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ORIGINAL RESEARCH ARTICLE

Sacubitril/Valsartan (LCZ696): A Novel Treatment for Heart Failure and its Estimated Cost Effectiveness, Budget Impact, and Disease Burden Reduction in Germany

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Abstract

Background Heart failure affects over 1 million people in Germany and contributes to morbidity, mortality, and high healthcare costs. A recent large randomized controlled trial compared the novel compound sacubitril/valsartan (LCZ696) with the angiotensin-converting enzyme (ACE) inhibitor enalapril and found a 16% reduction in mortality hazard. In Germany, sacubitril/valsartan was launched at the beginning of 2016.

Objective The purpose of this study was to conduct a post hoc analysis of the cost effectiveness, budget impact, and disease burden reduction of sacubitril/valsartan compared with ACE inhibitors for patients with heart failure from the perspective of the German social health insurance (SHI), based on the results of this trial.

Methods A Markov (cohort) state transition model was constructed to simulate treatment over a remaining lifetime. Based on the Markov model, a dynamic population model was developed that projects the incidence, prevalence, mortality, and healthcare costs of heart failure in the SHI population from 2017 to 2060. The population model follows prevalent and incident cohorts over time. Each year a new cohort is added, while the existing cohorts age by 1 year or die. To test for sensitivity of results, a Monte Carlo simulation was run.

Results Based on the price negotiated between manufacturer and representatives of the SHI, the base-case incremental cost-effectiveness ratio (ICER) of sacubitril/valsartan versus ACE inhibitors is €23,401 per life-year gained (in 2018 Euros). At a price of zero, the cost-effectiveness ratio is already €9594 per life-year gained due to high background costs of heart failure. Annual budget impact and reduction of disease burden reach a maximum at 4–8 years after launch (€221 million and 2.9%, respectively, in the base case).

Conclusions The ICER of sacubitril/valsartan is projected to be at or below the level of other accepted interventions for the treatment of asymptomatic to severe heart failure in Germany. Projected budget impact leads to an increase in SHI expenditures by < 0.04% per year.

Key Points for Decision Makers

The incremental cost-effectiveness ratio of sacubitril/valsartan in Germany is projected to be at or below the level of other accepted interventions for the treatment of heart failure.

As a result of introducing sacubitril/valsartan in Germany, expenditures by the social health insurance are expected to increase by < 0.04% per year.

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1 Introduction

Heart failure affects over 1 million people in Germany [1, 2] and contributes to morbidity, mortality, and high medical expenditures [2–4]. LCZ696, which consists of the neprilysin inhibitor sacubitril and the angiotensin II receptor antagonist valsartan, is a novel drug for the treatment of heart failure. In Germany, it was launched at the beginning of 2016. Its efficacy was established based on the results of a large, randomized, double-blinded, phase III trial, the PARADIGM-HF trial, comparing sacubitril/valsartan against enalapril [5], which enrolled 8442 patients with New York Heart Association (NYHA) class II, III, or IV symptoms, was conducted in 47 countries including Germany, and had a mean follow-up of 2.24 years. In this trial, sacubitril/valsartan led to a relative reduction in all-cause mortality hazard by approximately 16% compared with enalapril [5]. In addition, sacubitril/valsartan significantly decreased hospitalizations for any reason, as well as emergency department (ED) visits [6].

According to the prescribing information, the target population of sacubitril/valsartan includes patients with reduced ejection fraction ($\leq$40%) and NYHA class II, III, or IV symptoms. Most patients in the PARADIGM-HF trial had relatively mild symptoms compared with the real-world population [7, 8].

The purpose of this study was to assess the cost effectiveness, budget impact, and disease burden reduction of sacubitril/valsartan compared with angiotensin-converting enzyme (ACE) inhibitors for patients with heart failure from the perspective of the German social health insurance (SHI). The study was based on the results of the pivotal PARADIGM-HF trial and was conducted post hoc. Based on a previous systematic literature search [9], no other randomized controlled trials had been conducted for the same patient population and comparator. Reflecting the approval of several ACE inhibitors for the treatment of heart failure with similar effectiveness [10], the comparator comprised all ACE inhibitors available on the German market.

2 Methods

2.1 General

We conducted a cost-effectiveness analysis using life-years gained as a measure of health benefits, as well as a cost-utility analysis using quality-adjusted life-years (QALYs). The analyses were conducted over the remaining lifetime of a patient. A Markov (cohort) state transition model was constructed. Most model input data were from the PARADIGM-HF trial and official public data, while the remaining data were identified by literature search.

2.2 Costs

We did not exclude drug co-payments, which cover a portion of the (rebated) drug price, because they depend on factors such as insurance tariff, comorbidities, and income. By including co-payments in our analysis, strictly speaking, holds the perspective of SHI members, which is still in line with recommendations for German cost-effectiveness analyses [11].

We used a price of €5.33 per day for sacubitril/valsartan treatment (see Table 1 for input data) based on the largest package size (196 tablets) [13]. This price results from the price negotiation of the manufacturer with representatives of the SHI (the price discount from the launch price was 23%) and considers mandatory rebates for the SHI. It holds since the 13th month of launch. We assumed that after patent and regulatory data protection expiration (i.e. 10 years after launch), the market price of sacubitril/valsartan will drop over a 4-year period and then reach a plateau. Prices at 1, 2, and 4 years after patent expiry were calculated as weighted averages of the price of the off-patent branded drug and the price of generic drugs based on an analysis of German sickness fund data from 2007 to 2012 [14]. Four years after patent expiry, the price of the off-patent branded drug has a weight of 25% as a reflection of its market share [14]. Furthermore, 4 years after patent expiry (i.e. 14 years after launch), the price of the off-patent branded drug and the price of generics are 86 and 54% of the branded drug price before generic entry, respectively [14]. We varied off-patent prices in a sensitivity analysis (SA). For ACE inhibitors, we used the median price of the largest package size (100 tablets) of ACE inhibitors available on the German market (captopril, cilazapril, enalapril, lisinopril, perindopril, and ramipril), considering appropriate dosage for the treatment of heart failure and mandatory rebates for the SHI [13]. As discontinuation rates with sacubitril/valsartan and ACE inhibitors are implicitly considered in the efficacy estimates of the PARADIGM-HF trial, we applied them to drug costs, as well for consistency purposes.

In the PARADIGM-HF trial, the most common clinical side effects of sacubitril/valsartan and enalapril were hypotension, elevated serum potassium, and cough [5]. While hypotension occurred significantly more often in the sacubitril/valsartan arm, the opposite held for elevated serum potassium and cough [5]. In our analysis, disutility from side effects was not directly modelled as it was indirectly captured by the prespecified preference-weight assessments using the EuroQol-5D™ (see below); otherwise, double counting of disutility would result.

Table 1 Data used for the cost-effectiveness and population model

Variable	Base-case estimate	Range tested	Distribution[a]	Reference
Clinical data				
Probability of death at age 65 years (ACE inhibitor)	8.6%	5.9–11.6%	Beta	[12]
HR for all-cause mortality (sacubitril/valsartan vs. ACE inhibitor)	0.84	0.74–0.94	Normal	[5]
Annual probability of hospitalization for any reason (ACE inhibitor)	76.8%	43.0–76.8%	Beta	[6]
HR for all-cause hospitalization (sacubitril/valsartan vs. ACE inhibitor)	0.84	0.78–0.91	Normal	[6]
Annual probability of ED visit for heart failure (ACE inhibitor)	2.24%	2.20–2.24%	Beta	[6]
HR for ED visit (sacubitril/valsartan vs. ACE inhibitor)	0.70	0.52–0.94	Normal	[6]
Cost data				
Daily cost of sacubitril/valsartan year 1 after launch	€5.33	–		[13]
Price discount after generic entry year 11 after launch	16%	8–23%	Beta	[14]
Price discount after generic entry year 12 after launch	21%	16–25%	Beta	[14]
Price discount after generic entry year 14 + after launch	38%	31–44%	Beta	[14]
Daily cost of ACE inhibition	€0.13	–		[13]
Annual cost of heart failure	€3503	–		[4]
Annual cost of potassium and creatinine control	€11.96	–		[15]
Cost of hospitalization	€3467.30	–		[16]
Reimbursement for ED visit in hospital	€32	€17–€51	Gamma	[17]
General healthcare expenditures, excluding heart failure	€1437 (age 15–29 years) €1864 (age 30–44 years) €3334 (age 45–64 years) €7275 (age 65–84 years) €16,616 (age ≥ 85 years)			[18]
Epidemiological data				
Relative mortality risk of NYHA I vs. NYHA II	0.788	0.732–0.848	Normal	[3]
Relative mortality risk of NYHA III vs. NYHA II	1.410	1.354–1.467	Normal	[3]
Relative mortality risk of NYHA IV vs. NYHA II	1.684	1.580–1.796	Normal	[3]
1-year mortality of newly diagnosed heart failure	23%	22–24%	Beta	[1]
HR age 50–59 years	0.8	0.6–1.1		[1]
HR age 60–69 years	0.9	0.7–1.2		[1]
HR age 70–79 years	1.2	0.9–1.6		[1]
HR age 80–89 years	2.0	1.5–2.7		[1]
HR age ≥ 90 years	4.2	2.9–6.1		[1]
Additional data				
Utility of heart failure at baseline	0.781	0.676–0.814	Beta	[19]
Utility decrement after 3 years for ACE inhibitor	0.033	0.016–0.085	Beta	[19]
Utility gain of sacubitril/valsartan vs. ACE inhibitor after 3 years	0.026	0.024–0.033	Beta	[19]
Treatment discontinuation rate of ACE inhibitor	19.8%	18.6–21.0%	Beta	[5]
Treatment discontinuation rate of sacubitril/valsartan	17.8%	16.6–19.0%	Beta	[5]
Annual discount rate	3%	0–5%		[11]
Maximum market penetration rate of sacubitril/valsartan	20%	10–30%		Estimate

ED emergency department, *NYHA* New York Heart Association, *HR* hazard ratio, *ACE* angiotensin-converting enzyme

[a]Considered in the Monte-Carlo simulation

The cost of hospitalization for any reason was calculated based on the national base rate of the 2018 German Diagnosis-Related Group's catalogue [16], while costs of ED visits in hospitals were based on the average reimbursement rate for a sample of 37 hospitals in 2013 [17].

We calculated life-extension costs considering costs both related and unrelated to heart failure. Specifically, we assigned annual costs related and unrelated to heart failure to each cycle of the Markov model (see the Model section). In order to determine annual costs unrelated to heart failure, we adjusted age-specific healthcare expenditures in the general population, obtained from national statistics [18], for annual expenditures related to heart failure.

Costs were inflated to year 2018 Euros using data from the German consumer price index.

2.3 Survival

In the PARADIGM-HF trial, the probability of death under enalapril at age 65 years was 8.6% [12]. We adjusted this value upward in order to account for the fact that the trial population had relatively mild symptoms [7, 8]. To this end, we used results from an analysis of claims data of 7 million individuals insured by the SHI (approximately 10% of the SHI population) in 2013 [20]. While 70% of patients in the PARADIGM-HF trial were in NYHA class II [5], the claims data analysis shows that only 45% of the German heart failure population is classified as NYHA class I or II. In order to account for a mortality increase in higher NYHA classes, we used the MAGGIC risk score [3] (see Appendix 1 for our calculation). After adjustment, the probability of death under enalapril at age 65 years was 9.2%.

The probability of survival (s) under sacubitril/valsartan at time t was calculated based on the hazard ratio (HR) of all-cause mortality:

$$s_{\text{sacubitril/valsartan}}(t) = s_{\text{enalapril}}(t)^{\text{HR}}.$$

In the PARADIGM-HF trial, the HR of sacubitril/valsartan compared with enalapril was 0.84 [5]. The p value for interaction between HR and age was 0.94, and the authors concluded that the "effect of LCZ696 compared with enalapril was consistent across the spectrum of age" [21]. Still, the added benefit of sacubitril/valsartan compared with enalapril was shown to decrease above 80 years of age, and become zero at 95 years of age (see Fig. 2d in the EuroQol Group review [21]). Given that HR was the most critical variable in the SA (see the Results section), we applied an HR of 0.84 to all ages in the base case, and modelled a 50% probability that the HR increases with higher age (see Fig. 2d in the EuroQol Group review [21]) in the probabilistic SA. In addition, we analyzed the impact of a linear increase in HR (i.e. a diminishing effect on mortality) over 10 years regardless of age, starting from the post-trial period, i.e. year 3 of treatment.

2.4 Hospitalization

Our estimate for the probability of hospitalization for any reason under ACE inhibitors was based on PARADIGM-HF patients receiving ACE inhibitors. This probability was set independent of age, in line with the conclusion drawn by the investigators, who stated that the "rate of heart failure hospitalization in the enalapril group did not vary substantially across age categories (…), except possibly in the oldest patients" [21]. The same assumption was indirectly made for sacubitril/valsartan based on an age-independent HR compared with ACE inhibitors [6].

2.5 Quality of Life

Preference weights were estimated using the three-level version of the EuroQol-5D-3L™ (EQ-5D™) questionnaire. The EQ-5D™ measures health-related quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [22]. EQ-5D™ data were collected alongside the PARADIGM-HF trial at baseline and months 4, 8, 12, 24, and 36 [18]. Due to the lack of data availability, we used data at baseline and 36 months and performed a linear interpolation. As we did not model separate NYHA classes (see the Model section), we weighted NYHA-specific EQ-5D scores by the corresponding population sizes in PARADIGM-HF, thus applying an average utility score at baseline (the same for both comparators) and at 36 months (differentiated by comparator). In a probabilistic SA, we applied upper and lower limits of the range of EQ-5D scores.

2.6 Model

We constructed a Markov model to simulate the course of 1000 patients with NYHA class II, III, or IV symptoms and lifetime treatment with sacubitril/valsartan or an ACE inhibitor. A Markov model assumes that transition probabilities do not depend on history. This assumption was verified for the PARADIGM-HF trial; there was no evidence of a change in treatment effect with increased duration of exposure ($p = 0.998$) [12].

Our Markov model contains two health states—alive and dead. Hospitalizations and ED visits are modelled within the alive state. The age of entry into the simulation is 64 years, based on the baseline age in the PARADIGM-HF trial. An additional analysis was conducted for an entry age of 72 years, which represents the average age of new heart failure cases in Germany [1].

Patients may transit to death at any time; however, they do not switch to the other treatment arm based on the PARADIGM-HF trial design. During each cycle, patients accumulate (quality-adjusted) life-years and costs. We chose a cycle length of 1 year for the two health states. The life-table method [23] was applied to both costs and life-years based on the assumption that transition events occur, on average, halfway through each 12-month cycle. The simulation was performed until age 100 years. Hence, the time horizon was 36 years in the base case. The age of 100 years was chosen as a cutting point as no official German mortality data are available beyond this age. At this age, the proportion of patients still alive is < 0.2% in both arms.

In order to account for an increase in death rate with age, we added age-specific increases in death rates for other causes to the trial-based mortality rate with enalapril. To this end, we used the mortality table of the German Federal Office of Statistics [24].

In order to convert the cumulative transition probability for hospitalizations and ED visits into an annual transition probability (reflecting the 12-month cycle length), we calculated an annual hazard rate from the cumulative transition probability [25]. Next, we converted the annual hazard rate into an annual transition probability [25]. Given that this conversion requires the assumption that each patient has no more than one event over the trial period, we performed an alternative calculation of annual transition probabilities in an SA. This approach divides the number of events over the trial period by the trial duration in years, assuming that the probability of an event during a year is independent of the probability of an event during the previous year.

For the base-case analysis, we discounted both costs and effects at an annual rate of 3% [11]. All calculations were performed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

2.7 Population Analysis

The purpose of the dynamic population model is to estimate the budget impact and disease burden reduction of sacubitril/valsartan over time. Disease burden is defined by the number of undiscounted life-years lost by patients with heart failure treated with ACE inhibitors compared with the general population. Specifically, the model projects the incidence, prevalence, mortality, and healthcare costs of heart failure (subject to treatment by sacubitril/valsartan or ACE inhibitors) in the German SHI population from 2017 (i.e. 1 year after market launch of sacubitril/valsartan) to 2060. It is based on the Markov model described above and follows prevalent and incident cohorts over time. Based on the source of our prevalence and incidence data, a recently published study [1] on 6.3 million persons enrolled in the German SHI, the population is divided into eight age categories. Each age category starts with a prevalent cohort for the year 2017, the size of which is obtained by multiplying the published prevalence rate for that age category with the population size based on official data [26]. Each year a new cohort is added based on the incidence in that age category, while the existing cohort ages by 1 year or dies, according to the Markov model. Dynamics of the general population are taken into account using a prognosis of population changes by age group from the German Federal Office of Statistics [27].

For cohorts aging beyond 110 years, we relied on international data as no official mortality data are available for Germany. International data suggest that beyond the age of 110 years, the annual probability of death stays flat at a level of 50% [28]. We applied this value to both arms. For the age interval from 101 to 110 years, we assumed a linear increase in annual mortality, consistent with the official German life-table data from ages 93–100 years.

For cohorts below the age of 64 years, we extended the Markov model to lower ages by adjusting trial-based mortality rates downward. To this end, age-specific decreases in death rates for other causes (again using the official mortality table [24]) were subtracted. The resulting lower mortality of younger heart failure patients is in line with the result of a meta-analysis of individual-level data [3].

The 1-year all-cause mortality of newly diagnosed cases was 23% and was adjusted for age (see Table 3 in Ohlmeier et al. [1]). The claims data underlying the study by Ohlmeier et al. [1] are from the year 2006. As with any claims data, they are potentially limited by misclassification. Given that the case identification algorithm not only required coding of heart failure but also of medication for heart failure, the authors considered their prevalence and incidence estimates to be conservative. In order to limit the potential bias, we also used incidence data from a more recent German sickness fund data analysis by Störk et al. [2], with different data base and case identification algorithms. We pooled data of the two studies according to the underlying population size. We also extrapolated prevalence and incidence data to the whole SHI population, and adjusted prevalence and incidence data for changes in population size by age group over time. Furthermore, as both studies include patients with a normal ejection fraction or class I heart failure, we adjusted the size of the target population downward. Based on expert opinion [20] and previous studies [29–32], we assumed that the proportion of heart failure patients with a normal ejection fraction was 50% across age groups in the base case. This fraction varied in the probabilistic SA (between 40 and 71% [see Lewis et al. [29]]). In order to determine the proportion of patients with class I heart failure, we again relied on the claims data analysis of 7 million SHI members [20].

In the base case, we assumed a 20% market penetration rate of sacubitril/valsartan starting from the 5th year after launch. This rate considers withdrawals from treatment with sacubitril/valsartan, as reported in the PARADIGM-HF trial [5]. The reason for this rather conservative estimate is that sickness funds and physician associations have negotiated a minimum coverage of ACE inhibitors (and are assumed to do so in the future). In addition, as ACE inhibitors have been an established treatment for heart failure over many years, with no medical progress in the field, doctors may be less likely to switch to sacubitril/valsartan [20]. Moreover, ticagrelor is an example of a cardiovascular drug that also underwent an early benefit assessment in Germany and has achieved, with even lower acquisition costs, a higher proportion of the patient population with considerable added

treatment benefit, and, with a high-priced comparator (prasugrel), a penetration rate of just 20% in the 5th year after launch [33]. Finally, sacubitril/valsartan could face pressure in the near future from already approved sodium-glucose cotransporter-2 (SGLT-2) inhibitors [34]. We assumed a linear increase in the penetration rate up to the 5th year after launch, starting from the penetration rate in the first year after launch (which was 5.6%, based on 25,632 treated SHI patients in 2016).

In line with principles of good practice for budget impact analysis [35], no discounting was applied because payers are interested in the financial impact at each point in time [35].

2.8 Sensitivity Analysis

Along with one-way and two-way SAs, we performed a Monte-Carlo simulation in order to assess how a simultaneous change of several variables affects the incremental cost-effectiveness ratio (ICER), budget impact, and disease burden. With 1000 samples, we obtained stable results. Probabilities, percentages, and preference weights were assumed to follow a beta distribution because they are restricted to take on values between 0 and 1 (Table 1). Relative risks and HRs were assumed to follow a normal distribution after logarithmic transformation, and costs of ED visits were assumed to follow a gamma distribution. Incident cases were assumed to be normally distributed. Due to the absence of individual-level data, correlation between parameters was not modelled.

3 Results

3.1 Cost-Effectiveness Analysis

For treatment starting at age 64 years, the undiscounted gain in a lifetime of treatment with sacubitril/valsartan versus ACE inhibitors was 1.2 years. As shown in Table 2, the base-case ICER of sacubitril/valsartan versus ACE inhibitors was €23,401 per life-year gained (costs and life-years are discounted). The discounted cost-utility ratio is €26,278 per QALY gained. At a starting treatment age of 72 years, the discounted ICER increases to a small degree (to €25,484 per life-year gained).

3.2 Sensitivity Analysis

At a price of zero, the cost-effectiveness ratio is already €9594 per life-year gained due to high background costs of heart failure. In fact, more than one-third of the additional expenditures caused by sacubitril/valsartan are attributable to life extension, i.e. not caused by sacubitril/valsartan itself. In the one-way SA, the variable with the largest impact on the cost-effectiveness ratio of sacubitril/valsartan versus ACE inhibitors is the HR for mortality (Fig. 1).

Figure 2 shows the cost-effectiveness acceptability curve, which considers uncertainty in cost effectiveness. The probability of cost effectiveness is monotonically increasing in the range of €0–€100,000 per life-year gained. The probability of cost effectiveness at a threshold ICER of €30,000 per QALY was 80%.

3.3 Dynamic Population Model

As shown in Fig. 3, the annual budget impact and reduction of disease burden reach a maximum at 4–8 years after launch (2.9% and €221 million, respectively, in the base case), based on the assumption of a linear increase in the penetration rate up to the fifth year after launch. In contrast to the budget impact increase over an 8-year period (€221 million), the maximum year-to-year increase is considerably smaller and is expected to be €88 million. From the fifth year after launch, the impact of sacubitril/valsartan on disease burden decreases because the disease burden (defined as life-years lost by patients with heart failure treated with ACE inhibitors compared with the general population) grows over time as the general population accumulates life-years compared with the heart failure population.

Figure 4 displays the uncertainty in budget impact and disease burden over time based on the results of the Monte-Carlo simulation. Again, we assumed a market penetration rate of 20% of sacubitril/valsartan at 5 years after launch and beyond.

Table 2 Discounted incremental costs, effects, and cost-effectiveness ratio of sacubitril/valsartan versus angiotensin-converting enzyme inhibitors

	Drug-related costs[a] over a lifetime (€)	Total lifetime costs (€)	Life-years	QALYs	Incremental lifetime cost (€) per life-year gained	Incremental lifetime cost (€) per QALY gained
Sacubitril/valsartan	11,963	96,194	8.04	6.16	23,401	26,278
ACE inhibitor	349	76,043	7.18	5.40		

QALYs quality-adjusted life-years

[a]Including acquisition costs and costs of laboratory tests

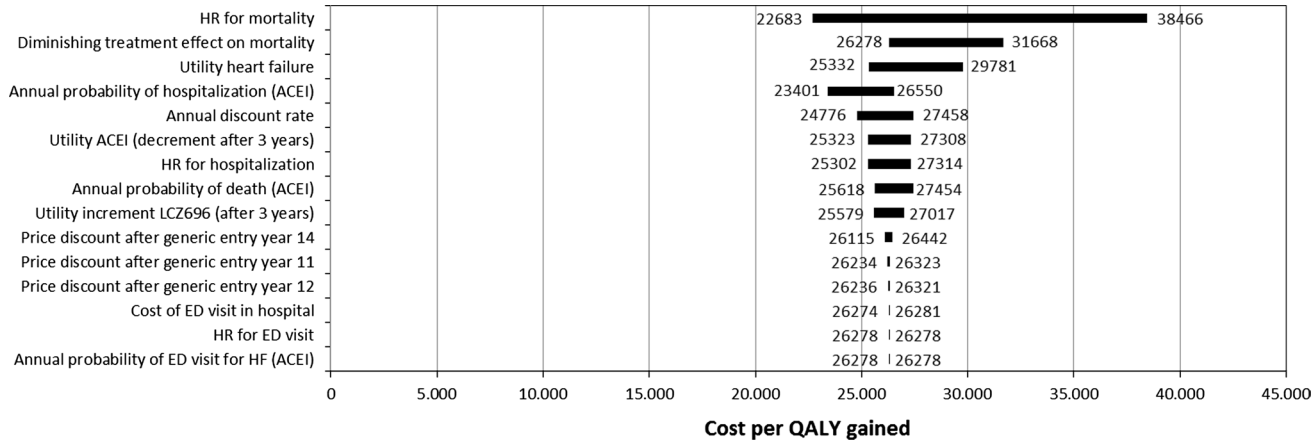

Fig. 1 Tornado diagram demonstrating the results of the one-way sensitivity analysis. Variables are ordered by impact on costs per QALY gained. Numbers indicate upper and lower bounds. *HR* hazard ratio, *ACEI* angiotensin-converting enzyme inhibitor, *ED* emergency department, *HF* heart failure, *QALY* quality-adjusted life-year

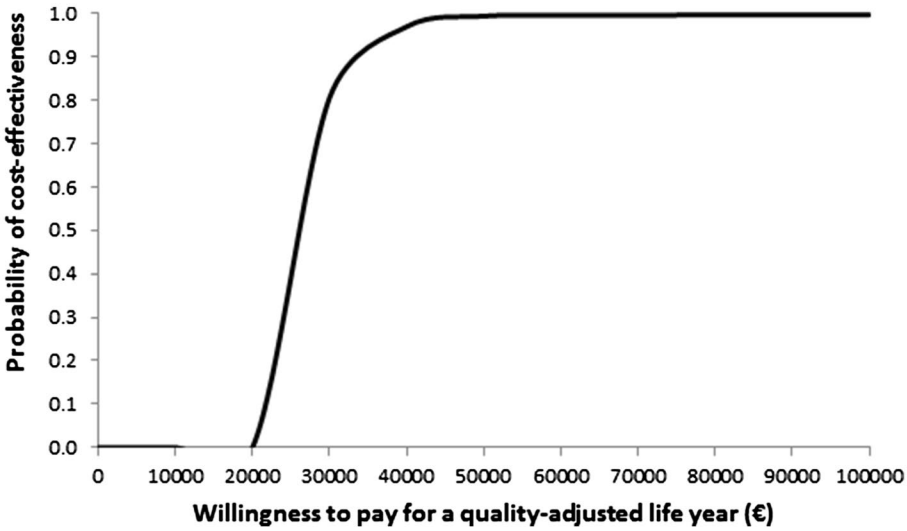

Fig. 2 Cost-effectiveness acceptability curve of sacubitril/valsartan

In a two-way SA, we varied heart failure incidence together with clinical and economic factors showing the largest impact in the one-way SA, i.e. the reduction of mortality and hospitalizations by sacubitril/valsartan. For peak annual budget impact, the range of variation is larger for incidence in combination with mortality reduction (€124–€382 million) than for incidence in combination with hospitalization reduction (Table 3), and in line with the variation shown in the Monte-Carlo simulation.

3.4 Model Validation

We performed a cross-validation of the model by comparing the ICER with those of cost-effectiveness modelling studies that are also based on a post hoc analysis of the PARADIGM-HF trial, and simulate costs and effects beyond the time horizon of the trial based on a Markov cohort model (see the Discussion section). We validated the modelled mortality increase between ages 64 and 74 years by direct comparison with data from the PARADIGM-HF trial. In patients with enalapril, the all-cause probability of death increased between the age categories 55–64 years and 65–74 years by 1.5% (from 7.5 to 9.0%) [21], yielding exactly the same increase as in our analysis. Moreover, we verified the overall small reduction in disease burden in the base case by a simple calculation: multiplying the reduction in the hazard rate of death (16%) by the penetration rate (20%) yields 3.2%. The remaining difference is explained by the increasing disease burden with time. Finally, we verified total SHI expenditures as follows. According to the study by Ohlmeier et al. [1], age-standardized prevalence of heart failure was 1.7% in 2006. Excluding 50% of patients due to an ejection

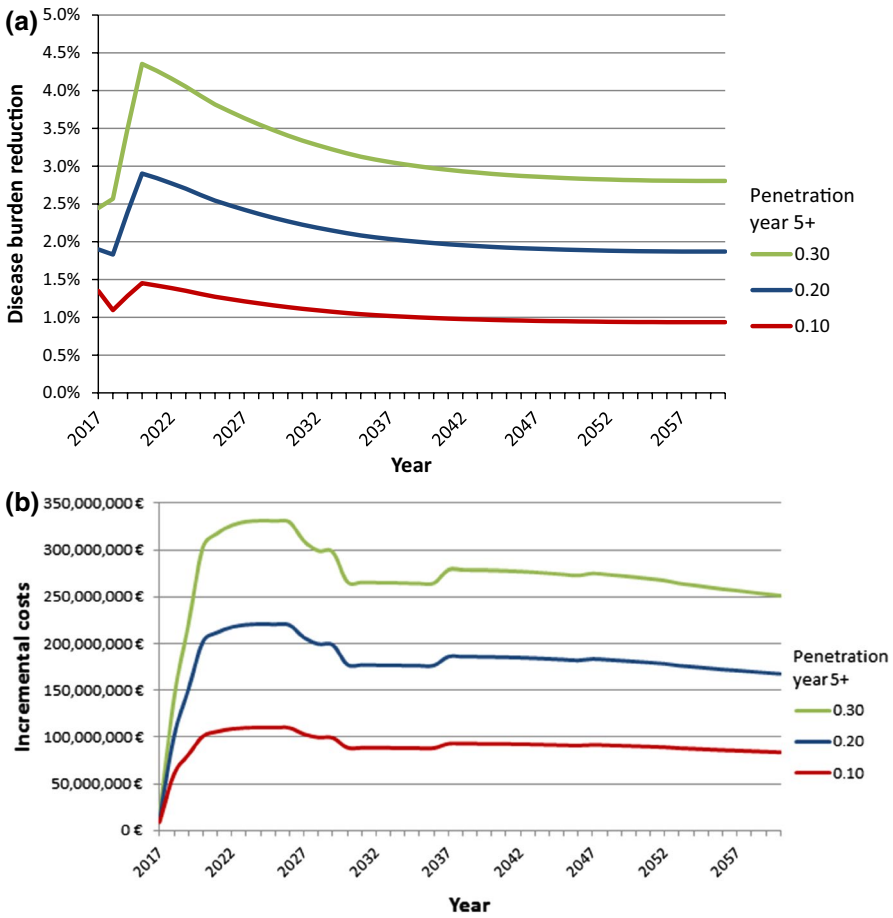

Fig. 3 **a** Reduction of disease burden by sacubitril/valsartan, and **b** undiscounted incremental annual social health insurance costs of sacubitril/valsartan from 2017 to 2060 depending on the market penetration rate of sacubitril/valsartan at 5 years after launch and beyond. Disease burden is defined as the number of undiscounted life-years lost by patients with heart failure treated with angiotensin-converting enzyme inhibitors compared with the general population

fraction > 40% [29–32], 10% thereof due to NYHA class I [9] and 80% thereof due to no prescription of sacubitril/valsartan, yields a population size of 105,000. Multiplication with the annual cost difference between sacubitril/valsartan and ACE inhibitors (€1560) yields a total of €164 million. The remaining difference in costs stems from the fact that survival costs caused by the mortality-reducing effect of sacubitril/valsartan outweighs a reduction in budget impact resulting from averted hospitalizations and ED visits, as well as a shrinkage in the size of the heart failure population over time (due to low incidence and shrinkage in the size of the general population).

4 Discussion

Based on the results of the PARADIGM-HF trial, this study simulated costs and health benefits of sacubitril/valsartan compared with ACE inhibitors in the German SHI population. It shows a cost-effectiveness ratio of €23,401 per life-year gained of sacubitril/valsartan versus ACE inhibitors. Abstracting from the fact that cost effectiveness does currently not have a role in reimbursing and pricing of new pharmaceuticals in Germany, the ratio is at or below the level of some other accepted interventions for the treatment of asymptomatic to severe heart failure in Germany [36, 37]. The cost-per-QALY ratio is only slightly higher but needs to be interpreted with caution because quality-of-life data could not be adjusted for the relatively mild symptoms of the trial population, as well as a decline of quality of life beyond the trial period.

For the budget impact analysis, we excluded patients with normal ejection fraction and/or class I heart failure in order to match the target population according to the prescribing information. The maximum annual increase in the budget due to funding for sacubitril/valsartan (€88 million) translates to an increase in SHI expenditures of < 0.04% per year.

Recently, a few cost-effectiveness modelling studies have been published that are also based on a post hoc analysis of the PARADIGM-HF trial and simulate costs and effects beyond the time horizon of the trial based on a Markov cohort model. They hold the perspective of the US society [38], US payer [39, 40], Dutch payer [41], Dutch society [42], and UK National Health Service [43]. Given that information on model structure and input data was not always fully transparent, we would like to highlight a few important differences compared with our model, without the pretense of being complete. In contrast to the models by Sandhu

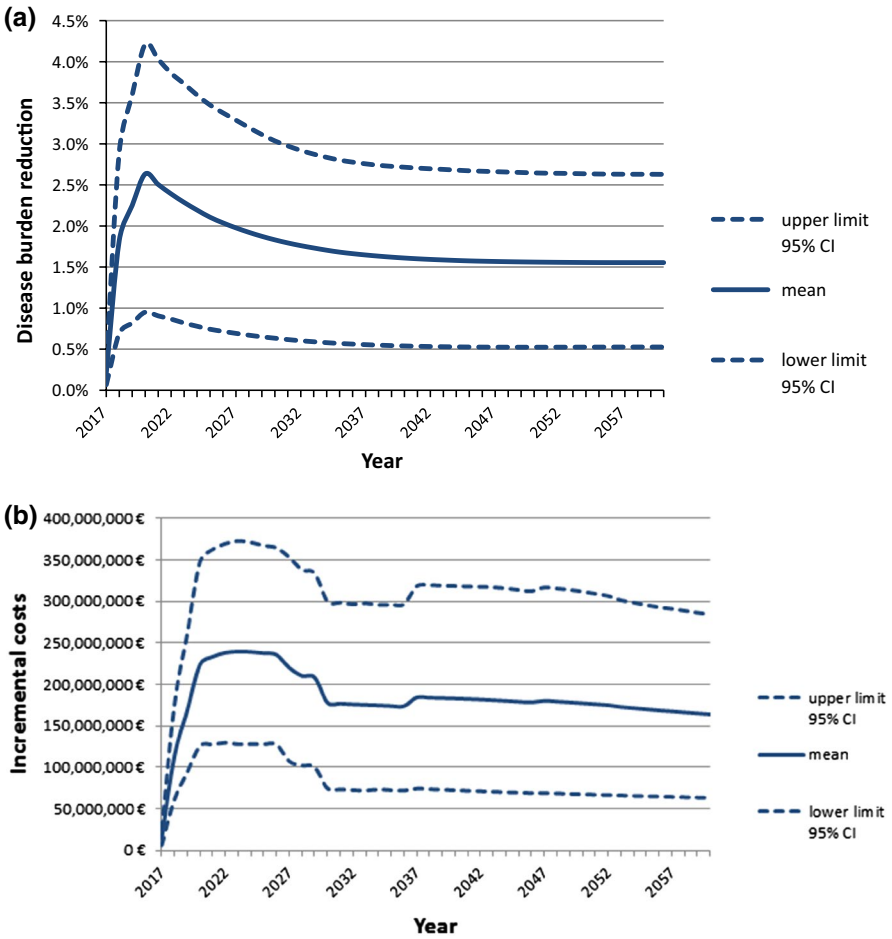

Fig. 4 Uncertainty around the **a** reduction of disease burden by sacubitril/valsartan, and **b** undiscounted incremental annual social health insurance costs of sacubitril/valsartan from 2017 to 2060. Market penetration rate was assumed to be 20% at 5 years after launch and beyond. *CI* confidence interval

Table 3 Two-way sensitivity analysis varying heart failure incidence in combination with reduction of mortality or reduction of hospitalizations by sacubitril/valsartan. Results are expressed in terms of undiscounted peak incremental budget impact of sacubitril/valsartan

	Heart failure incidence	
	Low	High
Reduction of mortality		
High	299,045,707	381,767,612
Low	123,993,495	157,588,522
Reduction of hospitalizations		
High	198,303,053	253,238,662
Low	212,042,198	270,253,103

et al. [37], King et al. [39], and van der Pol et al. [40], our Markov model has only two states. However, in our analysis, the additional states considered by Sandhu et al. [37] and van der Pol et al. [40] (i.e. hospitalizations, ED visits, and treatment intolerance) are modelled within the alive state. A disutility from hospitalizations, ED visits, and treatment intolerance is indirectly considered in the prespecified preference-weight assessments using the EuroQol-5D™ questionnaire. Arguably, a more fine-tuned approach would have elicited preference weights in the presence and absence of hospitalizations, ED visits, and treatment intolerance. On the other hand, attaching a disutility to these events post hoc amounts to double counting of the disutility. In any case, in the cost-utility analyses by van der Pol et al. [40] and Sandhu et al. [37], the impact of a disutility from avoided hospitalizations, ED visits, and treatment intolerance on the ICER was small.

In contrast to all other models published to date, the model by King et al. [39] is unique in considering the different NYHA classes as stages of the Markov model. In this model, disease progression is portrayed by transitions between NYHA classes over time. However, transition probabilities were not derived from the PARADIGM-HF trial and were not adjusted for confounders such as time since disease onset and age (instead, they were considered to be the same for all patients and constant over time). Consideration of the latter would have required an analysis of individual-level data. Nonetheless, even a trial as large as PARADIGM-HF ($n = 8442$) may not have enough statistical power to detect important differences and relationships given the wide age and severity range in the patient population.

The cost-per-QALY ratio in our study was higher than in the Dutch analysis by van der Pol et al. [40], but lower than in the US analyses [38–40] and the most likely cost-effectiveness estimate for the UK National Health Service (£26,000 per QALY gained) [43]. One reason is the acquisition cost of sacubitril/valsartan in Germany, which was higher than in The Netherlands but lower than in the US. Nonetheless, important differences in input parameters remain. In contrast to the Dutch cost-utility analysis by van der Pol et al. [40], we were able to use published utility values from the PARADIGM-HF trial and adjusted the trial-based probability of death in order to account for the distribution of NYHA classes in Germany. In contrast to the US studies, we fully accounted for non-heart-failure costs during added life-years, in line with recent recommendations by the Second US Panel on Cost-Effectiveness in Health and Medicine [44]. This approach was also taken by the Dutch society analysis [42], which showed a similar impact of background costs (€8891 per QALY gained) as our study. However, in contrast to all other cost-effectiveness analyses published to date, we modelled a price drop after generic entry. Modelling a price drop is appropriate if the purpose of the analysis is to estimate the real impact of a drug on costs. Conversely, if the purpose of the analysis is to inform the decision about reimbursing a drug (unlike the situation in Germany), only the current price may be relevant [45]. In addition, none of the above studies used a dynamic population model to calculate the budget impact and disease burden reduction over time.

Additional limitations of our study need to be acknowledged. First, it is possible to model disease-related and disease-unrelated mortality separately. It has been argued that non-cardiovascular mortality is likely to be overestimated in the PARADIGM-HF trial compared with Europe and North America "given that the trial included a considerable proportion of patients from countries where other causes of death, such as infection, are more prevalent than in Europe and North America" [43]. On the other hand, modelling all-cause mortality as such is able to account for the fact that risk factors underlying heart failure and other diseases overlap (e.g. smoking is a risk factor for both heart failure and cancer). The latter approach was also favoured by the PARADIGM-HF investigators [12], as well as a Dutch study group [42], in estimating the long-term treatment benefits of sacubitril/valsartan.

Second, the budget impact of sacubitril/valsartan may be over- or underestimated. It may be overestimated because mortality of newly diagnosed cases may be underestimated in the population model. This holds because the underlying publication by Ohlmeier et al. [1] includes patients with a normal ejection fraction or class I heart failure. It may also be overestimated because the claims data analysis [20] assumes the same distribution of NYHA classes for patients with an unspecific diagnosis of heart failure (i.e. lack of coding for NYHA class) as for specified cases. However, unspecified cases are more likely to occur at early disease stage and therefore should have been excluded from the target population. On the other hand, the budget impact may be underestimated because certain diagnoses were not considered in the claims-data analysis despite a potential indication for sacubitril/valsartan (e.g. cardiomyopathy). In addition, the case identification algorithm by Ohlmeier et al. [1] was rather restrictive, leading to underdiagnosis of heart failure and the resulting budget impact. Moreover, in the PARADIGM-HF trial, 6.2% of patients discontinued during the run-in phase due to adverse events or abnormal test results. Considering these patients, who are part of the real-world spectrum of patients, could also affect the budget impact.

As a third limitation, we assumed that the median price of ACE inhibitors would reflect the price of the current treatment mix for patients with heart failure. However, the median price may not mirror the market share of different ACE inhibitors.

In the future, patients with heart failure are expected to survive longer because of the development and implementation of new life-prolonging therapies [34, 46]. These treatments could lead to an increase in the population size and the prevalence of heart failure. This trend was not considered in the population model and may be considered in future analyses.

5 Conclusions

The ICER of sacubitril/valsartan in Germany is projected to be at or below the level of other accepted interventions for the treatment of heart failure. As a result of introducing sacubitril/valsartan in Germany, expenditures by the social health insurance are expected to increase by < 0.04% per year.

Author contributions AG was involved in model conceptualization, building, and validation, and wrote the first draft of the manuscript. DO was involved in model conceptualization and commented on the draft version of the manuscript.

Compliance with Ethical Standards

Data Availability Statement All data generated or analyzed during this study are included in this published article.

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Appendix 1

Calculation of the probability of death under enalapril at age 65 years under real-world conditions

$$p_{\text{real world}} = p_{\text{trial}} \cdot \frac{\sum_{i=1}^{4} \text{RR}_i \cdot f_{i,\text{real world}}}{\sum_{i=1}^{4} \text{RR}_i \cdot f_{i,\text{trial}}},$$

where p_{trial} is the probability of death under enalapril at age 65 years in the PARADIGM-HF trial, i is the New York Heart Association (NYHA) class, RR is the 'rate ratio' of the MAGGIC risk score (NYHA class II was set to 1.0) [3], and f is the fraction of patients.

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