Supplementary Material*

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Event Rates for Cardiovascular Mortality, Non-cardiovascular Mortality, Hospitalizations, and ED visits for Heart Failure

The cardiovascular mortality rate for patients on lisinopril or valsartan therapy was derived from the cardiovascular mortality of the control arm in the PARADIGM-HF trial.(4, 5, 7, 15) We assumed the cardiovascular mortality rate increased with age. A published study evaluating the association between long-term mortality and age in an observational cohort of 5,419 heart failure patients with an average age of 71.9 (95% CI: 51.9-91.9) and follow-up of 5-8 years. In a multivariate Cox proportional hazard model, it found that a 10-year increase in age in patients with systolic dysfunction was associated with a 29% increase in the mortality rate.(21) We assumed the annual relative increase in the cardiovascular mortality rate (compared with the preceding year) was constant at 2.58% to lead to a 29% increase over 10 years (Table S2). This was consistent with a Gompertz distribution of mortality with the following hazard function at age "x":

$$\text{Mortality Rate (x)} = \text{Mortality Rate}_{\text{Age 64}} * exp^{\,[\,(x-64)*\ln(1.0258)\,]}$$

The baseline mortality rates were adjusted to account for the age-associated increase in rates and match the mortality rates of the PARADIGM-HF trial over the median trial follow-up period of 27 months (see "Calibration of Baseline Rates and Rate Ratios" below). In the base case, we used a Gompertz distribution to have a constant 29% increase in the cardiovascular mortality rate over every 10-year increase in age. In a sensitivity analyses, we alternatively used a Weibull hazard function based on a 29% increase in cardiovascular mortality between age 64 and 74 (Table S2):

Weibull: Mortality Rate at Age x = Mortality Rate$_{\text{Age 64}}$ *(x-63)$^{0.1062}$

This hazard would lead to an annual increase in mortality that decreases as patients age. We have included the cost-effectiveness results with this alternate cardiovascular mortality extrapolation below ("Additional Sensitivity Analyses").

We assumed the rate of cardiovascular mortality, heart failure hospitalizations, and ED visits for heart failure without subsequent hospitalization were the same on lisinopril therapy and valsartan therapy given the lack of evidence of a treatment difference.(14) The cardiovascular mortality rate for patients on sacubitril-valsartan therapy was determined using the rate in the lisinopril arm and the hazard ratio of cardiovascular mortality with sacubitril-valsartan.

We assumed sacubitril-valsartan did not affect non-cardiovascular mortality. The non-cardiovascular mortality rate was derived from the total number of non-cardiac deaths and the total follow-up time of both arms combined in the PARADIGM-HF trial.(4, 15) We tested the effect of this assumption in sensitivity analyses (see "Additional Sensitivity Analyses" below). The change in non-cardiovascular mortality with increasing age was determined via CDC life tables that exclude cardiovascular mortality.(22) These life tables were designed to show the mortality rates of a hypothetical cohort in which cardiovascular death has been eliminated. We set the non-cardiovascular mortality at age 65 equal to the trial rate. We then assumed the relative rate increase

from age 65 to 70 would be equal to the relative rate increase in the CDC life table between those ages excluding cardiovascular mortality. The non-cardiovascular mortality rates were then adjusted to account for the age-associated increase in rates and match the non-cardiovascular mortality rates of the PARADIGM-HF trial (see "Calibration of Baseline Rates and Rate Ratios" below) over the median trial follow-up of 27 months. The non-cardiovascular mortality rate was assumed to be equal in all three therapeutic arms.(Table S3)

The rates of heart failure hospitalization and ED visit for heart failure for the lisinopril therapy arm were derived from the rates of the control arm in the PARADIGM-HF trial.(5) ED visits for heart failure were defined as those that did not require subsequent hospitalization. Each of these rates was also calibrated to the trial rate to adjust for potential differences secondary to the exponential increase in mortality.

We assumed the rate of non-heart failure hospitalizations was the same in those receiving sacubitril-valsartan and lisinopril. We estimated the NYHA distribution of non-heart failure hospitalizations within each treatment arm using the number of non-heart failure hospitalizations in each treatment arm and a previous literature estimate of a 16% increase in the risk of non-heart failure hospitalization in patients with NYHA Class III and NYHA Class IV disease.(46) In the base case, we assumed the rate was the same in both treatment arms, and estimated the rate with the total non-heart failure hospitalizations and total follow-up in NYHA Class II-IV (including both treatment arms).

In a sensitivity analysis, we used treatment-specific rates of non-heart failure hospitalization (see “Additional Sensitivity Analyses” below). In another sensitivity analysis, we divided hospitalizations into cardiovascular and non-cardiovascular hospitalizations and estimated the rate ratio of cardiovascular hospitalizations with sacubitril-valsartan, while assuming non-cardiovascular hospitalizations occurred at the same rate in both treatment arms.

Confidence intervals were not available for the natural history rates. We were unable to calculate confidence intervals (CI) using a negative binomial distribution because we did not have individual event data and event variance. The data is likely susceptible to over-dispersion and underestimating the range of the confidence interval because patients have different underlying risk of events (differing frailties).(47) Additionally, the results of a single trial likely underestimate the variability of different heart failure populations. Therefore, we assumed a dispersion parameter to determine confidence intervals for our one-way sensitivity analyses for the rate of cardiovascular mortality, non-cardiovascular mortality, heart failure hospitalization, non-heart failure hospitalization, and ED visits for heart failure. We used a dispersion parameter of 4 in the base case to obtain at least a +/- 20% change from the base case estimates (relative standard error of at least 10% of the base case) in our main sensitivity analyses.

The selected dispersion parameter only affected the confidence intervals tested in sensitivity analyses and not the point estimates. We included the relative standard error

for each event rate with alternative dispersion parameters (Table S4) and the range of control arm survival and hospitalization rates with alternative dispersion parameters to illustrate the effect of our assumption (Table S5). We have also repeated the probabilistic sensitivity analysis (evaluating the overall uncertainty of our model) with dispersion parameters of 1 (equivalent to a Poisson distribution) and 8 (Figures S1-S2).

Calibration of Baseline Event Rates and Rate Ratios

We calibrated our event rates and rate ratios to the trial results. This was necessary for two reasons: we included an age-associated increase in cardiovascular and non-cardiovascular mortality and we used intention-to-treat trial results. Without calibration, our model inputs would over-predict mortality during the initial trial period. The decreased survival and the use of intention-to-treat hazard ratios that are only applied to those receiving sacubitril-valsartan in the model would also underestimate treatment effect without calibration.

We are reporting our calibration methods as has been previously recommended.(48) We calibrated our model to the results of the PARADIGM-HF clinical trial.(7) The trial included 27 months of median follow-up between December 2009 and May 2014. The calibration was performed with a modeled cohort consisting of NYHA Class I-IV patients (matching the trial). We performed multiple sequential calibrations with multiple endpoints in each calibration.

We first calibrated mortality rates and the cardiovascular mortality hazard ratio over approximately 27 months: the lisinopril arm cardiovascular mortality rate, lisinopril arm non-cardiovascular mortality rate, sacubitril-valsartan cardiovascular mortality rate, sacubitril-valsartan non-cardiovascular mortality rate, and the hazard ratio of cardiovascular mortality with sacubitril-valsartan therapy relative to lisinopril therapy. Of note, we calibrated the non-cardiovascular mortality rates to the combined non-cardiovascular mortality rate of both arms in the trial, which we altered in sensitivity analyses. We performed a grid calibration by varying the model's monthly probability of cardiovascular death with lisinopril, non-cardiovascular death (in both arms), and hazard ratio of cardiovascular death with sacubitril-valsartan. All variables were varied simultaneously by +/- 25% at intervals of 1%. We assessed goodness-of-fit using the sum of squares of the absolute distance between endpoints. This increased the relative weight of the hazard ratio, a larger number with greater absolute differences in the calibration for similar relative differences compared with the other outcomes. This importance was acceptable because accurate estimation of the hazard ratio was critical to accurately modeling the treatment effect of sacubitril-valsartan. We accepted calibration of a single set of parameters that minimized sum of squares once each outcome was within 1% of the endpoint. We did not incorporate trial uncertainty because 1% variation was less than the uncertainty of the trial. We have displayed the results of the calibrations below as the model endpoints compared with the trial results (Table S6; Figure S3) and the value of model inputs before and after calibration (Table S7). The model was not validated to additional data given the presence of a single trial

testing sacubitril-valsartan. However, we did ensure the model performed adequately for the subgroups used in the manuscript: NYHA Class II-IV, NYHA Class II, and NYHA Class III-IV cohorts (Table S6). We used our calculated NYHA-class specific endpoints (described below) based on the trial data. We ensured that the hazard ratios from our model over approximately 2.2 years (median trial follow-up) were within 2.5% of our estimates of the trial results.

We then repeated the above calibration twice (including the mortality adjustments obtained from the initial calibration). First, we calibrated to the rate of heart failure hospitalizations in both arms and the rate ratio with sacubitril-valsartan relative to lisinopril; we then calibrated the rate of ED visits in both arms and the rate ratio of ED visits with sacubitril-valsartan relative to lisinopril. We did not perform angioedema or therapy intolerance calibrations because we calculated these event rates using median days of drug exposure. We did not calibrate non-heart failure hospitalization event rates because we assumed these were the same in both trial arms.

Rates of Therapy Intolerance and Angioedema

We determined chronic intolerance rates of sacubitril-valsartan and lisinopril therapy based on the number of discontinuations of each therapy due to adverse effects in each arm ((7): Table 52) and the median exposure of therapy.((7): Table 45) The denominator of median days of drug exposure is likely of interest given major treatment-

related adverse events are most likely during drug exposure and the risk is only applied to those receiving the given therapy. Additionally, safety evaluations were not actively evaluated after drug discontinuation.(7) This was applied as a monthly risk of in the model. We separately modeled rates of angioedema requiring hospitalization as this represented intolerance with greater associated costs and disutility. The rate of angioedema requiring hospitalization with sacubitril-valsartan or lisinopril were based on the number of adjudicated angioedema hospitalizations ((7): Table 55) and the median days of drug exposure in each arm of the trial. This was also applied as a monthly risk in the model. We assumed no intolerance or angioedema requiring hospitalization with ARB therapy.

In a scenario analysis, we modeled initial drug tolerance. We included a clinic visit for treatment initiation and used the run-in data to determine the proportion who would not tolerate the drug initially.((7): Table 50) We determined initial intolerance rate based on the number of adverse events leading to study drug discontinuation during the run-in period: 643 (6.1%) with enalapril and 532 (5.6%) with sacubitril-valsartan. For the proportion with discontinuation, we included the cost of the initial drug for one month along with the cost of an additional clinic visit for treatment cessation. There was only one episode of severe angioedema requiring hospitalization, which occurred in the enalapril arm of the trial. We therefore did not model additional severe angioedema in the run-in period.

Estimating Number of Events by NYHA Class

Sacubitril-valsartan was not intended nor approved for treatment for patients with NYHA Class I heart failure. These patients, however, constituted 4.7% of the PARADIGM-HF trial.(1) These were patients who were initially NYHA Class II-IV at enrollment but improved to NYHA Class I prior to randomization. We adjusted the rate of cardiovascular mortality, non-cardiovascular mortality, heart failure hospitalizations, non-heart failure hospitalizations, and ED visits for heart failure to estimate rates for a cohort that excluded NYHA Class I patients by estimating the number of events and the total patient follow-up time by NYHA class. FDA submission data included the proportion of patients with cardiovascular death by NYHA Class and treatment arm.((7): Table 35) A post-trial analysis also included the number of cardiovascular deaths by NYHA Class.(15) We estimated the number of cardiovascular deaths by NYHA Class and treatment arm using the FDA mortality probabilities and the number of patients by NYHA Class and treatment arm. We assumed the 13 patients with missing NYHA Class data in the primary analysis cohort had a similar NYHA Class distribution as the remaining 8,386 patients and adjusted for rounding errors to match the known number of cardiovascular deaths by NYHA Class (44 for NYHA Class I, 791 for NYHA Class II, 404 for NYHA Class III, and 12 for NYHA Class IV) and by treatment (693 for enalapril and 558 for sacubitril-valsartan). Our estimate is displayed in Table S8.

NYHA Class-specific event probabilities were not available for total heart failure hospitalizations or ED visits for heart failure without subsequent hospitalization but were

available for first heart failure hospitlaization ((7): Table 35). The total number of heart failure hospitalizations and ED visits without subsequent hospitalization by treatment arm have been published.(5) We assumed the NYHA Class distribution of first heart failure hospitalizations within a treatment arm matched the distribution of total heart failure hospitalizations and ED visits without subsequent hospitalization. These estimates are also displayed in Table S8.

Estimating Follow-up by NYHA Class

To estimate event rates, we had to correct for differential follow-up time between NYHA classes. Differences in average follow-up of different NYHA Classes will be secondary to differences in enrollment over time, mortality rate, and other causes of being lost to follow-up. We assumed the NYHA distribution of enrollment did not change over time. 35 patients (17 sacubitril-valsartan and 18 enalapril) did not complete the study: 28 withdrew consent (only 13 with unknown vital status) and 7 were lost to follow-up. We assumed the risk of withdrawing from the study was also similar across NYHA Classes. We therefore assumed differences in follow-up were secondary to differences in mortality. We used our calibrated model of the entire cohort to estimate median survival in those with death during the trial (Figures S3-4), assuming similar survival in those with death across NYHA classes. Based on a median survival of 1.27 years in patients who died on enalapril treatment and 1.29 years in patients who died on sacubitril-valsartan therapy, we calculated the total number of follow-up years in patients with death by NYHA Class and treatment. We divided the remaining years of follow-up (total

years by treatment arm minus the years in patients with death) by the proportion of surviving patients by NYHA Class and treatment among those in the randomized cohort. These calculations are displayed in Table S9. Compared to assuming proportionate follow-up, these assumptions led to a small increase in the estimate follow-up time of NYHA Class I-II patients and a small decrease in the follow-up time of NYHA Class III-IV (Table S10). We have labeled this Follow-up Estimate A.

We repeated the estimate of follow-up time using alternate assumptions. First (Follow-up Estimate B), we varied our estimate of the median survival of patients with death using the Kaplan-Meir curve for all-cause mortality ((4): Figure 2D). 19.8% of patients in the enalapril arm and 17.0% of patients with sacubitril-valsartan died during the trial; therefore, the median survival would be the point at which 9.9% of patients with enalapril and 8.5% of patients with sacubitril-valsartan died. We used a graphic digitizer to estimate median survival among those who died at 1.19 years for enalapril patients and 1.21 years for sacubitril-valsartan patients. As a second alternate estimate (Follow-up Estimate C), we assumed the distribution of follow-up matched the NYHA Class-distribution of median days of drug exposure for each treatment arm ((7): Table 45). Median drug exposure is secondary to both treatment discontinuation and death; therefore, this assumes that treatment discontinuation proportions match those who did not complete the study or died. As a final alternate estimate (Follow-up Estimate D), we assumed follow-up by NYHA Class was proportional to the number of patients (the same average follow-up of each NYHA class). We have displayed the follow-up times

(Table S10), rate ratios (Table S11) and the incremental cost-effectiveness ratios (Table S12) using each of these alternate estimates.

In the base case, we calculated event rates excluding NYHA Class I disease using our estimates of the number of events by NYHA Class and the follow-up time per NYHA Class with the "Follow-up Estimate A". Table S1 contains both event rates in the entire trial cohort (NYHA Class I-IV), event rates excluding NYHA Class I disease, and subgroup-specific NYHA event rates (NYHA Class I, Class II and Class III-IV).

Efficacy of Sacubitril-Valsartan

Our model assumed sacubitril-valsartan decreased the risk of cardiovascular mortality, heart failure hospitalization, and ED visits for heart failure without subsequent hospitalization compared with those on lisinopril or losartan. NYHA-class specific hazard ratios were only available for cardiovascular mortality ((7); Table 35). We estimated the cardiovascular mortality of combined NYHA classes (NYHA Class II-IV and NYHA Class III-IV) after log transformation and weighted by the proportion of the combined cohort from each NYHA Class. For total heart failure hospitalizations and ED visits without subsequent hospitalization, we calculated rate ratios based on the number of events and follow-up time (as calculated above).

Overall, our model slightly shifted the rate ratio estimates to account for the lack of NYHA Class I patients and the model design (Table S13). In our model, the rate ratio was applied to the baseline monthly event rate of those on lisinopril/losartan for those receiving sacubitril-valsartan. It did not apply to those previously on sacubitril-valsartan who have switched therapy; this contrasts with trial estimates of effectiveness that have used an intention-to-treat analysis. Therefore, we adjusted our rate ratios to match trial results (see “Calibration of Baseline Rates and Rate Ratios” above) over the median trial duration. Table S6 contains our calibration targets and final model output over the trial duration.

We did not assume sacubitril-valsartan efficacy varied with age. We assumed a constant efficacy based on a recent analysis that showed a relatively similar effect of the therapy across age groups.(49) For cardiovascular mortality, the hazard ratio was 0.84 (CI: 0.65-1.08) for those <55 years old, 0.79 (CI: 0.64-0.98) for those 55-65, 0.74 (CI: 0.60-0.90) for those 65-74, and 0.84 (0.67-1.06) for those over 75 years old. The p-value for the interaction between age and the hazard ratio for cardiovascular mortality was 0.92. For heart failure hospitalization, the p-value for the interaction between age and the hazard ratio for heart failure hospitalizations was 0.81.

In the base case, we assumed sacubitril-valsartan effectiveness was life-long. We varied this assumption in a sensitivity analysis in which we set a time cut-off after which the treatment would no longer have any benefit. However, we assumed that providers

and patients would be unable to ascertain when the therapy loses effectiveness for cardiovascular mortality, hospitalizations or quality of life and would continue therapy. Therefore, the risk of treatment intolerance and severe angioedema and the cost of treatment would persist. This is presented in the accompanying manuscript. In an alternative scenario, in which we assume that providers and patients would be able to determine effectiveness and switch therapy after this cut-off, the therapy's cost per QALY gained remains relatively similar to the base case even with much shorter durations of effectiveness ($47,660 per QALY at the trial mean duration of 27 months).

Utility of Chronic Heart Failure and Incremental Utility of Sacubitril-Valsartan

The baseline utility of the lisinopril/losartan arm was estimated from the average EQ-5D measurements of the control arm during the course of the PARADIGM-HF trial.(Novartis: personal communication, July 2015; (18)) We weighted each measurement period by the number of observations in calculating the average. Sacubitril-valsartan was also shown to improve quality of life in the PARADIGM-HF trial.(4) The intervention arm was shown to have a statistically significant higher score on the KCCQ score than the control arm, along with higher EQ-5D scores. The incremental utility for receiving sacubitril-valsartan in our model was based on the least squares mean of difference between the changes from baseline in the two arms (Table S14).(Novartis: personal communication, July 2015; (19)) There was not a clear linear relationship between the difference in differences measured at each follow-up period and the duration of follow-up, with the range being from 0.005-0.02. Additionally, the

number of observations decreased with increasing follow-up (7,759 to 2,406); therefore, we used an observation-weighted average of the difference-in-differences in EQ-5D scores to estimate the incremental utility (0.009).

Subgroup-specific utility values (specific for NYHA Class II or NYHA Class III/IV) were derived from baseline cohort EQ-5D values, proportion of each NYHA class in the PARADIGM-HF trial, and a published multivariate regression of the effect of NYHA class on utility value derived from the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study.(26)

Disutility of Adverse Events

Disutilities were modeled as a proportion of the cohort's baseline utility. Therefore, a given disutility would lead to the same number of days lost across cohorts with different baseline utilities. The disutility of a heart failure exacerbation requiring hospitalization was based on a published evaluation of patient utility during and after a heart failure hospitalization.(16) In this study of patients with NYHA Class III or IV heart failure, the health-related quality of life was assessed during hospitalization and six months later. The median value, based on a time-tradeoff, was 0.84 during admission and 0.93 after 180 days. This equated to a 9.7% lower utility during the exacerbation requiring hospitalization. We used a 9.7% decrease of our baseline utility for one month to calculate the disutility (-0.0066). This would be approximate a disutility toll of 3.0 days

for an acute exacerbation. This was tested in sensitivity analyses, with the disutility toll being varied from 0 days to 6 days. Heart failure exacerbations requiring an ED visit but not hospitalization were estimated at 2 days of disutility (-0.0045).

We performed an alternative analysis of heart hospitalization disutility with estimates of long-term utility dependent on the number of heart failure rehospitalizations.(21) We assumed the change in utility with heart failure rehospitalizations was proportional to baseline utility, which we estimated for our cohort using the multivariate model. In this case, one rehospitalization decreased long-term utility by 3.2% (11.5 days per year), a second rehospitalization led to a long-term utility that was 4.2% lower than baseline (for a total decrement of 14.9 days per year), and the third 7.2% lower than baseline (for a total decrement of 26.4 days per year). We used these estimates to calculate utility values over time for each cohort based on the number of heart failure hospitalizations at each time point (Table S15). This led to a longitudinal decrease in utility with increasing heart failure hospitalizations, which was greater in the routine care arm. We applied these as the base utility values over time. Individuals on sacubitril-valsartan therapy still received an incremental quality-of-life benefit.

A disutility of one day (-0.0023) was applied for therapy intolerance. We assumed angioedema requiring hospitalization would be more severe but short-lasting and thereby estimated a disutility of 2 days (-0.0045), which is the mean duration of hospitalization for anaphylaxis. We tested the effect of this assumption in one-way

sensitivity analyses, varying the disutility from 0 days to 8 days. We assumed other non-heart failure hospitalizations carried a similar disutility to heart failure hospitalizations (3 days).

Treatment Costs

Costs of all three treatments were estimated using wholesale acquisition prices from *The Red Book*.(6) For ACE-inhibitor therapy, we used the cost of lisinopril 20mg, which is a lower cost ACE-inhibitor than enalapril.(6) For ARB therapy, we used the cost of losartan 100mg, which is a lower cost ARB than valsartan.(6) The monthly cost was set to the average wholesale acquisition cost of listings of at least 90 pills; the range of prices tested in deterministic sensitivity analyses were derived from the minimum and maximum wholesale acquisition prices of these listings for both ACE-I and ARB therapy, which was approximately +/- 60% of the base case. For sacubitril-valsartan, it was set to +/-50% of the base case due to the current lack of variation in wholesale acquisition prices and the uncertainty of the cost for different healthcare groups.

We tested multiple alternative prices of sacubitril-valsartan.(Table S17) In the base case, we used the wholesale acquisition cost (WAC): the price listed by the manufacturer that approximates what conventional retail pharmacies pay wholesalers. An alternative published price is the average wholesale price (AWP), estimated at $15.00 per day in *The Red Book*.(6) This price, typically a 20-25% markup of the wholesale acquisition cost, was designed to represent the expected reimbursement to a private pharmacy. However, this is also not a transaction price and is arbitrarily linked to

the wholesale acquisition cost.((23))The average manufacturer price (AMP) is the average price paid to a drug manufacturer but is not publically available. A Congressional Budget Office analysis of single-source, brand name pharmaceuticals estimated an AMP of 79% of the AWP, which equates to $11.85.

We also estimated prices of the medication for different payers based on the Congressional Budget Office analysis.(23) The estimated retail pharmacy price with pharmacy benefits managers ($12.82/day) was based on a Novartis industry formula cited in a Congressional Budget Office analysis: a 15% discount of the average wholesale price plus a $2 filling charge, which we assumed occurred monthly.(23) Including the average rebate (7%) paid to the pharmacy benefits managers, this cost decreased to $11.92. The average cost of an uninsured patient paying cash at a retail pharmacy was 15% greater than the $12.82 paid by pharmacy benefits managers, $14.74. The average price paid by a mail order pharmacy to the manufacturer was 78% of the AWP, $11.70. The average price paid by nonretail providers (hospitals or health maintenance organizations) to manufacturers was estimated at no more than 66% of the AWP: $9.90. The average price paid by federal facilities (Veteran's Affairs, Indian Health Services, military) was estimated at 42% of the AWP: $6.30/day. We tested each of these prices in sensitivity analyses; the results are included in Table S17.

Heart Failure Costs

The cost of a heart failure hospitalization was extracted from literature estimates of AHRQ National Inpatient Sample costs.(20) This study analyzed the discharge data from the 2011 National Inpatient Sample from the Healthcare Cost and Utilization Project, finding the mean cost for all heart failure admissions to be $10,775. We inflated the cost to 2015 USD using the medical consumer price index, as the hospital cost in our main case analysis ($11,731 after inflation adjustment).(50) A multivariate linear regression analysis estimated the effect of patient and hospital characteristics on the average cost of a hospitalization. In deterministic sensitivity analyses, we estimated high-cost and low-cost hospitalization settings, which was adjusted for patient characteristics. Urban hospitals were associated with 12% higher costs compared with rural hospitals; teaching hospitals were associated with 17% higher costs compared with non-teaching hospitals. Hospitals in the Midwest were associated with 19% lower costs compared with hospitals in the Northeast. Private hospitals were associated with 13% lower costs compared with government hospitals. Large hospitals were associated with 8% higher costs compared with small hospitals. We combined the high cost characteristics and low cost characteristics. High-cost hospitals (urban, teaching, government hospitals in the Northeast) would cost 30.5% more than average. Low-cost hospitals (rural, non-teaching, private hospitals in the Midwest) would cost 35% less than average.

We also included the cost of physician care during a hospitalization using the Medicare physician fee schedule.(24) We used a frequency-weighted average of the length of stay for DRG 291-293 (Heart failure with major complications or comorbidities, with chronic conditions, and without either) from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project National Statistics on All Stays to determine a length of stay of 4.8 days.(51) We assumed patients would have a primary physician and a consulting cardiologist for the duration of the hospitalization. 80% of patients were assumed to be high complexity and 20% were assumed to be medium complexity given DRG codes in which 90% of patients had major complications or chronic conditions (DRG 291 or 292) and 10% had neither. We assumed a proportion of those patients with chronic conditions would still be classified as medium complexity. This led to a total cost of $1,127 per heart failure hospitalization for physician costs. In the sensitivity analysis of high and low costs of hospitalization, the change in hospital-level costs was also applied to physician-level costs as we assumed hospital-level cost variation represented difference in resource usage during hospitalization and duration of hospitalization that would also likely affect physician-level costs.

We adjusted the total cost of heart failure hospitalizations for the age of our analysis. The analysis of inpatient data found an 8% reduction in cost of heart failure hospitalization in those greater than or equal to 65 in the study, with our cohort having a starting age of 64. We applied this reduction to both hospital and physician-level costs.(20)

The cost of an ED visit for heart failure without subsequent hospitalization was estimated from Medicare Ambulatory Payment Classification (APC) and the physician fee schedule (CPT 99285). For APC costs, we assumed half of patients would be Level 4 Type A and half would be Level 5 Type A, which results in an average cost of $574.(52) For physician fees, we included ED physician care (CPT 99285), electrocardiogram interpretation (CPT 93000), chest x-ray interpretation (CPT 71020), and a cardiology consult (CPT 99285) for half of the patients. In total, we estimated the cost of an ED visit to be $885.

Additional medical costs for patients with heart failure were taken from an analysis of lifetime costs in patients with heart failure in Olmstead County.(25) We calculated the monthly outpatient costs per patient. We adjusted these costs for NYHA class derived from a regression model for costs with prevalent heart failure in a model conditional upon survival.(53) The adjusted cost of $477 per month was assumed to be the average monthly cost of all outpatient health care for a patient with heart failure at the age of 77 (average age of the patients in Olmstead County study). All hospitalizations costs were accounted for separately. This was adjusted for younger and older patients using a 0.88% increase in cost with each increase in age by one year.(53) For age-specific, NYHA cohort-specific monthly healthcare costs, refer to Table S18. In one-way sensitivity analyses we assumed a 25% increase or decrease from the base case monthly outpatient healthcare costs.

Additional Costs

The costs of non-heart failure hospitalization were based on an estimate of the Medicare reimbursement for a pneumonia hospitalization, the most common non-heart failure hospitalization in those with heart failure.(17, 24) These costs were also calculated using the average DRG-based (DRG 193-194) Medicare reimbursement ($6,888) and costs for physician care ($387) calculated from the Medicare physician fee schedule using the average duration of stay.(17, 24)

The cost of medication intolerance was set to the Medicare reimbursement of one primary care appointment (CPT 99215).(17) The cost of angioedema requiring hospitalization was set to the Medicare reimbursement for an allergic reaction (DRG 916).(17, 24) The additional costs of cardiovascular death and non-cardiovascular death were taken from literature estimates of inpatient care during the last year of care prior to death, from which model-based estimates of hospitalization costs were subtracted to avoid double counting.(54)

Probabilistic Sensitivity Analysis

We performed a probabilistic sensitivity analysis to analyze the uncertainty of the model and the cost-effectiveness estimates. We performed 10,000 simulations while sampling parameters simultaneously from their respective distributions (Tables S1, S14, S16). The distributions were generally calculated using the base case as the mean and the

range as the 95% confidence interval except as discussed below. We used beta distributions for probabilities and utility values, log-normal distributions for rate ratios, and normal distributions for costs.

As discussed above, we assumed a dispersion parameter of 4 to determine confidence intervals and to construct our distributions. We have alternatively performed the probabilistic sensitivity analysis using dispersion parameters of 1 (equivalent to a Poisson distribution) and 8 (Table S21, Figure S1). We have also demonstrated the effect on the cost-effectiveness acceptability curve of varying this assumption (Figure S2).

For most costs, we determined the 95% confidence interval via the relative standard errors (percent of the mean) of the average costs in the national inpatient sample data.(51) We used the same diagnosis-related groups that were used to estimate the base case (discussed above). We assumed the relative standard error was the same for the physician costs of a hospitalization as the relative standard error of the hospitalization costs. The 95% confidence intervals for the costs of monthly outpatient care and the additional costs of the final year of care were directly based on their respective sources.(25, 54)

Additional Sensitivity Analyses

In the base case, we used a Gompertz cardiovascular mortality hazard function, assuming cardiovascular mortality increased by 29% with each 10-year increase in age. If we instead used a Weibull hazard function that was based on a 29% increase in cardiovascular mortality between 64 and 74, we found an incremental survival of 0.70 years, incremental cost of $29,399, and incremental QALYs of 0.63 with sacubitril-valsartan. This led a cost per QALY gained of $46,415.

We tested the assumption that non-cardiovascular mortality and non-heart failure hospitalizations were the same in both treatment arms. If we modeled non-cardiovascular mortality and non-heart failure hospitalization rates dependent on the event rates in each treatment arm, the sacubitril-valsartan arm would have a slightly greater rate of non-cardiovascular mortality and a slightly lower rate of non-heart failure hospitalizations. In the NYHA Class II-IV cohort, the incremental cost with sacubitril-valsartan would decrease to $27,389 and the QALYs gained would decrease to 0.57, leading to a cost per QALY gained of $47,698.

In our main analysis, we assumed hospitalizations were heart failure-related or non-heart failure related. Sacubitril-valsartan reduced the risk of heart failure-related hospitalizations but not non-heart failure related hospitalizations. If we instead classified hospitalizations as cardiovascular hospitalizations and non-cardiovascular

hospitalizations and modeled the treatment effect of sacubitril-valsartan on cardiovascular hospitalizations – which is a lower risk reduction (RR of 0.87) on a greater baseline risk (2.3% monthly) – while modeling a similar non-cardiovascular hospitalization rate in both arms, the sacubitril-valsartan arm would experience on average 0.05 fewer cardiovascular hospitalizations (1.90 vs. 1.95) and 0.05 more total hospitalizations (3.08 vs. 3.03) over a lifetime. In the base case, the sacubitril-valsartan experienced 0.08 fewer heart failure hospitalizations (0.75 vs. 0.83) but 0.13 more total hospitalizations (3.09 vs. 2.96) over the lifetime. The increase in total hospitalizations in the sacubitril-valsartan arm is secondary to longer survival. Varying this assumption reduces the total hospitalizations in the sacubitril-valsartan arm because this arm also suffered fewer non-heart failure, cardiovascular hospitalizations in the trial.(5) If we assumed cardiovascular hospitalizations had a cost between heart failure hospitalizations and non-heart failure hospitalizations that was equal to the proportion of each in composite, the incremental cost would decrease to $28,930 the incremental QALYs would stay at 0.62 and the cost per QALY gained would decrease slightly to $46,575. If we assumed the cost of cardiovascular hospitalizations was the same as heart failure hospitalizations, the cost per QALY would decrease to $46,363.

If we assumed the maximum monthly probability of sacubitril-valsartan intolerance (0.56%), cost of intolerance ($220), and disutility of intolerance (2 days), the cost per QALY of sacubitril-valsartan increased to $46,897 . Simultaneously assuming the maximal monthly risk of severe angioedema with sacubitril-valsartan (0.62%), cost of

angioedema hospitalization ($3,112), and severe angioedema disutility (4 days) would increase the cost per QALY gained of sacubitril-valsartan to $46,908.

NYHA Class I patients were excluded in the base case analysis. In the NYHA Class I cohort, sacubitril-valsartan therapy was associated with a loss of 0.57 QALYs and $21,029 in increased costs. The lisinopril arm had a discounted survival of 9.79 years (12.64 undiscounted years) compared with 8.95 years in the sacubitril-valsartan arm (11.41 undiscounted years). This translated to 7.35 QALYs (9.50 undiscounted QALYs) in the lisinopril arm and 6.78 QALYs (8.64 undiscounted QALYs) in the sacubitril-valsartan arm. When evaluating a cohort including all PARADIGM-HF trial patients, including NYHA Class I patients, sacubitril-valsartan therapy was associated with 0.53 incremental QALYs and $28,807 more in costs, with a cost per QALY gained of $54,809.

Additional one-way (Table S19) and two-way (Table S20) sensitivity analyses are included below.

Additional Technical Details

The analysis adopted a societal perspective and discounted all healthcare costs and benefits at 3% annually. Rates were converted to monthly probabilities, which were adopted in the model. We used Microsoft Excel 2011 (Microsoft, Redmond,

Washington), TreeAge Pro 2014 (TreeAge Software, Williamstown, Massachusetts) and STATA 2013 (StataCorp, College Station, Texas) to perform the analysis.

Tables

Table S1. Transition Probabilities (Monthly) and Rate Ratios*

	Base Case (%)	95% CI (%)†	PSA Distribution‡	Source
Transition Probabilities				
Lisinopril/Losartan Therapy				
Cardiovascular Mortality, NYHA Class II-IV§	0.61	0.43-0.80†	Beta	4,7,15
NYHA Class I	0.34	0.00-0.92	---	4,7,15
NYHA Class II	0.55	0.34-0.75	Beta	4,7,15
NYHA Class III-IV	0.80	0.39-1.21	Beta	4,7,15
NYHA Class I-IV	0.60	0.42-0.78	---	4,7,15
HFH, NYHA Class II-IV	0.99	0.75-1.23	Beta	4,5,7
NYHA Class I	0.60	0.00-1.38	---	4,5,7
NYHA Class II	0.97	0.69-1.24	Beta	4,5,7
NYHA Class III-IV	1.05	0.57-1.53	Beta	4,5,7
NYHA Class I-IV	0.97	0.74-1.20	---	4,5,7
ED Visit for Heart Failure, NYHA Class II-IV	0.19	0.08-0.29†	Beta	4,5,7
NYHA Class I	0.11	0.00-0.29	Beta	4,5,7
NYHA Class II	0.19	0.06-0.31	Beta	4,5,7
NYHA Class III-IV	0.20	0.00-0.41	Beta	4,5,7
NYHA Class I-IV	0.19	0.08-0.29	Beta	4,5,7
Intolerance to Lisinopril, Chronic	0.51	0.47-0.56	Beta	4,7
Intolerance to Lisinopril, Initial**	6.12	5.66-6.57	---	4,7
Severe Angioedema with Lisinopril	0.0010	0-0.0030	Beta	4,7
Cardiovascular Hospitalization, NYHA Class II-IV††	2.31	---	---	4,5,7
Non-cardiovascular Hospitalization, NYHA Class II-IV††	1.37	----	---	4,5,7
Non-Heart Failure Hospitalization, NYHA Class II-IV‡‡	2.67	----	---	4,7,46
Non-cardiovascular Mortality, NYHA Class II-IV‡‡	0.13	----	---	4,7,15
Sacubitril-Valsartan Therapy				
Intolerance to Sacubitril-Valsartan, Chronic	0.43	0.39-0.48	Beta	4,7
Intolerance to Sacubitril-Valsartan, Initial**	5.65	5.18-6.11	---	4,7
Severe Angioedema with Sacubitril-Valsartan	0.0029	0-0.0062	Beta	4,7
Non-cardiovascular Hospitalization, NYHA Class II-IV††	1.20	----	---	4,5,7
Non-Heart Failure Hospitalization, NYHA Class II-IV‡‡	2.39	----	---	4,7,46
Non-cardiovascular Mortality, NYHA Class II-IV‡‡	0.14	----	---	4,7,15
Both Arms				
Non-Heart Failure Hospitalization, NYHA	2.53	2.46-2.59	Beta	4,7,46

Class II-IV				
NYHA Class I	2.43	1.26-3.59	---	4,7,46
NYHA Class II	2.43	2.36-2.51	Beta	4,7,46
NYHA Class III-IV	2.81	2.68-2.95	Beta	4,7,46
NYHA Class I-IV	2.52	2.26-2.78	---	4,7,46
Non-cardiovascular Mortality[§§], NYHA Class II-IV	0.13	0.07-0.18	Beta	4,7,46
NYHA Class I	0.08	0.04-0.12	---	4,7,15
NYHA Class II	0.13	0.07-0.18	Beta	4,7,15
NYHA Class III-IV	0.13	0.07-0.19	Beta	4,7,15
NYHA Class I-IV	0.12	0.07-0.18	---	4,7,15
Rate Ratios with Sacubitril-Valsartan[***]				
HR of Cardiovascular Mortality, NYHA Class II-IV [†††]	0.77	0.69-0.86	Log-Normal	4,7,15
NYHA Class I	1.34	0.74-2.43	---	4,7,15
NYHA Class II	0.75	0.66-0.86	Log-Normal	4,7,15
NYHA Class III-IV	0.81	0.66-0.98	Log-Normal	4,7,15
NYHA Class I-IV	0.79	0.71-0.88	---	4,7,15
RR of HFH, NYHA Class II-IV	0.77	0.70-0.84	Log-Normal	4,5,7
NYHA Class I	0.70	0.41-1.21	---	4,5,7
NYHA Class II	0.67	0.60-0.75	Log-Normal	4,5,7
NYHA Class III-IV	1.05	0.89-1.23	Log-Normal	4,5,7
NYHA Class I-IV	0.77	0.70-0.84	---	4,5,7
RR of ED Visit for Heart Failure, NYHA Class II-IV	0.70	0.57-0.87	Log-Normal	4,5,7
NYHA Class I	0.65	0.18-2.31	---	4,5,7
NYHA Class II	0.62	0.48-0.80	Log-Normal	4,5,7
NYHA Class III-IV	0.96	0.66-1.40	Log-Normal	4,5,7
NYHA Class I-IV	0.71	0.57-0.87	---	4,5,7
RR of Cardiovascular Hospitalization, NYHA Class II-IV[††]	0.87	---	---	4,5,7

[*] Abbreviations: HFH: heart failure hospitalizations; HR: hazard ratio; RR: rate ratio; NYHA: New York Heart Association

[†] Estimated using a dispersion factor of 4 for the natural history probabilities that varied between arms: the probability of cardiovascular death, heart failure hospitalization, and ED visits for heart failure (see above). Alternative PSA performed with a dispersion factor of 1 (more narrow CI) and 8 (more wide CI)

[‡] PSA was only performed for the base case NYHA Class II-IV cohort, the NYHA Class II subgroup and the NYHA Class III-IV subgroup so distributions were not constructed for NYHA Class I or NYHA Class I-IV estimates. Additionally, initial intolerance was not modeled in the PSA.

[§] The monthly baseline probability of cardiovascular mortality was increased by 2.6% by year to adjust for the lifetime horizon and the effect of aging. The probability was calibrated so the model matched the mortality rate seen in the trial period. (Table S2)

[**] Initial intolerance only modeled in a scenario analysis. Derived from the intolerance during the run-in period.

[††] Only modeled in a sensitivity analysis using cardiovascular and non-cardiovascular hospitalizations instead of heart failure and non-heart failure hospitalizations.

[‡‡] Only modeled in a sensitivity analysis that used non-cardiovascular mortality and non-heart failure hospitalization probabilities specific to each treatment arm in the trial.

§§ The increases in non-cardiovascular mortality probability with increases in age was based on the relative percentage change in mortality risk in CDC life tables that excluded cardiovascular mortality.(Table S3)
*** Rate ratios with sacubitril-valsartan therapy relative to lisinopril therapy. Rate ratios for heart failure hospitalization, ED visits, and cardiovascular hospitalizations were estimated from estimated number of events and follow-up in each arm of the PARADIGM-HF trial. The hazard ratios for cardiovascular mortality were from the reported NYHA Class-specific reported hazard ratios.
††† Probability in the sacubitril-valsartan arm was based on the probability in the lisinopril/losartan arms and the rate ratio of the event with sacubitril-valsartan compared with lisinopril/losartan therapy.

Table S2. Monthly Cardiovascular Mortality Rate by Cohort and Age, %*

Age	NYHA Class II-IV	NYHA Class II	NYHA Class III-IV	NYHA Class I-IV	NYHA Class I	NYHA Class II-IV (Weibull)†
60	0.56	0.50	0.72	0.54	0.30	---
65	0.63	0.56	0.82	0.62	0.35	0.64
70	0.72	0.64	0.93	0.70	0.39	0.73
75	0.81	0.72	1.06	0.79	0.45	0.77
80	0.92	0.82	1.20	0.9	0.51	0.8
85	1.05	0.93	1.36	1.02	0.57	0.82
90	1.19	1.06	1.55	1.16	0.65	0.84
95	1.35	1.20	1.76	1.32	0.74	0.86

* Abbreviations: NYHA: New York Heart Association
† For a sensitivity analysis using a Weibull distribution hazard function.

Table S3. Monthly Non-cardiovascular Mortality Rate by Cohort and Age, %*

Age	NYHA Class II-IV	NYHA Class II	NYHA Class III-IV	NYHA Class I-IV	NYHA Class I
60	0.09	0.09	0.09	0.09	0.06
65	0.13	0.13	0.13	0.13	0.08
70	0.2	0.2	0.2	0.19	0.12
75	0.3	0.3	0.3	0.3	0.19
80	0.45	0.45	0.46	0.45	0.29
85	0.67	0.67	0.67	0.66	0.42
90	0.97	0.97	0.97	0.95	0.61
95	1.42	1.41	1.42	1.39	0.89

* Abbreviations: NYHA: New York Heart Association

Table S4: Relative Standard Errors of Alternative Dispersion Parameter Assumptions*

Parameter	Dispersion Factor		
	1	4†	8
Probability of Cardiovascular Death	3.9%	15.4%	30.8%
Probability of Heart Failure Hospitalization	3.1%	12.4%	24.8%
Probability of ED Visits for Heart Failure	7.0%	28.2%	56.4%

* Standard error as a percent of the base case rate
† Used in the base case.

Table S5. Effect of Adjusting Range of Cardiovascular Mortality Rate and Heart Failure Hospitalization Rate by Varying Dispersion Factors on Survival and Heart Failure Hospitalization*†

Outcome	Dispersion Factor		
	1	4‡	8
Survival (LL-UL)§, years	8.08-8.83	7.15-10.25	6.19-12.91
Heart Failure Hospitalization Rate (LL-UL)**, hospitalizations/year	0.11-0.13	0.09-0.15	0.06-0.18

* Abbreviations: LL: Lower limit; UL: Upper limit
† Undiscounted results.
‡ Used in the base case.
§ Based on adjusting cardiovascular mortality rate between the lower and upper limit of the confidence interval (as determined by the dispersion factor)
** Based on adjusting heart failure hospitalization rate between the lower and upper limit of the confidence interval (as determined by the dispersion factor)

Table S6. Comparison of Model Output to Target Data Over the Mean Trial Duration of 2.2 years*†

Outcome	Source‡	NYHA Class Cohort				
		I-IV	II-IV	II	III-IV	I
Cardiovascular Mortality Rate, Lisinopril (Events/100 patient years)	Target	7.5	7.7	6.9	10.0	4.1
	Model	7.4	7.6	6.8	9.9	4.2
Hazard Ratio of Cardiovascular Mortality with Sacubitril-Valsartan	Target	0.80	0.78	0.77	0.82	1.37
	Model	0.80	0.78	0.77	0.82	1.32
Heart Failure Hospitalization Rate, Lisinopril: Events/100 patient years	Target	11.7	11.9	11.7	12.7	7.2
	Model	11.7	11.9	11.6	12.7	7.2
Rate Ratio of Heart Failure Hospitalization with Sacubitril-Valsartan	Target	0.78	0.78	0.68	1.07	0.72
	Model	0.78	0.78	0.69	1.04	0.71
ED Visits for Heart Failure Rate, Lisinopril: Events/100 patient years	Target	2.3	2.3	2.2	2.4	1.4
	Model	2.2	2.3	2.2	2.4	1.4
Rate Ratio of ED Visits for Heart Failure with Sacubitril-Valsartan	Target	0.72	0.72	0.63	0.98	0.66
	Model	0.72	0.72	0.64	0.96	0.66
Non-cardiovascular mortality Rate, Both Arms: Events/100 patient years§	Target	1.59	1.62	1.61	1.65	1.01
	Model (Lisinopril)	1.59	1.62	1.62	1.62	1.02
	Model (Sacubitril-Valsartan)	1.59	1.62	1.62	1.63	1.02

* Abbreviations: NYHA: New York Heart Association.
† Trial published hazard ratios/rate ratios for the entire cohort: cardiovascular mortality HR 0.80 (CI: 0.71-0.89), total heart failure hospitalizations RR 0.77 (CI: 0.67-0.89), total number of ED visits RR 0.70 (CI: 0.52-0.94).
‡ Targets were based on our estimate of the number of events and the follow-up in the given treatment arm and NYHA class except for the hazard ratio of cardiovascular mortality, which was based on reported cardiovascular mortality hazard ratios by NYHA Class.
§ For non-cardiovascular mortality, we assumed the same mortality rate in both treatment arms. We calibrated the rates to a combined non-cardiovascular mortality rate: the total number of non-cardiovascular deaths divided by the total follow-up. This was tested in sensitivity analyses with treatment-specific non-cardiovascular mortality.

Table S7. Event Probabilities and Rate Ratios Before and After Calibration*

Parameter	Pre-Calibration	Post-Calibration
Monthly Cardiovascular Mortality Risk, Lisinopril Arm (%)†	0.64	0.61
Hazard Ratio of Cardiovascular Mortality with Sacubitril-Valsartan‡	0.78	0.77
Monthly Heart Failure Hospitalization Risk, Lisinopril Arm (%)§	0.99	0.99
Rate Ratio of Heart Failure Hospitalization with Sacubitril-Valsartan§	0.78	0.77
Monthly ED for Heart Failure Risk, Lisinopril Arm (%)	0.19	0.19
Rate Ratio of ED with Heart Failure with Sacubitril-Valsartan	0.72	0.70
Monthly Non-cardiovascular Mortality Risk, Lisinopril Arm (%)**	0.13	0.12

* Displayed probabilities, rate ratios, and hazard ratio are for the NYHA Class II-IV cohort.
† This is the baseline cardiovascular mortality risk starting at age 64. Cardiovascular mortality increased annually by 2.6% by year to adjust for the lifetime horizon and the effect of aging (See Table S2).
‡ Hazard ratios for sacubitril-valsartan therapy relative to lisinopril therapy derived from the NYHA Class-specific hazard ratios in the PARADIGM-HF trial. The hazard ratio was applied to the baseline rate in the lisinopril/losartan arm to determine the rate in the sacubitril-valsartan arm.
§ Rate ratios are the event rate with sacubitril-valsartan therapy compared with the event rate with lisinopril/losartan therapy. The rate ratios were applied to the baseline rates in the lisinopril/losartan arm to determine the rate in the sacubitril-valsartan arm.
** This is the baseline non-cardiovascular mortality risk at age 64. Non-cardiovascular mortality increased with increasing age at the same relative rate as the CDC life table excluding cardiovascular mortality (See Table S3).

Table S8. Estimation of Events by NYHA Class and Treatment Arm*†‡

Event	Treatment Arm	Total Events	NYHA Subgroups			
			I	II	III	IV
Cardiovascular Deaths§	Enalapril	**693**	20	442	225	6
	Sacubitril-Valsartan	**558**	24	349	179	6
	Combined	**1,251**	**44**	**791**	**404**	**12**

Non-Cardiovascular Deaths[**]	Enalapril	**142**	5	102	34	1
	Sacubitril-Valsartan	**153**	4	110	38	1
	Combined	**295**	**9**	**212**	**72**	**2**
Heart Failure Hospitalizations[††]	Enalapril	**1079**	34.8	751.6	281.2	11.4
	Sacubitril-Valsartan	**851**	20.8	536.4	281.3	12.6
	Combined	**1,930**	55.6	1,287.9	562.5	24.0
Non-heart Failure Hospitalizations[**‡‡]	Enalapril	**2,974**	137.1	2,035.0	778.8	23.1
	Sacubitril-Valsartan	**2,713**	125.1	1,856.4	710.4	21.1
	Combined	**5,687**	262.2	3,891.4	1,489.2	44.1
ED Visits for Heart Failure[††]	Enalapril	**208**	6.7	144.9	54.2	2.2
	Sacubitril-Valsartan	**151**	3.7	95.2	49.9	2.2
	Combined	**359**	10.4	240.1	104.1	4.4

[*] Abbreviations: NYHA: New York Heart Association.
[†] Numbers may not add to totals due to rounding.
[‡] Numbers in bold are cited in the literature. Non-bolded numbers are estimated.
[§] Cardiovascular deaths by NYHA class estimated using the probability of cardiovascular death specific to both NYHA Class and treatment arm.
[**] In the base case, modeled based on the combined number of non-cardiovascular deaths. This was varied in sensitivity analyses.
[††] NYHA class distribution of events estimated based on the NYHA distribution of first heart failure hospitalization.
[‡‡] Distribution of non-heart failure hospitalizations by NYHA Class within a treatment arm estimated using estimates of the relative risk of non-heart failure hospitalization in NYHA Class III/IV patients compared with NYHA Class I/II patients.

Table S9. Estimation of Years of Follow-up by NYHA Class and Treatment Arm[*†]

Cohort[‡]	# Die[§]	F/u Years (Die)[**]	% of Surviving[††]	F/u Years (Survivors)[‡‡§§]	Total Years[***]	% of F/u[†††]	% of Pts[‡‡‡]
S/V I	28	36.2	4.3	366.9	403.0	4.3	4.3
S/V II	459	592.9	73.2	6,142.6	6,735.5	72.4	71.7
S/V III	217	280.3	21.7	1,817.4	2,097.7	22.5	23.2
S/V IV	7	9.0	0.7	62.8	71.8	0.8	0.8
Ena I	25	31.7	5.5	453.4	485.0	5.3	5.0
Ena II	544	689.1	70.4	5,753.8	6,442.9	69.8	69.3
Ena III	259	328.1	23.5	1,922.0	2,250.0	24.4	25.0
Ena IV	7	8.9	0.6	48.2	57.1	0.6	0.6

[*] May not sum due to rounding.
[†] Abbreviations: S/V: sacubitril-valsartan arm; Ena: enalapril arm; F/u: Follow-up; Pts: Patients.
[‡] Roman numeral refers to NYHA class.
[§] Number of patients in each NYHA Class and treatment group who died during the trial.
[**] Total follow-up years in patients who died: Number of patients who died * Median Survival (1.267 in enalapril arm and 1.292 in sacubitril-valsartan arm)
[††] Proportion of patients surviving by NYHA Class of total surviving in each treatment arm.
[‡‡] Total follow-up years by treatment arm among those surviving equals total number of years by treatment arm (9,308 for sacubitril/valsartan and 9,325 for enalapril) (7; Table 28) minus follow-up years in those who have died.

§§ Follow-up years for survivors by NYHA Class and treatment: Total follow-up years among surviving by treatment * Percentage of surviving by NYHA class in each arm
*** Total years by treatment arm and NYHA Class = Follow-up years in patients who died + Follow-up years in those who survive.
††† Percentage of total follow-up of treatment arm by NYHA class.
‡‡‡ Based on NYHA distribution among those randomized (7; Table 12).

Table S10. % of Total Treatment Arm Follow-up by NYHA Class[* †]

Treatment Arm	NYHA Class	Follow-up Estimate Method[‡]			
		A: Base Case	B: Kaplan-Meier	C: Drug Exposure	D: Proportion of Patients
Enalapril	I	5.3	5.3	4.8	5.0
	II	69.8	69.8	71.7	69.3
	III	24.4	24.3	22.8	25.0
	IV	0.6	0.6	0.7	0.6
Sacubitril-Valsartan	I	4.3	4.3	4.1	4.3
	II	72.4	72.4	73	71.7
	III	22.5	22.5	22.1	23.2
	IV	0.8	0.8	0.8	0.8

* Abbreviations; NYHA: New York Heart Association.
† May not sum to 100% due to rounding.
‡ For explanation of follow-up estimation methods, see "Estimating Follow-up by NYHA Class".

Table S11. Rate Ratio with Alternate Estimates of NYHA Class-Specific Follow-Up[*†‡§]

Parameter[**]	NYHA Cohort[††]	Follow-up Estimation Method			
		A: Base Case	B: Kaplan-Meier	C: Drug Exposure	D: Proportion of Patients
RR Heart Failure Hospitalization	Class II-IV	0.77	0.77	0.77	0.77
	Class II	0.67	0.67	0.68	0.67
	Class III-IV	1.05	1.04	1	1.04
RR ED Visit for Heart Failure	Class II-IV	0.70	0.71	0.71	0.71
	Class II	0.62	0.62	0.63	0.62
	Class III-IV	0.96	0.96	0.92	0.96

* Abbreviations: NYHA: New York Heart Association; RR: Rate Ratio.
† For explanation of follow-up estimation methods, see "Estimating Follow-up by NYHA Class".
‡ Event rates on lisinopril therapy also varied with different follow-up estimation methods (not displayed).
§ The follow-up estimate was not used to calculate NYHA-cohort specific rate ratios of cardiovascular mortality because NYHA-specific hazard ratios were available from the PARADIGM-HF trial results.
** Rate ratio refers to the rate with sacubitril-valsartan therapy compared with lisinopril therapy.
†† Rate ratios for the entire trial cohort (NYHA Class I-IV) did not vary based on alternative estimates of NYHA Class-specific follow-up.

Table S12. Incremental Cost-Effectiveness Ratio ($ per QALY gained) with Alternate Estimates of Follow-Up[*†‡]

Cohort	Follow-up Estimation Method			
	A: Base Case	B: Kaplan-Meier[§]	C: Drug Exposure	D: Proportion of Patients
NYHA Class II-IV	47,053	47,048	47,184	47,118
NYHA Class II	44,531	44,539	45,282	44,416
NYHA Class III-IV	58,194	57,891	56,228	58,335
NYHA Class I-IV	50,422	50,422	50,422	50,422

[*] Abbreviations: NYHA: New York Heart Association
[†] For explanation of follow-up estimation methods, see "Estimating Follow-up by NYHA Class".
[‡] Alternate estimates of follow-up adjusted the baseline rates and rate ratios for cohorts that excluded NYHA Class I: NYHA Class II-IV (base case), NYHA Class II, and NYHA Class III-IV.
[§] Median survival of those who died based on trial Kaplan-Meier as opposed to model estimate in the base case; see above "Estimating Follow-up by NYHA Class."

Table S13. Comparison of Modeled Rate Ratios with Sacubitril-Valsartan Excluding NYHA Class I Disease and Trial Hazard Rates/Rate Ratios[*†]

Rate Ratio Parameter	Modeled Rate Ratio[‡] (95% CI[§])	Trial Hazard/Rate Ratio[**] (95% CI)
Cardiovascular Mortality	0.77 (0.69-0.86)	0.80 (0.71-0.89)
Heart Failure Hospitalizations	0.77 (0.70-0.84)	0.77 (0.67-0.89)
ED Visits for Heart Failure without Hospitalization	0.70 (0.57-0.87)	0.70 (0.52-0.94)

[*] Abbreviations; NYHA: New York Heart Association
[†] Rate ratios are the event rate with sacubitril-valsartan therapy compared with the event rate with lisinopril/losartan therapy. Rate ratios were applied to the baseline rate in the lisinopril/losartan arm to determine the rate in the sacubitril-valsartan arm.
[‡] Excludes patients with NYHA Class I heart failure (as above).
[§] Confidence intervals were estimated using the point estimate calculated from events excluding NYHA Class I disease and standard error estimated from trial's 95% confidence interval.
[**] Hazard ratios from Cox proportional hazards model for cardiovascular mortality. Rate ratios from negative binomial model for heart failure hospitalizations and ED visits for heart failure.

Table S14. Utility Inputs[*†]

Utility Parameter	Point Estimate	95% CI	PSA Distribution[‡]	Source
Baseline Utility, NYHA Class II-IV	0.822	0.706-0.938	Beta	18§
NYHA Class I	0.918	0.789-1.000	---	18, 26
NYHA Class II	0.847	0.728-0.966	Beta	18, 26
NYHA Class III/IV	0.754	0.648-0.860	Beta	18, 26
NYHA Class I-IV	0.827	0.710-0.943	---	18, 26
Utility Increment in Sacubitril-Valsartan Arm	0.009	0.005-0.013	Beta	18, 19
Event Disutilities				
Heart Failure Hospitalization	-0.0066 (3 days)	0- -0.0135	Beta	16
Non-Heart Failure Hospitalization	-0.0066 (3 days)	0- -0.0135	Beta	Estimate
Therapy Intolerance	-0.0023 (1 day)	0- -0.0045	Beta	Estimate
Angioedema Hospitalization[**]	-0.0045 (2 days)	0 - -0.0090	Beta	Estimate

Heart Failure ED Visit	-0.0045 (2 days)	0 - -0.0090	Beta	Estimate

* Abbreviations: CI: confidence interval; NYHA: New York Heart Association; PSA: probabilistic sensitivity analysis.
† All disutilities are negative utility values.
‡ PSA was performed on the NYHA Class II-IV cohort, the NYHA Class II subgroup and the NYHA Class III/IV subgroups. No PSA distributions were created for NYHA Class I or NYHA Class I-IV subgroups.
§ Baseline utility values derived from EQ-5D data obtained via personal communication with Novartis (July 2015).
** In one way-sensitivity analyses, we estimated the effect of a greater disutility of angioedema (-0.0180 or 8 days).

Table S15. Chronic Utility Modeled as a Function of Heart Failure Hospitalizations

Time from Start of Model (Years)	Sacubitril-Valsartan Arm Utility	Lisinopril Arm Utility
0	0.822	0.822
0.5	0.821	0.820
1.0	0.820	0.819
1.5	0.818	0.818
2.0	0.817	0.816
2.5	0.816	0.815
3.0	0.815	0.814
3.5	0.814	0.813
4.0	0.813	0.812
4.5	0.813	0.811
5.0	0.812	0.810
5.5	0.811	0.809
6.0	0.810	0.808
6.5	0.809	0.807
7.0	0.809	0.806
7.5	0.808	0.805
8.0	0.807	0.805
8.5	0.807	0.804
9.0	0.806	0.803
9.5	0.805	0.803
10.0	0.805	0.802

Table S16. Cost Inputs*

Cost Parameter*	Point Estimate†	95% CI	PSA Distribution	Source
Sacubitril-Valsartan Therapy, Monthly	380.21	190.11-570.32	Normal	6
ACE-Inhibitor Therapy, Monthly	1.87	0.73-3.01	Normal	6
ARB Therapy, Monthly	6.93	2.87-10.99	Normal	6
Heart Failure Hospitalization	11,829	11,541-12,117‡	Normal	17, 20
Heart Failure ED Visit	885	663-1,106	Normal	17,20,52
Non-Heart Failure Hospitalization	7,275	6,929-7,620	Normal	17, 24
Intolerance Event, Clinic Visit	147	73-220	Normal	17
Angioedema Hospitalization	3,012	2,913-3,112	Normal	17, 24
Additional Outpatient Healthcare Costs	Age-dependent	75%-125%§	Normal	25

Cardiovascular Death**	83,982	47,036-120,928	Normal	[54]
Non-Cardiovascular Death**	91,264	46,878-135,650	Normal	[54]

* Abbreviations: CI: confidence interval; PSA: probabilistic sensitivity analysis.
† Costs in 2015 USD.
‡ In deterministic sensitivity analyses, we used a range from the average cost of hospitalization at a high-cost hospital setting ($16,783) to the average cost of hospitalization at a low-cost hospital setting ($8,357)
§ In 95% CI, age-dependent cost varied from 75% to 125% of the base case.
** The number of heart failure hospitalizations and non-heart failure hospitalizations based on the model and the expected costs of these hospitalizations were subtracted from this baseline cost.

Table S17. Incremental Cost-Effectiveness Ratio with Alternate Estimates of Cost of Sacubitril-Valsartan*

Cost Estimates†	Daily Cost ($)	% of WAC‡	Cost per QALY Gained
Wholesale Acquisition Cost	12.50	100	47,053
Average Wholesale Price	15.00	120	55,585
Average Manufacturer Price	11.85	95	44,834
Retail Pharmacy Payment with Pharmacy Benefits Manager	12.82	103	48,145
Retail Pharmacy Payment with Manufacturer Rebate	11.92	95	45,073
Retail Pharmacy Payment of Uninsured Patent	14.74	118	54,698
Mail Order Pharmacy Manufacturer Payment	11.70	94	44,323
Average Nonretail Provider Manufacturer Payment	9.90	79	38,179
Federal Facility Manufacturer Payment	6.30	50	25,892

* Abbreviations: QALY: Quality-adjusted life-year; WAC: Wholesale acquisition cost.
† Wholesale acquisition cost and average wholesale price based on *The Red Book*. Additional cost estimates calculated from those costs and the average relative cost for single-source, brand-name drugs in a Congressional Budget Office analysis.(48) These are not actual transaction costs.
‡ Wholesale acquisition cost used in the base case.

Table S18. Outpatient Costs by Age and Cohort*†

Age	NYHA Class II-IV	NYHA Class II	NYHA Class III-IV	NYHA Class I-IV	NYHA Class I
60	412	399	449	411	399
61	416	402	453	415	402
62	419	406	457	419	406
63	423	409	461	422	409
64	427	413	466	426	413
65	430	417	470	430	417
66	434	420	474	434	420
67	438	424	478	437	424
68	442	428	482	441	428
69	446	431	486	445	431
70	450	435	491	449	435
71	454	439	495	453	439
72	458	443	499	457	443
73	462	447	504	461	447

74	466	451	508	465	451
75	470	455	513	469	455
76	474	459	517	473	459
77	478	463	522	477	463
78	482	467	526	482	467
79	487	471	531	486	471
80	491	475	536	490	475

* Abbreviations: NYHA: New York Heart Association.
† Costs in 2015 USD.

Table S19. Additional One-Way Sensitivity Analysis Results

Parameter	Lower Limit (LL)	ICER ($/QALY gained) with LL	Upper Limit (UL)	ICER ($/QALY gained) with UL
Starting Age of Cohort	54	46,548	74	49,400
Cost of Angioedema Hospitalization ($)	2,913	47,053	3,112	47,053
Cost of Lisinopril Therapy, Month ($)	0.73	47,133	3.00	46,972
Cost of Sacubitril-Valsartan Therapy, Month ($)	190.10	25,721	570.31	68,384
Cost of Valsartan Therapy, Month ($)	2.87	47,168	10.99	46,938
Cost of Cardiovascular Death ($)	47,036	49,910	120,928	44,196
Cost of ED Visit ($)	663	47,061	1,106	47,044
Cost of Heart Failure Hospitalization ($)	7,688	47,585	15,440	46,588
Cost of Non-Cardiovascular Death ($)	46,878	45,079	135,650	49,027
Cost of Non-Heart Failure Hospitalization	6,929	46,937	7,620	47,169
Cost of Outpatient Healthcare, % vs. base case	-25%	45,495	+25%	48,611
Cost of Therapy Intolerance/ Clinic Visit ($)	73	47,044	220	47,062
Discount Factor	0	44,798	0.05	48,685
Disutility of Angioedema Hospitalization	0	47,055	-0.018 (8 days)	47,052
Disutility of ED Visit	0	47,061	-0.009 (4 days)	47,045
Disutility of Heart Failure Hospitalization	0	47,131	-0.014 (6 days)	46,975
Disutility of Therapy Intolerance	0	47,210	-0.005 (2 days)	46,897

Table S20. Additional Two-Way Sensitivity Analysis Results: Incremental Cost-Effectiveness Ratios (Cost per QALY gained) with Upper Limit and Lower Limit*

		Hazard Ratio of Cardiovascular Death	
		LL	UL
Probability of Cardiovascular Death	LL	44,126	78,893
	UL	34,635	61,495
		Rate Ratio of ED Visit	
		LL	UL
Probability of ED Visit	LL	47,061	47,093
	UL	46,981	47,091
		Rate Ratio of Heart Failure Hospitalization	
		LL	UL
Probability of Heart Failure Hospitalization	LL	46,740	48,170
	UL	45,558	47,894
		Hazard Ratio of Cardiovascular Mortality	
		LL	UL
Rate Ratio of Heart Failure Hospitalization	LL	37,252	66,218
	UL	38,680	69,147
		Hazard Ratio of Cardiovascular Mortality	
		LL	UL
Rate Ratio of ED Visit	LL	37,915	67,573
	UL	37,967	67,691
		Rate Ratio of ED Visit	
		LL	UL
Rate Ratio of Heart Failure Hospitalization	LL	46,115	46,186
	UL	47,999	48,071
		Utility Benefit from Sacubitril-Valsartan	
		LL	UL
Hazard Ratio of Cardiovascular Death	LL	38,989	36,966
	UL	71,511	64,219
		Baseline Utility	
		LL	UL
Hazard Ratio of Cardiovascular Death	LL	43,694	33,523
	UL	77,054	60,253

* Abbreviations: LL: Lower limit; QALY: quality adjusted life-year; UL: upper limit.

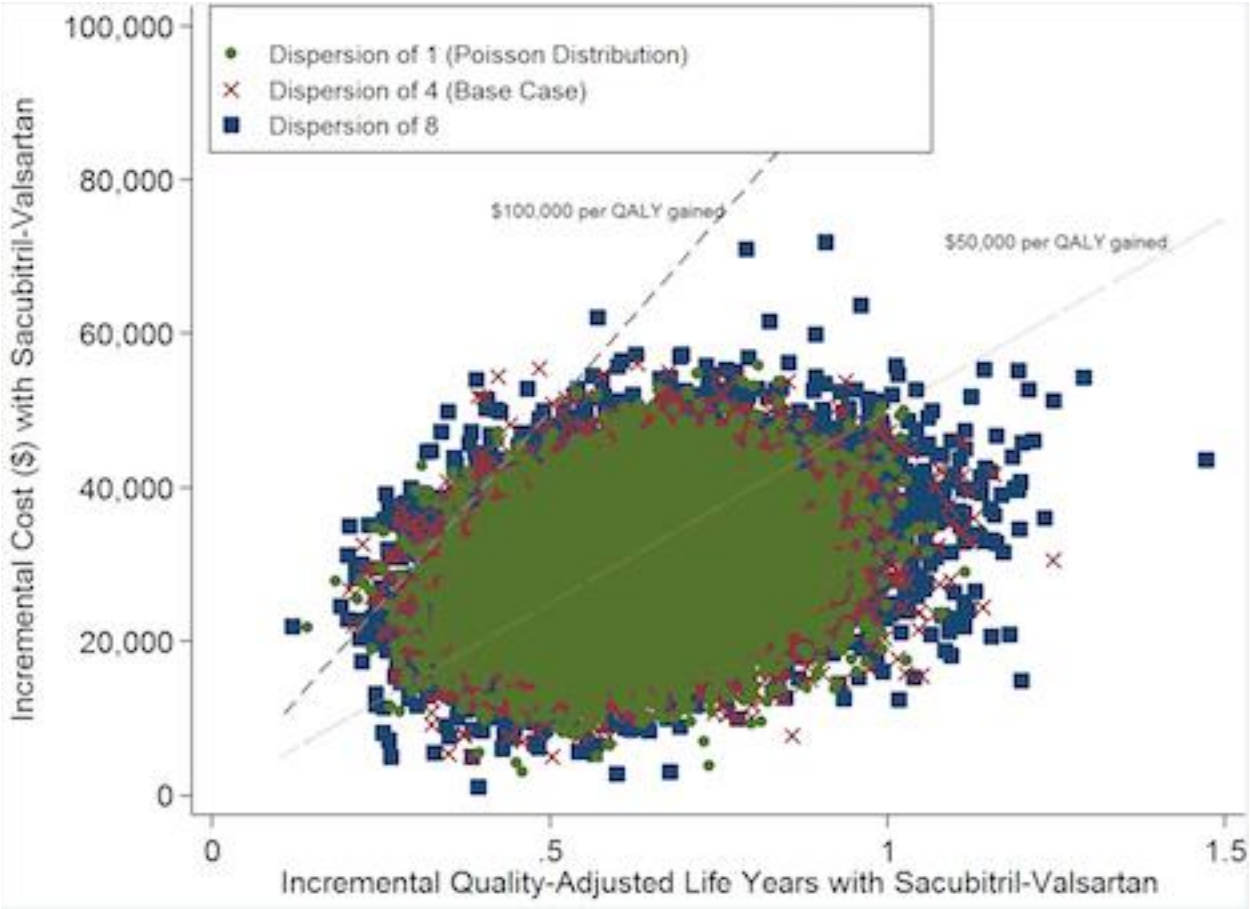
Table S21. Probabilistic Sensitivity Analysis Results with Alternative Dispersion Factors: Percentage of Cost-Effective Simulations for Sacubitril-Valsartan at Given Thresholds

Willingness-to-Pay Threshold	Dispersion Factor		
	1	4*	8
$50,000 / QALY	59.7%	57.5%	54.5%
$100,000 / QALY	99.6%	99.4%	98.7%
$150,000/ QALY	100.0%	100.0%	100.0%

* Base case

Figures

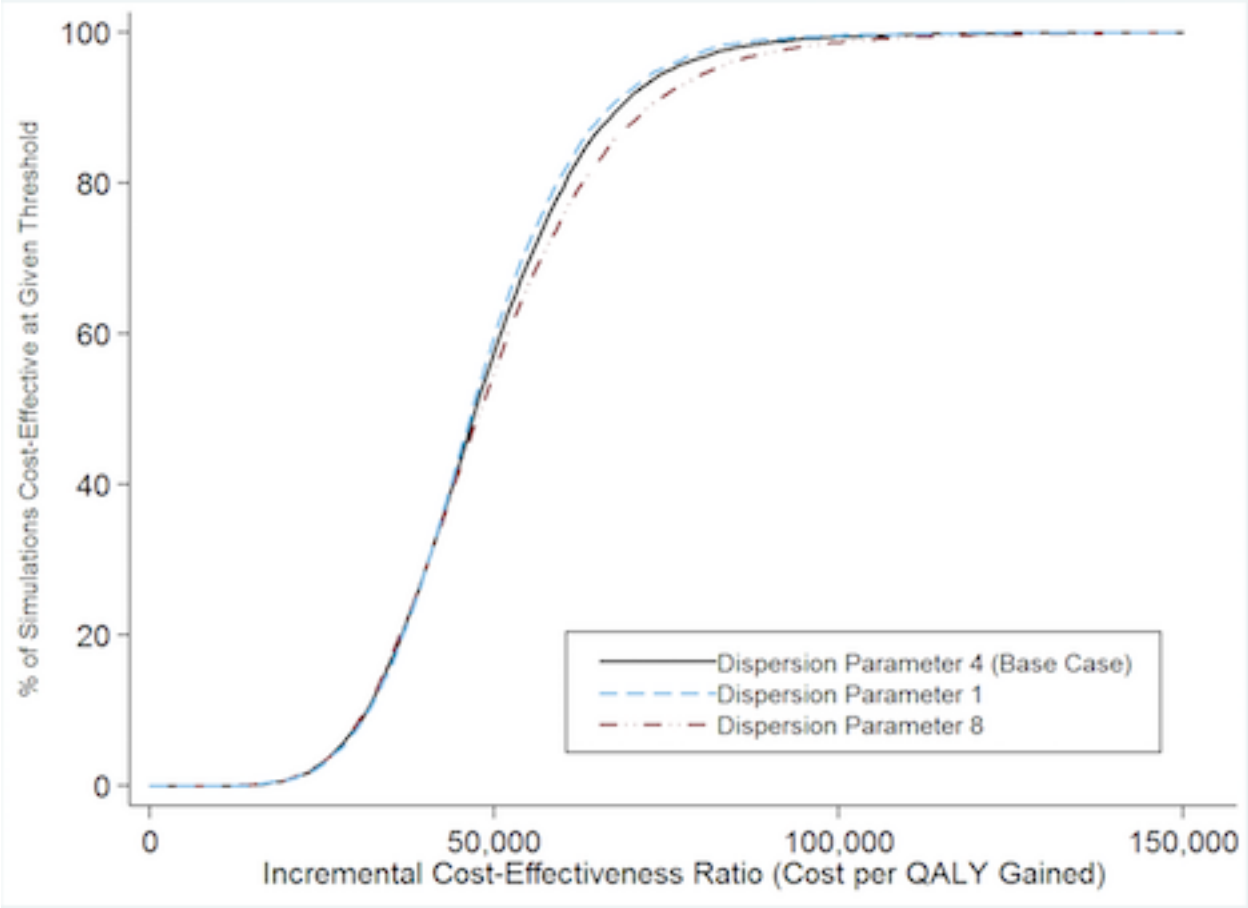
Figure S1: Probabilistic Sensitivity Analysis Scatter Plot with Varied Dispersion Factors



This is a scatter plot of the incremental QALYs and incremental cost for each simulation performed in a PSA. We have simultaneously overlaid the simulations performed with dispersion factors of 8(back), 4, and 1(front) in that order. There is a greater spread in the results of the analysis with a dispersion factor of 8 and the least spread in the analysis with the dispersion factor of 1, as is to be expected. Most of the simulations of all three analyses remain below a cut-off line

of $100,000 per QALY and just over half with each of the three dispersion parameters are below a cut-off line of $50,000 per QALY.

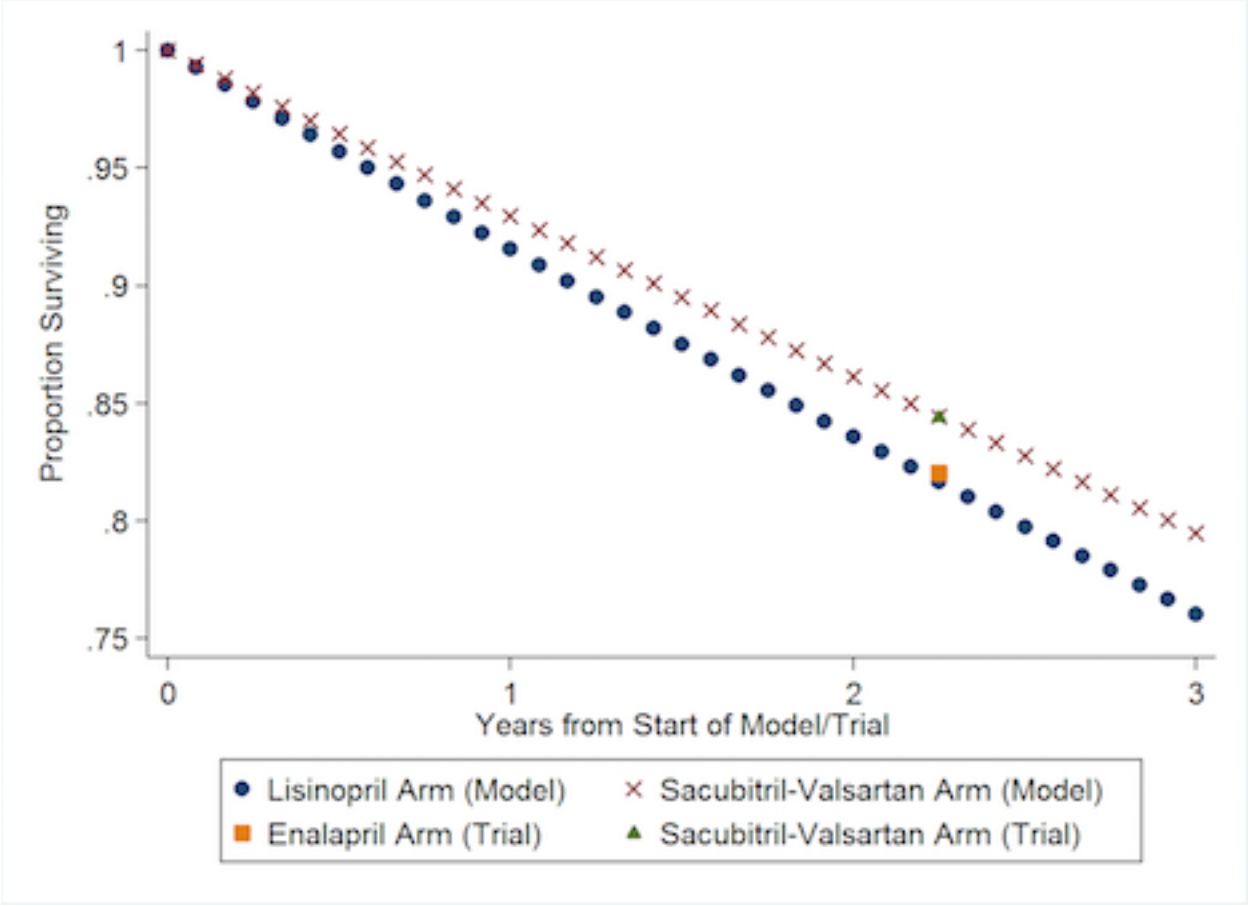
Figure S2. Cost-Effectiveness Acceptability Curve with Alterative Dispersion Factors



This demonstrates the percentage of simulations that are optimal for each strategy at given willingness-to-pay thresholds using each of the three dispersion parameters. The two graphs differ based on the dispersion factor. The overall results of the PSA are fairly similar with dispersion factors of 1, 4(the base case), and 8. There is a slight increase in the percentage of simulations that are optimal

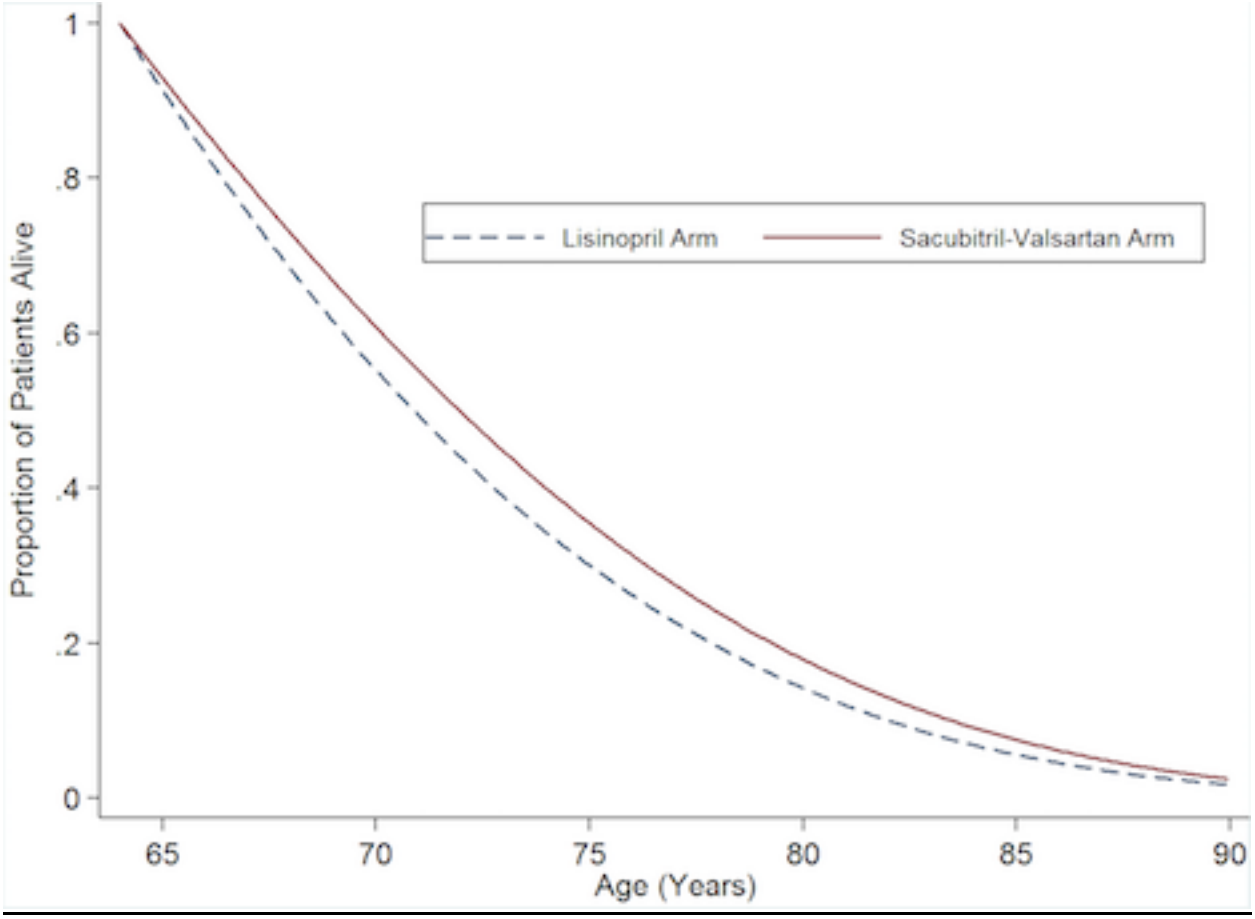
at low willingness-to-pay thresholds and a slight decrease in the percentage of simulations that are optimal at higher willingness-to-pay thresholds with a greater dispersion parameter.

Figure S3: Calibration of Modeled Mortality to Trial Mortality in NYHA Class I-IV patients



This is the proportion of the entire cohort (NYHA Class I-IV) alive in our model over time in both treatment arms after calibration to the trial mortality (also displayed).

Figure S4: Survival Curve of NYHA Class II-IV Patients



This is the modeled survival curve of the cohort of NYHA Class II-IV patients starting at age 64.