QALYs were discounted at a rate of 3% annually.
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
(8.40 life-years) (Table 5). This resulted in an incremental cost-effectiveness ratio (ICER) for sacubitril-valsartan versus enalapril of $50,959 per QALY gained.

Duration of treatment was a major determinant of cost-effectiveness (Figure 2). At 3 years of follow-up, the ICER per QALY gained was around $250,000. This value fell below $100,000 per QALY by year 9.
and approached but never reached $50,000 per QALY over a lifetime. At 10 years (median survival with sacubitril-valsartan), the ICER was $91,424.

**ONE-WAY SENSITIVITY ANALYSIS.** A tornado diagram was used to depict the variables with the largest impact on outcomes (Figure 3). Only those parameters that affected the ICER by more than $1,000 are depicted. The parameters with the largest impact on the model were the cardiovascular death rates associated with the sacubitril-valsartan and enalapril groups. At the high end of cardiovascular death for the sacubitril-valsartan group (22.1% per year) and the low end for the enalapril group (13.8% per year), enalapril became the dominant option (i.e., enalapril cost less and was more effective than sacubitril-valsartan). After risk of cardiovascular death, the cost of sacubitril-valsartan had the most impact on ICER. Variation in other model parameters had minor impact on the model outcomes in deterministic SAs (<±$10,000 per QALY).

**PROBABILISTIC SENSITIVITY ANALYSIS.** The results of the PSA are presented graphically in Figure 4 in a cost-effectiveness scatterplot. Over a lifetime, the incremental costs were slightly lower in the PSA compared with the base case (−$2,609), and no difference was observed in incremental QALYs. The resulting ICER was $47,550 per QALY gained. Sacubitril-valsartan was consistently more expensive (95% of simulations) and more effective (81% of simulations) than enalapril. Sacubitril-valsartan was the dominant treatment option in 3% of simulations compared with 17% of simulations for enalapril. A cost-effectiveness acceptability curve was plotted to demonstrate the proportion of simulations that were considered cost-effective at multiple willingness-to-pay (WTP) values (Online Appendix 1). At a WTP of $50,000 per QALY, sacubitril-valsartan was cost-effective in 57% of the simulations. This number increased to 80% at a WTP of $100,000 per QALY.

**ALTERNATE SCENARIOS. Medication costs.** We examined the impact that alternative medication pricing had on model results (Online Appendix 2). When we used National Average Drug Acquisition...
Cost pricing rather than Red Book pricing (sacubitril-valsartan: $1,095 vs $1,140; enalapril: $43 vs $70), we found minimal impact on the ICER ($49,905 per QALY gained). Similarly, a nominal impact on the ICER was found when we assumed a $10 per 3-month price for generic enalapril ($53,618 per QALY gained).

**30-day readmission.** We explored the assumption that 30-day readmission rates were equivalent between the 2 treatments by reducing the relative risk of experiencing a readmission by 36% in the sacubitril-valsartan group compared with the enalapril group (Online Appendix 2). This approach also had a minimal impact on the results, decreasing the ICER to $49,267 per QALY gained.

**Generically available ARNI.** Finally, we sought to determine the impact of a generic ARNI becoming available in the future on the ICER, which required assumptions regarding the timing and cost of the generic drug. These assumptions were based on expert opinion and were evaluated in a 2-way SA, in which time to availability of the generic drug was varied between 7 and 12 years, and the cost of generic was 10% to 50% of the current cost of the brand-name medication (Online Appendix 3). The lifetime ICER fell below $50,000 per QALY gained in all situations, ranging from $27,382 to $43,808.

**MODEL VALIDATION. Survival.** Microsimulation with tracker variables was utilized to compare the simulation model results with those of PARADIGM-HF. Comparisons of mortality predicted by the model versus that observed in PARADIGM-HF are shown graphically in Figure 5, and Kaplan-Meier curves from the model are provided in Online Appendix 4. Mortality estimates produced by the model compared well with the 1-, 2-, and 3-year mortality rates observed in the PARADIGM-HF trial, as well as with projected lifetime expectancy estimates (10,30). Mean survival in the model for the sacubitril-valsartan and enalapril groups was 12.4 and 10.8 years, respectively. This compares to the mean estimated life expectancy for a 60-year-old patient in PARADIGM-HF, which was 12.4 (sacubitril-valsartan) and 11.2 (enalapril) years (mean difference, 1.1 years; 95% confidence interval: −0.1 to 2.3 years) (30).

**Hospitalizations.** Overall, total number of HF hospitalizations per person were comparable between the simulation model and PARADIGM-HF, with a maximum absolute difference of 1.4 HF hospitalizations per 100 persons at 3 years (Table 6) (15). These results suggest that the model structure and baseline probabilities accurately represent our current best estimates of the comparative effects of sacubitril-valsartan and enalapril on mortality and HF hospitalization rates.

**DISCUSSION**

In this non-industry-sponsored CEA evaluating sacubitril-valsartan combination therapy, we found...
TABLE 6 Comparison of Model Results With the PARADIGM-HF Trial Results on Heart Failure Hospitalization Rates

<table>
<thead>
<tr>
<th>Year</th>
<th>Enalapril</th>
<th>Sacubitril-Valsartan</th>
<th>Decision Model</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.7</td>
<td>10.0</td>
<td>13.2</td>
<td>10.4</td>
</tr>
<tr>
<td>2</td>
<td>24.3</td>
<td>19.1</td>
<td>24.8</td>
<td>19.3</td>
</tr>
<tr>
<td>3</td>
<td>34.6</td>
<td>27.1</td>
<td>35.9</td>
<td>28.5</td>
</tr>
</tbody>
</table>

Outcome was cumulative heart failure hospitalization rates per 100 persons. Results from the PARADIGM-HF trial were graphically estimated from published figures.

PARADIGM-HF – Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

that sacubitril-valsartan therapy costs payers $50,959 per QALY gained compared with enalapril therapy. At the current price, the use of sacubitril-valsartan to reduce HF hospitalizations is unlikely to be cost saving. However, the benefits of increased quantity and quality of life may be cost-effective depending on WTP. In sensitivity analyses, the model results were robust to most assumptions and parameter uncertainty. Cardiovascular death rates and the timing and cost of a generic ARNI medication had the greatest impact on the model results. Overall, our study provides a valuable, quantitative assessment of sacubitril-valsartan to assist decision makers (e.g., third-party payers, prescribers, patients).

The decision to describe an intervention as cost-effective is based on WTP for the outcome of interest. A commonly accepted WTP threshold in the United States is $50,000 per QALY. It has been suggested that this value is too low in the United States and should therefore be thought of as a lower-bound estimate (31). A more appropriate threshold may be $100,000 to $150,000 per QALY, or even higher (31,32). However, WTP does not take into account disease prevalence and budget impact, which also influence decisions. The choice of WTP threshold is of particular interest with ARNI because our results found that sacubitril-valsartan was highly likely to be cost-effective given a WTP of $100,000 per QALY or higher (≥80% of simulations in PSA were cost-effective at this value) but not at a WTP of $50,000 per QALY.

The ICER for ARNI was sensitive to the probability of cardiovascular death. These probabilities and the range of variation were derived directly from the PARADIGM-HF trial. Because this variable has the largest impact on model outcomes, its accuracy is of utmost importance. Recently published results from PARADIGM-HF suggest that the effect size for sacubitril-valsartan relative to enalapril varies depending on the baseline risk of cardiovascular death or HF hospitalization, with higher-risk patients experiencing a larger benefit over a shorter time period (33). Because of this, sacubitril-valsartan may be more cost-effective among patients with higher baseline risk, but differences in baseline risk and its impact on cost-effectiveness were not assessed in this evaluation because of a lack of data. Conversely, sacubitril-valsartan may prove to be a non-cost-effective option among patients with a low baseline risk for these events.

The Institute for Clinical and Economic Review released a draft report on October 9, 2015, evaluating the effectiveness, value, and value-based price of sacubitril-valsartan (34). Similar to our study, a Markov model was developed, and the use of sacubitril-valsartan was compared with the ACEI lisinopril. The results from the draft report are similar to the results of the present evaluation. Our model resulted in marginally higher QALYs achieved in both the sacubitril-valsartan group (6.49 in our study vs 6.13) and the ACEI group (5.74 in our study vs 5.56), as well as an incremental QALY (0.75 in our study vs 0.57). The base-case ICERs observed in the 2 analyses were nearly identical ($50,959 vs. $50,915 per QALY). These findings corroborate our model and validate the outcomes.

A recent actuarial analysis of expected survival time using data from the PARADIGM-HF trial predicted results similar to our simulation model estimates (30). The survival estimates in the sacubitril-valsartan groups were nearly identical between our simulation model and the actuarial analysis. We predicted slightly lower survival in the enalapril group compared with the actuarial analysis (10.5 years in our study vs 11.2 years). Improvement in overall survival, and subsequently quality-adjusted survival, is a major determinant of cost-effectiveness with sacubitril-valsartan. Underestimation of survival in the enalapril group would then favor the cost-effectiveness of sacubitril-valsartan, which means the ICER per QALY gained with sacubitril-valsartan might be higher than our model suggests. However, because all current survival projections are estimates, the true difference in lifetime survival between trial and real-world settings is unclear.

The combination of sacubitril-valsartan has potential for widespread use among patients with HFREF who are able to tolerate its hemodynamic effects. Given the low-cost generic status of ACEIs and the rising incidence of HF caused by an aging U.S. population, the increased price of ARNIs will likely place a significant cost burden on payers, particularly Medicare. Decision makers must determine whether the extra benefit with sacubitril-valsartan observed in PARADIGM-HF is worth the additional costs. This is the first peer-reviewed study to examine the cost-
CONCLUSIONS

As with all new therapies, healthcare decision makers do not have the luxury of waiting for real-world estimates before making coverage and treatment decisions. This analysis provides insight into the cost-effectiveness of the novel ARNI approach to HFrEF treatment to help guide its use. Sacubitril-valsartan use is associated with improved survival and increased costs. This therapy has the potential to improve quantity and quality of life in patients with HFrEF, but at a cost. For most patients, this combination might prove to be a cost-effective choice of care depending on the WTP. However, to fully understand the cost-effectiveness of this intervention, robust long-term, real-world estimates of effectiveness are needed.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Phase 3 clinical trial data have demonstrated a survival and reduced HF hospitalization benefit associated with sacubitril-valsartan, but this novel agent comes with a substantially higher cost than older, generically available ACEIs or ARBs. Selection of appropriate pharmacotherapy in this population must also consider factors apart from what is studied in clinical trials, such as patient preference and affordability.

TRANSLATIONAL OUTLOOK: Within healthcare systems, observational studies can be used to enhance simulation models, which can then inform the relative value of various treatment options. The knowledge gained from this approach catalyzes shared decision making among patients, providers, and health plan administrators.

REFERENCES

KEY WORDS: angiotensin inhibition, cost utility, LCZ696, neprilysin inhibition

APPENDIX: For supplemental tables and figures, please see the online version of this article.