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Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction

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Summary

AIMS: We aimed to assess the cost effectiveness of sacubitril/valsartan compared to angiotensin-converting enzyme inhibitors (ACEIs) for the treatment of individuals with chronic heart failure and reduced-ejection fraction (HFrEF) from the perspective of the Swiss health care system.

METHODS: The cost-effectiveness analysis was implemented as a lifelong regression-based cohort model. We compared sacubitril/valsartan with enalapril in chronic heart failure patients with HFrEF and New York-Heart Association Functional Classification II–IV symptoms. Regression models based on the randomised clinical phase III PARADIGM-HF trials were used to predict events (all-cause mortality, hospitalisations, adverse events and quality of life) for each treatment strategy modelled over the lifetime horizon, with adjustments for patient characteristics. Unit costs were obtained from Swiss public sources for the year 2014, and costs and effects were discounted by 3%. The main outcome of interest was the incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life years (QALYs) gained. Deterministic sensitivity analysis (DSA) and scenario and probabilistic sensitivity analysis (PSA) were performed.

RESULTS: In the base-case analysis, the sacubitril/valsartan strategy showed a decrease in the number of hospitalisations (6.0% per year absolute reduction) and lifetime hospital costs by 8.0% (discounted) when compared with enalapril. Sacubitril/valsartan was predicted to improve overall and quality-adjusted survival by 0.50 years and 0.42 QALYs, respectively. Additional net-total costs were CHF 10 926. This led to an ICER of CHF 25 684. In PSA, the probability of sacubitril/valsartan being cost-effective at thresholds of CHF 50 000 was 99.0%.

CONCLUSION: The treatment of HFrEF patients with sacubitril/valsartan versus enalapril is cost effective, if a willingness-to-pay threshold of CHF 50 000 per QALY gained ratio is assumed.

Key words: cost-effectiveness, chronic heart failure, drug treatment

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Introduction

Heart failure is a progressive and incurable disease, with high morbidity and mortality in high-income countries including Switzerland. The reported prevalence of heart failure varies from between 1 and 2%, and increases for individuals aged above 65 years [1]. Estimates for 2010 expected 15 million people with heart failure in Europe and 6.6 million in the United States [2, 3]. Chronic heart failure has a prevalence of 1 to 2% and heart failure with reduced ejection fraction (HFrEF) accounts for about 50% of all heart failure cases [4]. In general, the condition requires complex management and treatment protocols that require substantial effort from patients, care givers, and healthcare services, and therefore poses a high cost burden on society [5]. Morbidity is very prominent in terms of severity of symptoms, reduced quality of life, hospitalisations and continuous need for treatment [6, 7]. Previous guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers as initial treatment, as well as diuretics if there is a fluid overload [8]. These treatments appear to reduce the risk of death and improve exercise capacity. Angiotensin receptor blockers (ARBs) are controversial and less well tolerated than ACEIs, but remain a treatment option where ACEIs are not tolerated. Other treatments such as anti-platelets and lipid-lowering agents are added if necessary [9]. Advances in chronic heart failure treatment have been quite limited in the last decade.

Sacubitril/valsartan, an angiotensin-receptor-neprilysin-inhibitor (ARNI), is a novel oral therapy proposed in the cur-

rent guidelines for the treatment of heart failure in patients with reduced left ventricular ejection fraction (LVEF) [9]. The phase-III prospective double-blind randomised controlled trial PARADIGM-HF (prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure) compared morbidity and mortality between sacubitril/valsartan and the ACEI enalapril in a population with HFrEF [10]. The primary outcome was a composite of death from cardiovascular causes or hospitalisation for heart failure. After a median follow-up of 27 months, sacubitril/valsartan was associated with a significant reduction in time to the primary outcome (hazard ratio [HR] 0.80, 95% confidence interval [95% CI] 0.73–0.87; p <0.001), all-cause mortality (HR 0.84, 95% CI 0.76–0.93; p <0.001) and cardiovascular mortality (HR 0.80, 95% CI 0.71–0.89; p <0.001). In addition, sacubitril/valsartan was also associated with a reduced risk of hospitalisation for heart failure of 21% (p <0.001) and a reduction in the symptoms and physical limitations of heart failure (p = 0.001) [10].

The aim of this study was to assess the clinical effectiveness in terms of quality-adjusted life years (QALYs) gained, the direct medical cost, and the cost-effectiveness of sacubitril/valsartan (in addition to standard care) compared to ACEIs (in addition to standard care) from the perspective of the Swiss healthcare system.

Methods

Overview of approach and model

A model-based cost-utility analysis was undertaken comparing sacubitril/valsartan and standard care to ACEI and standard care. The incremental cost-effectiveness ratio (ICER) was expressed as cost per QALY gained. The analysis was conducted from the perspective of the Swiss healthcare system. Costs and effects occurring after one year were discounted by 3% in the base-case analysis.

A two-state Markov model [11] was implemented for the current analyses. In brief, the model is structured as a two-state Markov model (with health states “alive” and “dead”). Regression models were used to predict events and outcomes such as mortality, hospitalisations, adverse events and health-related quality of life over the lifelong time horizon of the model, based on patient characteristics and treatment received (fig. 1). This type of model was chosen as the benefits of treatment and costs continue to accrue beyond the observation period of the PARADIGM-HF trial. Cycle length is one month and a half-cycle correction is applied. The model permits both deterministic (DSA) and probabilistic sensitivity analyses (PSA). Death can occur at any point in time. Model outcomes include survival time (i.e., life years), QALYs, medical resource utilisation, accrued lifetime and total and disaggregated costs, and other clinical events such as number of hospitalisations and adverse events.

Patient population

The patient population considered for the economic model was the same as that enrolled on the PARADIGM-HF trial [10] i.e., adult HErEF and a mean age of 64 years. The following eligibility criteria were applied: age of at least 18 years, NYHA class II–IV symptoms, ejection fraction of 40% or less (which was changed to 35% or less) [12], and plasma B-type natriuretic peptide (BNP) level of at least 150 pg/ml or hospitalisation for heart failure within the previous 12 months and a BNP of at least 100 pg/ml. Patients taking stable doses of ACEIs or ARBs four weeks before screening were considered for participation in the study. Implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) are increasingly used in patients with HFrEF. In the PARADIGM-HF trial [10], 1,857 (22%) of the eligible patients used either ICDs or CRT at baseline. After screening, patients had a run-in phase with enalapril or sacubitril/valsartan, which was followed by the main double-blind randomised treatment phase [13]. Of 8,442 patients randomised, 43 patients were excluded for the full analysis set (FAS) due to invalid randomisation (n = 6) and good clinical practice (GCP) violations (n = 37). The analysis population consisted of 4187 patients receiving sacubitril/valsartan and 4212 patients receiving enalapril. The baseline characteristics of the trial population are presented in supplementary table S1 in appendix 2.

Treatment strategies

The average daily dose at the end of the PARADIGM-HF trial [10] for sacubitril/valsartan (in addition to standard care) was 375 mg compared to a treatment strategy with a daily dose of the ACEI enalapril (in addition to standard care) of 18.9 mg. Standard care included the use of diuretics, beta-blockers, aldosterone antagonists, digoxin, anticoagulants, aspirin, adenosine diphosphate antagonists and lipid-lowering medications. The choice of standard care is based on medication classes observed in the PARADIGM-HF trial [10].

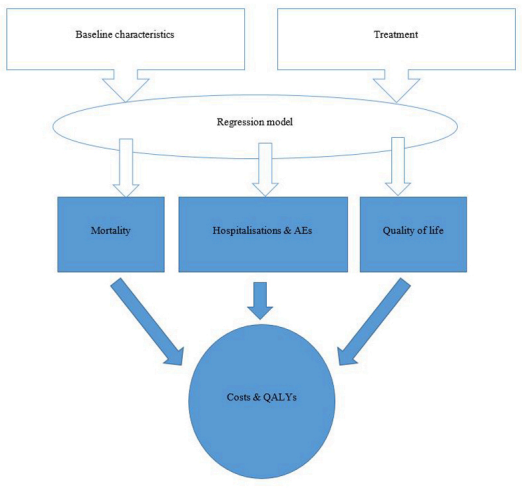
Clinical model inputs

Clinical information regarding all-cause mortality, hospitalisation rates, health-related quality of life and adverse events was obtained from the PARADIGM-HF trial [10].

Mortality

The base-case analysis used a multivariable parametric survival model of all-cause mortality, which was based on the treatment arm, baseline characteristics of the patients,

Figure 1: Model structure.AEs = adverse events; QALYs = quality adjusted life years



and time since randomisation (supplementary table S2 in appendix 2).

An alternative scenario analysis used multivariable parametric survival for cardiovascular mortality from the PARADIGM-HF trial [10] (supplementary table S3), and non-cardiovascular mortality from Swiss national life-tables (table S6). The monthly probability of non-cardiovascular mortality was obtained by subtracting the probability of cardiovascular mortality from the probability of all-cause mortality as calculated with data provided by the Swiss Federal Office of Public Health (SFOPH) [14] and the Swiss Federal Office of Statistics (SFOS) tables [15]. A death rate including cardiovascular death for five-year age bands was calculated by dividing the number of deaths obtained from Swiss life tables [15] by the number of persons in the relevant age group sourced from the SFOPH [14]. The death rates were converted to yearly probabilities of death using the formula $p = 1 - e^{-central\ death\ rate*time}$ (time is 1/12 years in this case, as we derived monthly probabilities). All-cause mortality and cardiovascular mortality were assumed to be constant within the 5-year age bands provided by the SFOS, and constant in the age group of persons aged 85 years or above, as we had no additional data for this age category. Additional information about Swiss population and related mortality is available in tables S4, S5 and S6.

Hospitalisation and adverse events

The model predicted the risk of all-cause hospitalisation beyond the PARADIGM-HF trial using negative binomial regression [11]. Briefly, predicted hospitalisation rates were adjusted for baseline characteristics of the subjects included in the PARADIGM-HF trial such as age, race, and region, and were dependent on the treatment arm. The model for all-cause hospitalisation showed that a treatment strategy with a daily dose of sacubitril/valsartan compared to ACEI treatment reduced all-cause hospitalisation (supplementary table S7).

More serious adverse events were considered to be covered by all-cause hospitalisations (table S7), whereas less serious adverse events were considered independently. Rates of these adverse events (hypotension, elevated serum creatinine and potassium, cough and non-severe angio-oedema) were estimated from the PARADIGM-HF trial) [10]. Occurrence of less serious adverse events can be found in the additional material provided in table S8.

Health-related quality of life (HRQoL)

A mixed-effects regression model derived from the PARADIGM-HF trial based on patient-level EQ-5D data was estimated to allow the prediction of the EQ-5D-based utility values as a function of baseline characteristics (including baseline EQ-5D), hospitalisations, adverse events, treatment arm and time since randomisation. The EQ-5D 3-level questionnaire was administered at baseline and at months 4, 8, 12, 24, 36, and end of study. The UK EQ-5D tariff published by Dolan et al. was applied to EQ-5D patient responses [16]. Details are available in table S9. Hospitalisations in the 30 days before EQ-5D measurement (to capture the acute effect of hospitalisation), and hospitalisations 30–90 days before EQ-5D measurement (to capture any long term effect during rehabilitation) were implemented. Utility decrements in the model were applied to subjects experiencing hospitalisations or adverse events.

Resource use

Drug dosage (primary and background drug therapy) data from the PARADIGM-HF trial were validated by using the recommendations of the Swiss Heart Failure Working Group of the Swiss Society of Cardiology [17], which are based on 2012 European Society of Cardiology (ESC) guidelines [8]. Drug dosages used for the Swiss model can be found in supplementary table S10. The proportional occurrence of hospitalisations for surgical procedures (4.0%), interventional procedures (8.0%), or medical management only (88.0%), was obtained from the Western European population of the PARADIGM-HF trial (table S11).

A background medical resource utilisation per unit of time was assumed to be the same in both treatment strategies of the model. We assumed that patients with heart failure would need to have at least 12 primary-care physician (PCP) visits per year. This was based on an article by Muntwyler et al. [18], which measured the quality of the diagnosis and management of heart failure in primary care in 1999 in Switzerland. Over 82 PCPs from all over Switzerland participated in the study. A total of 474 patients were included.

Milder adverse events reported in the PARADIGM-HF trial [10] were modelled separately, as mentioned previously. The following assumptions were applied for resource use associated with adverse events; (a) if a patient experiences hypotension, he/she needs 2 additional PCP visits, (b) if a patient experiences cough, he/she needs 2 additional PCP visits and blood tests, (c) in the case of angio-oedema, patients can experience milder or severe angio-oedema. Milder angio-oedema patients require use of antihistamines and 2 additional outpatient visits, while patients experiencing more severe angio-oedema need 2 additional outpatient visits and use of glucocorticoids, (d) if patients show signs of elevated serum creatinine, they need 2 additional PCP visits and a blood test, (e) if patients show signs of elevated serum potassium, they need 2 additional PCP visits and a blood test.

Unit costs

The cost of sacubitril/valsartan per day in the base-case analyses was CHF 5.79 (375 mg per day), and unit costs of background therapies were sourced from SFOPH data (Spezialitätenliste) relevant to 2015 [19]. For each reported therapeutic substance used in the PARADIGM-HF trial, we collected and mapped drugs representing the same substance, based on the number of available producers in the Swiss pharmaceutical market. For example, if there were three pharmaceutical producers of enalapril 10 mg on the market, then the average cost per tablet strength was calculated. Monthly costs were calculated by multiplying the daily costs by 365.25/12. Daily costs of primary therapies and background therapies can be found in supplementary table S10.

Unit costs of hospitalisations were estimated on the basis of diagnosis-related group (DRG) costs, and by mapping each reported hospitalisation in the PARADIGM-HF trial to relevant Swiss DRG codes [20]. For this mapping procedure, we used the proportional occurrence of hospitalisations involving surgery, interventional procedures or med-

ical management. Where several suitable Swiss DRG codes were identified, the weighted mean was used based on their activity and cost as reported for 2012, which is when the latest data was published [20]. Details about hospitalisations, the proportional occurrence of diagnoses reported in the PARADIGM-HF trial, and Swiss DRGs assigned are provided in table S11. The weighted mean cost per hospitalisation provided information on the unit cost per hospitalisation event rather than cost per day in hospital. For the year 2012, the average cost per hospitalisation was CHF 13 847; these costs were then updated to 2014 values using the Swiss consumer price index [21]. The consumer price index values for 2012 and 2014 were 99.9 and 98.1. The resulting cost per hospitalisation in 2014 was CHF 13 598.

As described previously, the estimated number of PCP visits per year was informed by the European IMPROVEMENT-HF study [18]. The unit costs of a PCP visit were derived from the santésuisse web page, and amounted to CHF 113 in 2007. Based on the consumer price index [21] the updated value for one PCP visit in 2014 was CHF 110.30. Unit costs for the treatment of each relevant type of adverse event were estimated from Swiss literature and information publicly available from the SFOPH, Tarmed, and santésuisse websites [19] [22].

Subgroup analyses

Subgroup analyses based on the *a priori* subgroups in PARADIGM-HF were undertaken to understand variation of the main results between subgroups of patients enrolled in the PARADIGM-HF trial.

Sensitivity analysis

To assess the impact of different assumptions on the model results, a series of scenario analyses were performed. Some were of general relevance. Additional analyses were regarded as specifically relevant for the Swiss setting (see appendix 1 for description). A series of deterministic sensitivity analyses (DSA) were performed to assess the impact of uncertainty surrounding key input parameters. Important parameters were varied independently over plausible ranges determined by the 95% confidence intervals (CI) surrounding point estimates. Where 95% CIs were not available, upper and lower values of ±25% surrounding point estimates were used (supplementary table S12). The ICERs resulting from each analysis were recorded for the upper and lower value and are presented in a Tornado diagram.

Probabilistic sensitivity analysis was undertaken to explore joint parameter uncertainty (details about their respective distributions in table S12). A total of 10 000 iterations were run and the results are shown as a cost-effectiveness plan.

Results

Base-case analyses

In the base-case analysis, the sacubitril/valsartan strategy compared to enalapril showed a decrease in the number of hospitalisations (6.0%/year absolute reduction) and lifetime hospital costs by 8.0% (discounted). Total QALYs per person over a lifetime horizon were 4.99 and 4.56 in the sacubitril/valsartan and ACEI treatment strategies respectively (table 1). This led to an incremental difference of 0.425 QALYs. The total incremental costs difference was CHF 10 926 (table 1) and the ICER for sacubitril/valsartan treatment versus ACEI was CHF 25 684 per QALY gained. Alternatively, the use of Swiss life-tables for non-cardiovascular mortality and cardiovascular mortality rates from the PARADIGM-HF trial led to an ICER of CHF 24 490.

Cost-effectiveness results for subgroups of patients are presented in full in supplementary table S13 in appendix 2. The ICER was quite stable, with ±1–11% variation from the base-case result. In brief, if the baseline eGFR was <60, the ICER decreased by 8.0%. No use of beta-blockers at baseline decreased the ICER by 11.0%, and where ≤1 year since diagnosis of heart failure was recorded, this increased the ICER by 8.0%.

Sensitivity analysis

The most influential parameters in univariate sensitivity analysis were related to all-cause mortality, hospitalisations and HRQoL (fig. 2). Table 2 shows the scenario analysis results. An ICER of > CHF 48 000 per QALY occurred if all treatment effects of sacubitril/valsartan were assumed to cease after year 5 (while the treatment costs of sacubitril/valsartan continued for life). An analysis based on two years of follow-up led to an increased ICER of CHF 58 679. An ICER of CHF 30 812 per QALY gained was observed where there was assumed to be no effect of sacu-

Table 1: Base case results (all costs are expressed in CHF).

Parameter	Sacubitril/valsartan	ACEI	Difference
Clinical effectiveness parameters (discounted)			
Total life years	6.67	6.17	0.50
Total QALYs	4.99	4.565	0.4254
Cost parameters (discounted)			
Primary therapy	14 119	1757	12 362
Titration	220	0.00	220
Adverse events	307	290	17
Background drug therapy	8072	7467	605
Management of HF by physicians	8830	8168	662
Hospitalisation	32 857	35 797	−2940
Total costs	69 683	53 479	10 926
Cost-effectiveness parameters			
Cost per LYG			**CHF21 855**
Cost per QALY gained			**CHF25 684**

ACEI = angiotensin-converting enzyme; HF = chronic heart failure patients; LYG = life year gained; QALY = quality adjusted life year

bitril/valsartan on HRQoL. Using the German and French EQ-5D value sets instead of that for the UK led to slightly more favourable ICER results. Other scenario analyses did not have a major impact on the ICER.

PSA results are presented in figure 3 as a cost-effectiveness plane. All simulation fell within the northeast quadrant of the cost-effectiveness plane (meaning in all simulations sacubitril/valsartan was both more effective and costlier than enalapril), with a 95% confidence interval range of CHF 18 798 to CHF 43 974 per QALY gained. The cost-effectiveness threshold of CHF 30 000 per QALY gained

Figure 2: Tornado diagram summarising univariate sensitivity analysis results.

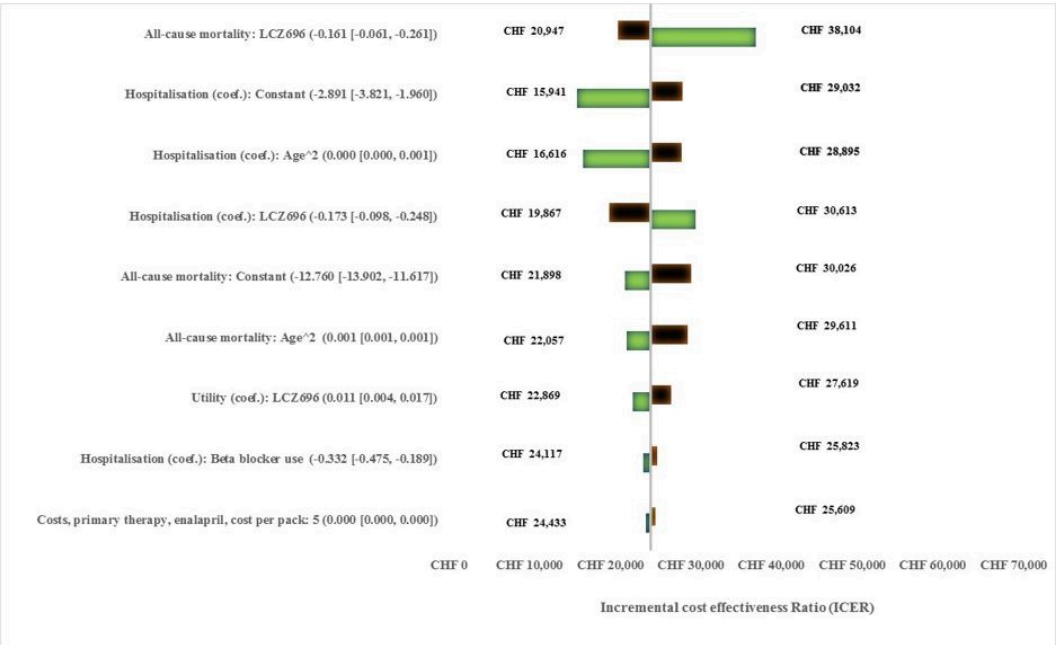
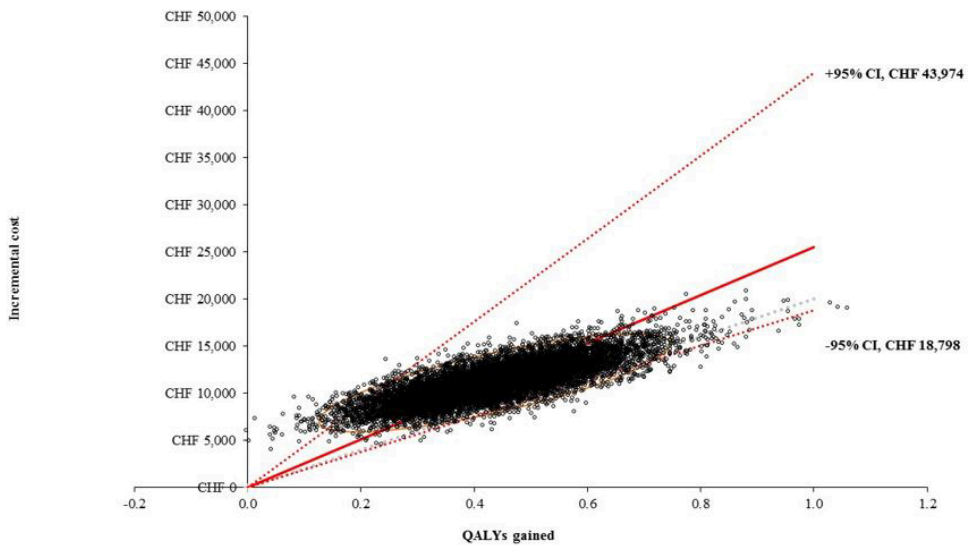


Table 2: Results of scenario analyses.

Area of uncertainty	Scenario	ICER (cost per QALY in CHF)
Base case (patient level data)		**25 684**
Discount rate	Discount rate: 1.5% benefits; 6% costs	18 951
Time horizon	2 years	58 679
CV mortality PARADIGM, non-CV mortality life tables		24 490
HRQL time trend	Time trend halved	24 648
HRQL time trend	Time trend doubled	28 041
HRQL time trend	No decrease in HRQL	23 693
HRQL time trend	HRQL constant at 5 years	24 648
HRQL time trend	HRQL constant at 10 years	25 311
Treatment effect on HRQL	No absolute benefit in HRQL for sacubitril/valsartan	30 812
Treatment effect on hospitalisation	sacubitril/valsartan treatment effect applied only to HF hospitalisations (rather than CV mortality and utility)	36 472
Effect of hospitalisation on HRQL	Decrements for hospitalisation set to zero	25 810
Extrapolation of treatment effects	All treatment effects cease at year 5	47 062
Extrapolation of treatment effects	All treatment effects cease at year 10	30 132
Discontinuation	Include discontinuation as seen in PARADIGM-HF	25 242
Discontinuation	No discontinuation after year 3	25 455
Hospitalisation costs	Double cost per hospitalisation	25 684
Adverse event rates	All adverse event rates set to zero	25 621
Cost of primary therapies	Cost of ACEI/ sacubitril/valsartan based on PARADIGM-HF target doses	26 245
French EQ-5D tariff used	Using EQ-5D tariff instead of UK tariffs	23 359
German EQ-5D tariff used	Using EQ-5D German tariffs instead of UK tariff	24 038
NT-pronBNP test inclusion		26 159
HF management outpatient visits (40)	4.6 visits per year	25 200

CV = cardiovascular; HF = heart failure; EQ-5D = European quality of life-5 dimensions; HQRL = health-related quality of life; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; NT-pronBNP = N-terminal pro-brain natriuretic peptide; PCP = primary care physician

Figure 3: Cost-effectiveness scatterplot and 95% confidence range (10 000 simulations).



was met in 78.0% of 10 000 runs, and threshold of CHF 50 000 per QALY gained was met in 99.0% of 10 000 runs.

Discussion

Given limited healthcare budgets throughout the world, the health economic aspects of new drug evaluations can be as important as efficacy, safety and the ability to serve important medical needs under routine clinical practice. In most developed countries, heart failure poses a great economic burden. Estimates show that management of heart failure accounts for 2–5% [2, 3] of total healthcare budgets. Long-term drug treatment is a cornerstone of heart failure therapy.

The cost-effectiveness of sacubitril/valsartan plus standard care compared to enalapril plus standard care has been assessed, from the perspective of the Swiss health care system. The base-case analysis indicated an ICER of CHF 25 684 per QALY gained.

The findings presented were robust to changes in assumptions, and the ICER results were similar across multiple patient subgroups. When model input parameters were varied on the basis of their 95% confidence intervals (as observed in the PARADIGM-HF trial or estimated in regression analyses based thereupon), the ICER remained below CHF 50 000 per QALY gained in most of the cases. In the scenario analyses performed, the ICER also remained below CHF 50 000 per QALY gained, except in the extreme scenarios of the treatment effect of sacubitril/valsartan that persisted for only two or five years.

It should be noted that there is no formally accepted cost-effectiveness threshold in Switzerland. In this study, we tentatively assume a threshold of CHF 30 000 and CHF 50 000 per QALY gained to distinguish between favourable and unfavourable ICER results [23, 24]. This threshold level is similar to the upper limit of the threshold range of £20 000–£30 000 accepted in the United Kingdom (UK) [25]. A few years ago, a court in Switzerland hinted at a CHF 100 000 per QALY threshold [26].

Findings were similar to the results of three previously published cost-effectiveness analyses in the United States [27–29]. These studies (Gaziano et al., King et al. and Sandhu et al.) found sacubitril/valsartan to be cost-effective. The first published economic analysis for the US [27] used the same analytical framework over a 30-year time horizon and displayed an ICER of US$45 017 per QALY gained. Differences observed with our study affected costs and quality of life. Incremental costs and effects were higher in the US population. For example, the monthly cost for sacubitril/valsartan in the US was $375, whereas in Switzerland it was CHF 176. The cost of heart failure hospitalisation were $18 158 in the US and CHF 13 599 in Switzerland. Incremental QALYs gained were 0.78 for the US population and 0.42 for the Swiss population.

The second set of cost-effectiveness analyses undertaken by King et al. [28] found similar results with an ICER of $50 959 per QALY gained over a lifetime. However, their model included population with NYHA class I [28], whereas NYHA class I population was excluded from the PARADIGM-HF trial. The third economic evaluation by Sadhu et al. [29] displayed a cost per QALY gained of $47 053, and differences with our study were mainly due to modelling techniques and input parameters. Monthly cost for sacubitril/valsartan in the study by Sadhu et al. [29] was assumed to be $380, and heart failure hospitalisation costs were assumed as $11 829. In terms of health outcomes, the study by Sadhu et al. [29] displayed a higher incremental QALY gained of 0.62, as compared to that of the Swiss population (0.42).

Another recent study from the Netherlands, using a Markov model and using the effectiveness data from the PARADIGM-HF trial over a lifetime horizon, showed that

sacubitril/valsartan was considered cost effective at an ICER of 19 113 per QALY gained [30]. Differences observed with our study were mainly in terms of model structure, but also in terms of input parameters, such as quality of life. The Dutch study was not able to utilise patient level PARADIGM-HF trial data. The reported incremental QALY gained was 0.29 for the Dutch population, which was lower than that for the Swiss population (0.42). However, the monthly cost for sacubitril/valsartan in the Dutch and Swiss models was quite similar; the amounts were €161.7 and CHF 176 respectively.

In recent years, there have been a number of cost-effectiveness studies undertaken for heart failure patients. The interventions considered included ivabradine, eplerenone, ACEI, and beta blockers. These were compared with placebo or standard of care. In particular, ivabradine was one of the most studied drugs in heart failure patients. Lifetime ICERs ranged from €7634 in Poland [31] to $53 710 in Mexico [32] within these studies [31, 33–38]. ICERs for sacubitril/valsartan appear to be in a comparable range.

Strengths and limitations

Patient-level data from a large international randomised clinical trial formed the basis of this analysis. Use of data from PARADIGM-HF, a large randomized controlled trial comparing sacubitril/valsartan to a real-world standard of care, allowed for a high level of internal consistency in the model. Multivariate risk equations allowed us to characterise and take into account between-patient heterogeneity. A relatively novel approach was used to predict quality of life, by extrapolating EQ-5D utility values based on time trends observed in PARADIGM-HF. The use of local data with regards to non-cardiovascular deaths and unit costs allowed for adjustment to the Swiss healthcare environment. Consistency across countries with regards to medical resource use was partially improved by using the Western European part of the PARADIGM-HF population for the calculation of some parameters, such as hospitalisations. However, the transferability of clinical trial results is necessarily affected by simplifications and assumptions, as these are required in all health economic models.

The main limitation was extrapolation of the treatment effect beyond the observation period of the PARADIGM-HF trial. This is a common limitation shared by most economic evaluation studies when the lifetime impact of an emerging treatment is assessed. Assumptions made with regards to the long-term effects of treatment on mortality, health-related quality of life and all-cause hospitalisation were addressed by performing state-of-the-art sensitivity and scenario analyses. When these assumptions were changed one at a time, they were found to have a relatively modest impact on the final results. Hence, results derived in the base-case analysis seem to be realistic based upon assumptions in the economic evaluation.

The mean age of patients treated in the PARADIGM–HF trial was 64 years, while the mean age of patients in the Swiss population might be higher. This may have led to an over- or underestimation of the true differences between sacubitril/valsartan and standard treatment to be expected for Switzerland, with unclear implications for the ICER. However, in a subgroup analysis including only PARADIGM-HF [39] patients aged at least 75 at baseline, the resulting ICER was very similar to the base case ICER.

The model used Swiss input data where relevant and available, but some approximations were required due to lack of data. One related limitation was the lack of information with regards to medical resource use in heart failure patients. This highlights the need for high-quality Swiss data to cover the aspects of resource utilisation. In the absence of such data, we have adopted resource-use estimates from the UK and verified these with the Swiss literature published as far as possible. This approach may have led to an underestimation of the medical resource use of Swiss CHF patients, which is expected to have a relatively unclear impact on this ICER. In addition, we were not able to capture out-of-pocket expenses incurred by patients themselves with regards to heart failure, and this information should be included in future assessments of costs from the perspective of the Swiss healthcare system.

Conclusion

From the perspective of the Swiss healthcare system, sacubitril/valsartan represents a cost-effective treatment option in patients with HFrEF versus enalapril if a willingness-to-pay threshold of CHF 50 000 per QALY gained is assumed.

Disclosure statement

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Appendix 1

Scenario analyses

Basing non-cardiovascular death from Swiss life tables, observations from the PARADIGM-HF trial were used for cardiovascular (CV) mortality. Towards this end, CV mortality parametric survival model was used where an effect of sacubitril/valsartan on CV mortality was considered.

Sacubitril/valsartan showed a small positive effect on European Quality of Life-5 Dimensions (EQ-5D) score (0.011, $p = 0.001$). To test the impact of this assumption, in the scenario analysis this effect was set to zero.

The treatment effect of sacubitril/valsartan was applied to heart failure (HF) hospitalisations only, whereas the base-case analyses modelled the observed impact of sacubitril/valsartan treatment on all cause hospitalisations.

Hospitalisation-related utility decrements were set to zero whereas in the base-case analyses, utility decrements for hospitalisation in the previous 30 days and in the previous 30-90 days were incorporated.

The median follow-up time in the PARADIGM-HF trial was 27 months. In the absence of long term follow up data, the base-case analyses assumed that the treatment effect of sacubitril/valsartan on mortality, hospitalisations and health-related quality of life (HRQoL) would continue over a lifetime horizon. In scenario analyses, all sacubitril/valsartan treatment effects were assumed to cease after 5 or 10 years (but the accrual of sacubitril/valsartan treatment costs was assumed to continue).

While the base-case analyses included discontinuation as seen in PARADIGM-HF, scenario analysis assumed an exponential survival model of treatment discontinuation, implying a constant rate of discontinuation. Upon discontinuation, costs and efficacy for sacubitril/valsartan patients were assumed to revert to that of angiotensin converting-enzyme inhibitors (ACEIs). This change in efficacy was assumed for all treatment effects, i.e. mortality, hospitalisations, HRQoL and adverse event occurrence. Costs for discontinued ACEI patients were based on angiotensin receptor blocker (ARB) costs, with efficacy assumed to be the same for ACEI and ARBs. (ARBs were shown to have comparable efficacy to ACEI [40].) Another scenario assumed there would be no discontinuation after 3 years.

Given geographical proximity, we additionally applied utility estimates based on the French and German EQ-5D value sets. The former was based on a French time trade-off study by Chevalier et al. [41]. This study recruited a total of 452 respondents aged over 18 years who were representative of the French population with regard to age, gender, and socio-professional group [41]. Secondly, Greiner et al. provided a German value set for the EQ-5D [42] based on the stated preferences of the German general public. A sample of 339 individuals in northern Germany valued 15 different health states from a sample of 36 states. Similarly as described for the base-case model, mixed-effects regression models based on patient-level EQ-5D utility values were estimated to predict EQ-5D utility as a function of baseline characteristics (including baseline EQ-5D), hospitalisations, adverse events, treatment arm and time since randomisation [42].

Another scenario analysis assumed that N-terminal pro-brain natriuretic peptide tests would be routinely performed in heart failure patients.

A last scenario analysis, assumed 4.6 times HF outpatient visits per year, instead of 12 times per year as per base case analysis. 4.6 times HF outpatient visits per year as per Agvall et al. 2005 [43].

Appendix 2

Supplementary tables

Table S1: Baseline characteristics of the PARADIGM-HF trial population (full analysis set).

Variable	Enalapril 10 mg twice daily	Sacubitril/valsartan 200 mg twice daily	p-value
No.	4212	4187	
Age (years), mean (SD)	63.8 (11.3)	63.8 (11.5)	0.93
Female, n (%)	953 (22.6%)	879 (21.0%)	0.070
Race, n (%)			
White	2781 (66.0%)	2763 (66.0%)	0.97
Black	215 (5.1%)	213 (5.1%)	
Asian	750 (17.8%)	759 (18.1%)	
Other	466 (11.1%)	452 (10.8%)	
Region, n (%)			
North America	292 (6.9%)	310 (7.4%)	0.90
Latin America	720 (17.1%)	713 (17.0%)	
Western Europe and other	1025 (24.3%)	1026 (24.5%)	
Central Europe	1433 (34.0%)	1393 (33.3%)	
Asia-Pacific	742 (17.6%)	745 (17.8%)	
Systolic blood pressure (mm Hg), mean (SD)	121.2 (15.4)	121.6 (15.2)	0.31
Heart rate (bpm), mean (SD)	72.5 (12.1)	72.2 (12.0)	0.26
Body mass index (kg/m^2), mean (SD)	28.2 (5.5)	28.1 (5.5)	0.65
Serum creatinine (mg/l), mean (SD)	1.1 (0.3)	1.1 (0.3)	0.39
Ischaemic aetiology, n (%	2530 (60.1%)	2506 (59.9%)	0.84
Ejection fraction (%), mean (SD)	29.4 (6.3)	29.6 (6.1)	0.30
NT-proBNP (pg/ml), median (IQR)	188.4 (104.8–390.8)	192.8 (104.7–373.0)	0.94
BNP (pg/ml), median (IQR)	72.4 (44.4–134.1)	73.6 (44.6–136.6)	0.57
NYHA class, n (%)			
I	209 (5.0%)	180 (4.3%)	0.077
II	2921 (69.3%)	2998 (71.6%)	
III	1049 (24.9%)	969 (23.1%)	
IV	27 (0.6%)	33 (0.8%)	
Missing	6 (0.1%)	7 (0.2%)	
Hypertension status, n (%)	2971 (70.5%)	2969 (70.9%)	0.71
Diabetic status, n (%)	1450 (34.4%)	1446 (34.5%)	0.92
Atrial fibrillation based on history, n (%)	1574 (37.4%)	1517 (36.2%)	0.28
Prior HF hospitalisation, n (%)	2667 (63.3%)	2607 (62.3%)	0.32
Prior myocardial infarction, n (%)	1816 (43.1%)	1818 (43.4%)	0.78
Prior stroke, n (%)	370 (8.8%)	355 (8.5%)	0.62
Prior use of ACEI, n (%)	3266 (77.5%)	3266 (78.0%)	0.61
Prior use of ARB, n (%)	963 (22.9%)	929 (22.2%)	0.46
Diuretic use, n (%)	3375 (80.1%)	3363 (80.3%)	0.83
Beta-blocker use, n (%)	3912 (92.9%)	3899 (93.1%)	0.66
Digoxin use, n (%)	1316 (31.2%)	1223 (29.2%)	0.042
Use of mineralocorticoid receptor antagonist, n (%)	2400 (57.0%)	2271 (54.2%)	0.011
Cardioverter-defibrillator implanted, n (%)	620 (14.7%)	623 (14.9%)	0.84
Use of cardiac resynchronisation therapy, n (%)	282 (6.7%)	292 (7.0%)	0.61

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BNP = brain natriuretic peptide; HF = heart failure; IQR = interquartile range; NT-pro-BNP = N-terminal pro-brain natriuretic peptide

Table S2: Gompertz regression model for all-mortality (n = 8399).

	Coefficient	SE	z	P>z	95% LCI	95% UCI
Sacubitril/valsartan	−0.161	0.051	–3.150	0.002	–0.261	–0.061
Age	–0.101	0.016	–6.220	0.000	–0.133	–0.069
Age squared	0.001	0.000	6.780	0.000	0.001	0.001
Female	–0.389	0.070	–5.600	0.000	–0.525	–0.253
Region - Latin America (vs North America)	0.527	0.127	4.150	0.000	0.278	0.776
Region - Western Europe (vs North America)	0.128	0.112	1.140	0.254	–0.091	0.346
Region - Central Europe (vs North America)	0.348	0.115	3.030	0.002	0.123	0.573
Region - Other (vs North America)	–0.211	0.298	–0.710	0.479	–0.796	0.373
Race - Black (vs Caucasian)	0.285	0.130	2.190	0.029	0.030	0.540
Race - Asian (vs Caucasian)	0.709	0.283	2.500	0.012	0.154	1.265
Race - Other (vs Caucasian)	0.083	0.110	0.760	0.449	–0.132	0.298
NYHA class III/IV (vs I/II)	0.202	0.061	3.300	0.001	0.082	0.322
LVEF	–0.014	0.004	–3.300	0.001	–0.022	–0.006
Heart rate	0.005	0.002	2.540	0.011	0.001	0.010
log(eGFR)	–0.236	0.095	–2.470	0.013	–0.422	–0.049
log(NT-proBNP)	0.387	0.027	14.140	0.000	0.333	0.440
Sodium	–0.031	0.009	–3.430	0.001	–0.048	–0.013
QRS duration	0.002	0.001	3.080	0.002	0.001	0.003
Diabetes	0.215	0.054	3.950	0.000	0.108	0.321
Beta-blocker use	–0.287	0.088	–3.260	0.001	–0.460	–0.115
Lipid lowering medication use	–0.086	0.057	–1.520	0.129	–0.197	0.025
1–5 years since HF diagnosis (vs ≤1 year)	0.205	0.067	3.040	0.002	0.073	0.337
>5 years since HF diagnosis (vs ≤1 year)	0.290	0.072	4.010	0.000	0.148	0.432
Ischaemic aetiology	0.186	0.059	3.140	0.002	0.070	0.302
Prior stroke	0.171	0.083	2.070	0.039	0.009	0.333
Previously hospitalised for HF	0.152	0.055	2.750	0.006	0.044	0.261
EQ-5D	–0.541	0.115	–4.700	0.000	–0.767	–0.315
Constant	–12.760	0.583	–21.890	0.000	–13.902	–11.617
Gamma	0.000	0.000	4.560	0.000	0.000	0.001

eGFR = estimated glomerular filtration rate; EQ-5D, European Quality of Life-5 Dimensions; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA II–IV = New York Heart Association class II–IV; SE = standard error

Table S3: Gompertz regression model for CV mortality (n = 8399).

Mortality	Hazard ratio	Coefficient	SE	z	P>z	95% CI	
Sacubitril/valsartan	0.81	–0.216	0.0570	–3.79	0.000	–0.328	–0.104
Age†	0.91	–0.092	0.0180	–5.13	0.000	–0.128	–0.057
Age squared	1.00	0.001	0.0001	5.35	0.000	0.000	0.001
Female	0.70	–0.357	0.0766	–4.67	0.000	–0.508	–0.207
Region							
Latin America	1.87	0.625	0.1455	4.3	0.000	0.340	0.910
Western Europe	1.18	0.168	0.1307	1.28	0.200	–0.089	0.424
Central Europe	1.70	0.529	0.1319	4.01	0.000	0.270	0.787
Asia-Pacific	0.83	–0.187	0.3172	–0.59	0.556	–0.809	0.435
Race							
Black	1.50	0.409	0.1440	2.84	0.005	0.126	0.691
Asian	2.62	0.962	0.2989	3.22	0.001	0.377	1.548
Other	1.18	0.168	0.1226	1.37	0.169	–0.072	0.409
NYHA III/IV	1.34	0.296	0.0669	4.42	0.000	0.165	0.427
Ejection fraction†	0.98	–0.017	0.0046	–3.6	0.000	–0.026	–0.008
Log(eGFR)†	0.79	–0.238	0.1054	–2.26	0.024	–0.444	–0.031
Log(NT-proBNP)†	1.56	0.443	0.0299	14.84	0.000	0.385	0.502
Sodium†	0.97	–0.027	0.0099	–2.69	0.007	–0.046	–0.007
QRS duration	1.00	0.002	0.0007	3.04	0.002	0.001	0.003
Diabetes	1.26	0.229	0.0599	3.82	0.000	0.111	0.346
Beta-blocker use	0.73	–0.320	0.0964	–3.32	0.001	–0.509	–0.131
Time since diagnosis of HF							
1–5 years	1.23	0.210	0.0748	2.8	0.005	0.063	0.356
>5 years	1.41	0.344	0.0805	4.28	0.000	0.186	0.502
Ischaemic disease	1.17	0.156	0.0626	2.48	0.013	0.033	0.278
Prior HF hospitalisation	1.17	0.159	0.0617	2.57	0.010	0.038	0.280
Baseline EQ-5D	0.57	–0.563	0.1275	–4.42	0.000	–0.813	–0.313
Constant‡	0.00	–12.665	0.6477	–19.55	0.000	–13.934	–11.395
Gamma§	1.00	0.000	0.0001	2.56	0.010	0.000	0.000

eGFR = estimated glomerular filtration rate; EQ-5D, European Quality of Life-5 Dimensions; HF = heart failure; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA II–IV = New York Heart Association class II–IV; SE = standard error † Variable centred on mean ‡ Constant term in Gompertz regression § The ancillary parameter that controls the shape of the baseline hazard

Table S4: All-cause mortality of the Swiss population in 2012.

Age group (years)	Population		Deaths males	Death rate males	Annual probability males	Death females	Death rates females	Annual probability females
	Males	Females						
<1	41 914	39 495	156	0.00372	0.003715	140	0.00354	0.003538
1–4	169 732	160 469	26	0.00015	0.000153	15	0.00009	0.000093
5–9	204 230	193 511	11	0.00005	0.000054	17	0.00009	0.000087
10–14	206 846	196 080	20	0.00009	0.000097	11	0.00005	0.000056
15–19	226 301	214 933	85	0.00038	0.000376	26	0.00012	0.000121
20–24	253 574	245 387	112	0.00044	0.000442	40	0.00016	0.000163
25–29	274 522	268 685	118	0.00043	0.000429	65	0.00024	0.000242
30–34	288 145	282 589	152	0.00053	0.000527	71	0.00025	0.000251
35–39	281 336	278 235	204	0.00073	0.000724	106	0.00038	0.000381
40–44	304 469	300 842	368	0.00121	0.001207	08	0.00069	0.000691
45–49	338 087	330 167	590	0.00175	0.001744	388	0.00118	0.001174
50–54	314 108	307 365	958	0.00305	0.003045	569	0.00185	0.001849
55–59	266 125	261 023	1306	0.00491	0.004895	803	0.00308	0.003071
60–64	226 250	232 464	1960	0.00866	0.008626	1107	0.00476	0.004751
65–69	207 158	220 268	2638	0.01273	0.012654	1604	0.00728	0.007256
70–74	159 179	181 893	3012	0.01892	0.018744	2020	0.01111	0.011044
75–79	116 891	148 637	4124	0.03528	0.034666	3078	0.02071	0.020495
80–84	81 364	123 189	5146	0.06325	0.061288	5459	0.04431	0.043347
85+	61 860	132 308	9711	0.15698	0.145282	17 749	0.13415	0.125540

Table S5: Cardiovascular mortality of the Swiss population in 2012.

Age group (years)	Population		Deaths males	Death rate males	Annual probability males	Death females	Death rates females	Annual probability females
	Males	Females						
<1	41 914	39 495	1	0.00002	0.000024	1	0.00003	0.000025
1–4	169 732	160 469	1	0.00001	0.000006	1	0.00001	0.000006
5–9	204 230	193 511	0	0	0	1	0.00001	0.000005
10–14	206 846	196 080	2	0.00001	0.000009	0	0	0
15–19	226 301	214 933	2	0.00001	0.000009	2	0.00001	0.000009
20–24	253 574	245 387	4	0.00002	0.000016	3	0.00001	0.000012
25–29	274 522	268 685	6	0.00002	0.000022	5	0.00002	0.000019
30–34	288 145	282,589	11	0.00004	0.000038	7	0.00002	0.000025
35–39	281 336	278 235	25	0.00009	0.000089	9	0.00003	0.000032
40–44	304 469	300 842	70	0.00023	0.000229	26	0.00009	0.000086
45–49	338 087	330 167	115	0.00034	0.000340	48	0.00015	0.000145
50–54	314 108	307 365	211	0.00067	0.000672	57	0.00019	0.000185
55–59	266 125	261 023	306	0.00115	0.001149	89	0.00034	0.000341
60–64	226 250	232 464	456	0.00202	0.002013	139	0.00060	0.000598
65–69	207 158	220 268	641	0.00309	0.003089	242	0.00110	0.001098
70–74	159 179	181 893	769	0.00483	0.004819	448	0.00246	0.002459
75–79	116 891	148 637	1265	0.01082	0.010764	882	0.00593	0.005916
80–84	81 364	123 189	1793	0.02204	0.021796	1931	0.01568	0.015553
85+	61 860	132 308	4067	0.06575	0.063631	8038	0.06075	0.058944

Table S6: Non-cardiovascular mortality of the Swiss population in 2012.

Age group (years)	All-cause mortality males (%)	All-cause mortality females (%)	CV mortality males (%)	CV mortality females (%)	Non-CV mortality males (%)	Non-CV mortality females (%)
<1	0.3715	0.3538	0.0024	0.0025	0.3691	0.3513
1–4	0.0153	0.0093	0.0006	0.0006	0.0147	0.0087
5–9	0.0054	0.0087	0	0.0005	0.0054	0.0082
10–14	0.0097	0.0056	0.0009	0	0.0088	0.0056
15–19	0.0376	0.0121	0.0009	0.0009	0.0367	0.0112
20–24	0.0442	0.0163	0.0016	0.0012	0.0426	0.0151
25–29	0.0429	0.0242	0.0022	0.0019	0.0407	0.0223
30–34	0.0527	0.0251	0.0038	0.0025	0.0489	0.0226
35–39	0.0724	0.0381	0.0089	0.0032	0.0635	0.0349
40–44	0.1207	0.0691	0.0229	0.0086	0.0978	0.0605
45–49	0.1744	0.1174	0.0340	0.0145	0.1404	0.1029
50–54	0.3045	0.1849	0.0672	0.0185	0.2373	0.1664
55–59	0.4895	0.3071	0.1149	0.0341	0.3746	0.2730
60–64	0.8626	0.4751	0.2013	0.0598	0.6613	0.4153
65–69	1.2654	0.7256	0.3089	0.1098	0.9565	0.6158
70–74	1.8744	1.1044	0.4819	0.2459	1.3925	0.8585
75–79	3.4666	2.0495	1.0764	0.5916	2.3902	1.4579
80–84	6.1288	4.3347	2.1796	1.5553	3.9492	2.7794
85+	14.5282	12.5540	6.3631	5.8944	8.1651	6.6596

Table S7: Negative binomial regression model for all-cause hospitalisation.

	IRR	Coefficient	SE	z	P>z	95% CI	
Sacubitril/valsartan	0.84	–0.173	0.038	–4.540	0.000	–0.248	–0.098
Age†	0.95	–0.055	0.013	–4.130	0.000	–0.082	–0.029
Age squared	1.00	0.000	0.000	4.350	0.000	0.000	0.001
Female	0.74	–0.299	0.049	–6.050	0.000	–0.396	–0.202
Region							
Latin America	0.70	–0.364	0.085	–4.300	0.000	–0.530	–0.198
Western Europe	1.02	0.016	0.074	0.220	0.828	–0.129	0.162
Central Europe	0.72	–0.323	0.076	–4.270	0.000	–0.471	–0.175
Asia-Pacific	0.70	–0.352	0.085	–4.130	0.000	–0.519	–0.185
Heart rate†	1.01	0.007	0.002	4.320	0.000	0.004	0.010
Log (eGFR)†	0.62	–0.479	0.072	–6.610	0.000	–0.621	–0.337
Log (NT-proBNP)†	1.26	0.229	0.020	11.260	0.000	0.189	0.269
Sodium†	0.98	–0.021	0.007	–3.220	0.001	–0.035	–0.008
QRS duration†	1.00	0.003	0.001	5.370	0.000	0.002	0.004
Diabetes	1.40	0.334	0.040	8.250	0.000	0.255	0.413
Prior ACEi use	0.90	–0.104	0.047	–2.220	0.026	–0.196	–0.012
Beta-blocker use	0.72	–0.332	0.073	–4.560	0.000	–0.475	–0.189
Lipid lowering medication use	1.07	0.072	0.043	1.680	0.094	–0.012	0.157
Time since diagnosis of HF							
1–5 years	1.30	0.265	0.049	5.390	0.000	0.169	0.362
>5 years	1.50	0.404	0.052	7.740	0.000	0.302	0.506
Ischaemic disease	1.09	0.086	0.044	1.940	0.052	–0.001	0.173
Prior stroke	1.16	0.147	0.065	2.250	0.024	0.019	0.275
Atrial fibrillation	1.10	0.094	0.042	2.250	0.024	0.012	0.176
Prior cancer	1.18	0.163	0.088	1.850	0.064	–0.010	0.335
Current smoker	1.24	0.212	0.054	3.920	0.000	0.106	0.318
Prior HF hospitalisation	1.40	0.334	0.041	8.230	0.000	0.255	0.414
Baseline EQ-5D†	0.62	–0.485	0.090	–5.410	0.000	–0.661	–0.309
Constant	0.06	–2.891	0.475	–6.090	0.000	–3.821	–1.960
ln(exposure)	0.84	–0.173	0.038	–4.540	0.000	–0.248	–0.098

ACEi = angiotensin converting-enzyme inhibitor; GFR = estimated glomerular filtration rate; EQ-5D, European Quality of Life-5 Dimensions; HF = heart failure; IRR = incidence rate ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA II–IV = New York Heart Association class II–IV; SE = standard error † Variable centred on mean

Table S8: Occurrence of less serious adverse events in the PARADIGM-HF trial.

Event	Sacubitril/valsartan (n = 4187)			Angiotensin converting-enzyme inhibitor (n = 4212)			p-value
	Number†	Mean annual rate	Mean monthly probability	Number†	Mean annual rate	Mean monthly probability	
Hypotension	588	0.063	0.0052	388	0.042	0.0035	<0.001
Elevated serum creatinine	139	0.015	0.0012	188	0.020	0.0017	0.007
Elevated serum potassium	674	0.073	0.0061	727	0.079	0.0066	0.15
Cough	474	0.051	0.0042	601	0.065	0.0054	<0.001
Angio-oedema	19	0.002	0.0002	10	0.001	0.0001	0.19‡ 0.52§ 0.31¶

† Absolute number of each adverse event taken from McMurray et al (10) ‡ No treatment or use of antihistamines § Use of catecholamines or glucocorticoids without hospitalisation ¶ Hospitalisation without airway compromise

Table S9: Mixed model for EQ-5D-based utility values.

	Coefficient	SE	z	P>z	95% CI	
Sacubitril/valsartan	0.011	0.003	3.35	0.001	0.004	0.017
Age†	–0.001	0.000	–4.96	0.000	–0.001	0.000
Female	–0.031	0.004	–7.8	0.000	–0.039	–0.023
Region						
Latin America	0.041	0.007	5.72	0.000	0.027	0.055
Western Europe	0.013	0.007	1.86	0.063	–0.001	0.026
Central Europe	0.000	0.007	–0.04	0.969	–0.014	0.013
Asia-Pacific	0.041	0.008	5.37	0.000	0.026	0.056
NYHA						
II (vs I)	–0.009	0.008	–1.22	0.224	–0.024	0.006
III (vs I)	–0.051	0.008	–6.05	0.000	–0.067	–0.034
IV (vs I)	–0.092	0.021	–4.46	0.000	–0.132	–0.051
Heart rate†	0.000	0.000	–1.97	0.049	–0.001	0.000
Log(NT-proBNP)†	–0.009	0.002	–5.35	0.000	–0.013	–0.006
Sodium†	0.001	0.001	1.8	0.071	0.000	0.002
BMI	–0.002	0.000	–6	0.000	–0.003	–0.001
Diabetes	–0.014	0.003	–4.02	0.000	–0.021	–0.007
Time since diagnosis of HF						
1–5 years	–0.017	0.004	–4.21	0.000	–0.024	–0.009
>5 years	–0.023	0.004	–5.34	0.000	–0.031	–0.014
Ischaemic aetiology	–0.007	0.003	–2.13	0.033	–0.014	–0.001
Prior stroke	–0.012	0.006	–2.06	0.039	–0.023	–0.001
Current smoker	–0.013	0.005	–2.8	0.005	–0.022	–0.004
Baseline EQ-5D†	0.488	0.008	61.39	0.000	0.473	0.504
Hosp 0–30 days	–0.105	0.006	–18.31	0.000	–0.116	–0.094
Hosp 30–90 days	–0.054	0.004	–12.43	0.000	–0.062	–0.045
AE – cough	–0.028	0.007	–4.33	0.000	–0.041	–0.015
AE – hypotension	–0.029	0.006	–4.63	0.000	–0.042	–0.017
Time (years)	–0.008	0.001	–8.56	0.000	–0.010	–0.006
_cons	0.822	0.010	79.67	0.000	0.802	0.843

AE = adverse event; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; EQ-5D, European Quality of Life-5 Dimensions; HF = heart failure; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA II–IV = New York Heart Association class II–IV; SE = standard error † Variable centred on mean

Table S10: Swiss drug costs of primary and background therapy for heart failure.

Tab strength (mg)	Cost/pack (CHF)	Tabs/pack	Cost/tab (CHF)	Cost/mg (CHF)	Daily dose	Daily cost (CHF)	Monthly cost (CHF)
Primary therapy							
Angiotensin converting-enzyme inhibitor – enalapril							
5	7.30	30	0.244	0.05	18.9 mg	0.78	23.72
10	9.40	28	0.337	0.03			
20	17.80	28	0.636	0.03			
Angiotensin converting enzyme inhibitor – ramipril							
2.5	11.80	20	0.59	0.24			
5	14.40	20	0.72	0.14	2 × 5 mg	1.44	43.75
10	15.10	20	0.75	0.08			
Angiotensin converting enzyme inhibitor – perindopril							
2	12.73	30	0.42	0.21			
4	18.27	30	0.61	0.15	8 mg	0.79	23.91
8	23.57	30	0.79	0.10			
Angiotensin converting-enzyme inhibitor – lisinopril							
5	7.07	30	0.24	0.05			
10	9.42	30	0.31	0.03	1 × 20 mg 1 × 10 mg	0.86	26.21
20	16.42	30	0.55	0.03			
Angiotensin receptor blocker – losartan							
25	14.00	28	0.50	0.02			
50	17.00	28	0.61	0.01	1 × 100 mg 1 × 50 mg	1.21	36.96
100	17.00	28	0.61	0.01			
Angiotensin receptor blocker – candesartan							
4	5.85	7	0.84	0.21			
8	16.00	30	0.53	0.07			
16	17.60	30	0.59	0.04			
32	26.50	30	0.88	0.03	1 × 32 mg	0.88	26.89
Angiotensin receptor blocker – valsartan							
80	20.20	28	0.72	0.01			
160	26.75	28	0.96	0.01	2 × 160 mg	1.96	58.16
Background therapy							
Beta-blocker – carvedilol							
3.125	6.95	30	0.23	0.07			
6.25	7.45	22	0.34	0.05			
12.5	17.80	30	0.59	0.05			
25	26.63	30	0.89	0.04	2 × 25 mg	1.78	54.03
Beta-blocker – bisoprolol							
5	15.90	30	0.53	0.11			
10	26.05	30	0.87	0.09	1 × 10 mg	0.87	26.43
Aldosterone antagonist – spironolactone							
25	7.85	20	0.39	0.02	1 × 25 mg 1 × 50 mg	0.58	17.77
50	15.50	20	0.78	0.02			
100	35.85	30	1.20	0.01			
Digoxin							
125µg	7.10	100	0.07	0.001	1 × 125 µg	0.08	2.42
250µg	8.80	100	0.09	0.0004			
Lipid lowering medication – atorvastatin							
10	28.20	30	0.94	0.09	1 × 10 mg 1 × 20mg	0.94	28.61
20	28.20	30	0.94	0.05			
40	28.20	30	0.94	0.02			
80	28.20	30	0.94	0.01			
Lipid lowering medication – simvastatin							
20	37.35	28	1.33	0.07			
40	37.35	28	1.33	0.03	1 × 40 mg 1 × 80 mg	1.33	40.60
80	37.35	28	1.33	0.02			
Loop diuretics – furosemide							
40	4.85	12	0.40	0.01	1 × 20 mg 1 × 40 mg	0.40	12.30
Aspirin							
100	6.60	28	0.24	0.0024	1 × 100 mg	0.24	7.17
Marcoumar							
3	7.65	25	0.31	0.1	1 × 3 mg	0.25	7.61

Tab strength (mg)	Cost/pack (CHF)	Tabs/pack	Cost/tab (CHF)	Cost/mg (CHF)	Daily dose	Daily cost (CHF)	Monthly cost (CHF)
3	20.80	100	0.21	0.07			
Clopidogrel							
75	44.98	28	1.58	0.02	1 × 75 mg	1.61	48.90

Table S11: Swiss DRG codes for hospitalisation costs (description of surgical procedures).

Hospitalisations and related DRG codes	PARADIGM-HF frequency		Activity	Unit cost
Hospitalisations involving a surgical procedure (4% of total hospitalisations)				
Coronary artery bypass grafting				
F05Z	16.0%		88	CHF 51 950
F06A			28	CHF 90 987
F06B			42	CHF 59 328
F06C			119	CHF 46 807
F06D			160	CHF 40 015
F06E				CHF 33 424
Mitral valve repair/replacement and other valve surgery				
F03A	28.0%		93	CHF 71 993
F03B			100	CHF 51 165
F03C			175	CHF 49 118
F03D			442	CHF 42 270
F07Z			217	CHF 49 795
F98Z			258	CHF 61 777
F69Z			218	CHF 11 203
Other cardiac surgeries				
F08Z	39.0%		58	CHF 61 110
F09Z	24	CHF 38 057		
F13A	166	CHF 42 882		
F13B	87	CHF 21 845		
F13C	436	CHF 14 250		
F14A	73	CHF 33 106		
F14B	213	CHF 22 372		
F20Z	65	CHF 7 844		
F28A	118	CHF 57 969		
F28B	120	CHF 34 680		
F28C	56	CHF 20 726		
F30Z	36	CHF 48 685		
F31Z	128	CHF 34 456		
F33A	127	CHF 43 072		
F33B	243	CHF 25 924		
F34A	272	CHF 37 873		
F34B	821	CHF 20 207		
F35A	86	CHF 27 309		
F35B	110	CHF 15 845		
F38Z	63	CHF 17 622		
F39A	1965	CHF 6397		
F39B	2873	CHF 5097		
F54Z	1731	CHF 12 408		
F59A	813	CHF 20 232		
F59B	2240	CHF 7912		
F51A	41	CHF 35 034		
F51B	55	CHF 38 129		
F51C	203	CHF 29 486		
F61A	30	CHF 34 597		
F61B	140	CHF 26 897		
Ventricular assist device (VAD)				
ZE-2015-04.04	16.0%		2	28 967.45
ZE-2015-04.05			1	57 934.90
ZE-2015-04.08			1	36 439.15
ZE-2015-04.08			1	36,439.15
ZE-2015-04.09			-	71 839.55
ZE-2015-04.11			12	115 918.95
ZE-2015-04.11			13	115 918.95
ZE-2015-04.12			2	182 347.20
Heart transplantation				
A05B	1.0%		51	CHF 147 414
A06Z			35	CHF 545 196
Hospitalisations involving an interventional procedure (8% of total hospitalisations)				
Implantable cardioverter/defibrillator				

Hospitalisations and related DRG codes	PARADIGM-HF frequency	Activity	Unit cost
F01A	36.0%	31	CHF 94 070
F01B		130	CHF 55 862
F01C		63	CHF 72 725
F01D		198	CHF 48 903
F02Z		54	CHF 49 105
F10Z		22	CHF 41 700
Cardiac pacemaker (biventricular, defibrillating CRT-D), conventional			
F12A	53.0%	64	CHF 36 719
F12B		46	CHF 41 076
F12C		147	CHF 33 472
F12D		902	CHF 21 423
F12E		581	CHF 20 250
F17A		227	CHF 17 182
F17B		101	CHF 13 006
F18A		49	CHF 25 039
F18B		170	CHF 11 025
Coronary angioplasty, percutaneous coronary intervention single / percutaneous coronary intervention (multiple)			
F52A	11.0%	189	CHF 23 547
F52B		1322	CHF 14 285
F56A		187	CHF 22 494
F56B		1632	CHF 14 139
F57A		62	CHF 14 470
F57B		1351	CHF 9703
F58Z		178	CHF 9730
F24A		180	CHF 34 746
F24B		1338	CHF 19 645
F15Z		101	CHF 39 039
Hospitalisations involving medical management procedures (88.0% of total hospitalisations)			
Cardiac failure / pneumonia / chronic obstructive pulmonary disease			
F62A	65.0%	364	CHF 19 068
F62B		1532	CHF 14 350
F62C		7112	CHF 8656
Ventricular tachycardia / atrial fibrillation			
F50A	11.0%	310	CHF 18 850
F50B		30	CHF 20 239
F50C		528	CHF 11 921
F50D		210	CHF 10 889
F71B		772	CHF 7606
Cerebrovascular accident			
B04B	2.0%	32	CHF 30 082
B39A		41	CHF 63 370
B39B		68	CHF 37 476
B39C		40	CHF 27 626
B70A		350	CHF 25 839
B70B		255	CHF 19 414
B70C		945	CHF 15 791
B70D		650	CHF 14 717
B70E		4093	CHF 11 456
B70G		126	CHF 6122
B70H		433	CHF 3721
Angina pectoris			
F71A	2.0%	374	CHF 13 020
F72A		144	CHF 7495
F72B		3584	CHF 4444
Acute myocardial infarction			
F41A	2.0%	39	CHF 26 184
F41B		411	CHF 10 447
F60A		472	CHF 14 707
F60B		2301	CHF 7635
Syncope			
F73Z	3.0%	4765	CHF 4829
Non-cardiac chest pain			

Hospitalisations and related DRG codes	PARADIGM-HF frequency	Activity	Unit cost
F74Z	5.0%	2462	CHF 3400
E65C		–	–
Renal failure acute			
L60B	3.0%	128	CHF 26 224
Dyspnoea			
F43B	3.0%	208	CHF 30 377
Transient ischaemic attack			
B69A	1.0%	–	–
B69B		22	CHF 10 926
B69C		1591	CHF 8643
B69D		174	CHF 9866
Urinary tract infection			
L63D	1.0%	560	CHF 5669
Anaemia			
Q61D	2.0%	256	CHF 13 030

Proportion of hospitalisations per procedure were derived from the Western European population of the PARADIGM-HF trial, including patients from Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Portugal, Spain, Sweden, UK, Israel and South Africa.

Table S12: Parameters used in univariate and probabilistic sensitivity analyses. Cost parameters are in CHF.

Parameter	Mean value	Lower value for univariate SA	Upper value for univariate SA	Reference for uncertainty	Distribution used in PSA
CV mortality (coef.): sacubitril/valsartan	–0.2159	–0.3275	–0.1042	95% CI	Multivariate normal
CV mortality (coef.): Age*	–0.0924	–0.1277	–0.0571	95% CI	Multivariate normal
CV mortality (coef.): Age squared	0.0008	0.0005	0.0011	95% CI	Multivariate normal
CV mortality (coef.): Female	–0.3575	–0.5076	–0.2073	95% CI	Multivariate normal
CV mortality (coef.): Region – Latin America (vs North America)	0.6252	0.3401	0.9103	95% CI	Multivariate normal
CV mortality (coef.): Region – Western Europe (vs North America)	0.1675	–0.0886	0.4237	95% CI	Multivariate normal
CV mortality (coef.): Region – Central Europe (vs North America)	0.5286	0.2701	0.7871	95% CI	Multivariate normal
CV mortality (coef.): Region – Other (vs North America)	–0.1869	–0.8086	0.4348	95% CI	Multivariate normal
CV mortality (coef.): Race – Black (vs Caucasian)	0.4086	0.1264	0.6908	95% CI	Multivariate normal
CV mortality (coef.): Race – Asian (vs Caucasian)	0.9624	0.3766	1.5482	95% CI	Multivariate normal
CV mortality (coef.): Race – Other (vs Caucasian)	0.1685	–0.0717	0.4087	95% CI	Multivariate normal
CV mortality (coef.): NYHA class III/IV (vs I/II)	0.2959	0.1648	0.4270	95% CI	Multivariate normal
CV mortality (coef.): LVEF*	–0.0167	–0.0257	–0.0076	95% CI	Multivariate normal
CV mortality (coef.): log(eGFR)*	–0.2377	–0.4442	–0.0312	95% CI	Multivariate normal
CV mortality (coef.): log(NT–proBNP)*	0.4432	0.3846	0.5017	95% CI	Multivariate normal
CV mortality (coef.): Sodium*	–0.0267	–0.0462	–0.0072	95% CI	Multivariate normal
CV mortality (coef.): QRS duration*	0.0020	0.0007	0.0033	95% CI	Multivariate normal
CV mortality (coef.): Diabetes	0.2289	0.1114	0.3464	95% CI	Multivariate normal
CV mortality (coef.): Beta blocker use	–0.3202	–0.5092	–0.1312	95% CI	Multivariate normal
CV mortality (coef.): 1–5 years since HF diagnosis (vs ≤1 year)	0.2096	0.0630	0.3562	95% CI	Multivariate normal
CV mortality (coef.): >5 years since HF diagnosis (vs ≤1 year)	0.3441	0.1864	0.5018	95% CI	Multivariate normal
CV mortality (coef.): Ischaemic aetiology	0.1555	0.0328	0.2783	95% CI	Multivariate normal
CV mortality (coef.): Previously hospitalised for HF	0.1588	0.0379	0.2797	95% CI	Multivariate normal
CV mortality (coef.): EQ–5D*	–0.5631	–0.8129	–0.3132	95% CI	Multivariate normal
CV mortality (coef.): Constant	–12.6648	–13.9344	–11.3953	95% CI	Multivariate normal
CV mortality (coef.): Gamma	0.0002	0.0001	0.0004	95% CI	Multivariate normal
All-cause mortality: sacubitril/valsartan	–0.1608	–0.2610	–0.0606	95% CI	Multivariate normal
All-cause mortality: Age*	–0.1011	–0.1329	–0.0692	95% CI	Multivariate normal
All-cause mortality: Age squared	0.0009	0.0006	0.0011	95% CI	Multivariate normal
All-cause mortality: Female	–0.3891	–0.5253	–0.2528	95% CI	Multivariate normal
All-cause mortality: Region - Latin America (vs North America)	0.5271	0.2779	0.7763	95% CI	Multivariate normal
All-cause mortality: Region - Western Europe (vs North America)	0.1275	–0.0914	0.3464	95% CI	Multivariate normal
All-cause mortality: Region - Central Europe (vs North America)	0.3482	0.1232	0.5732	95% CI	Multivariate normal
All-cause mortality: Region - Other (vs North America)	–0.2111	–0.7956	0.3734	95% CI	Multivariate normal
All-cause mortality: Race - Black (vs Caucasian)	0.2848	0.0296	0.5400	95% CI	Multivariate normal
All-cause mortality: Race - Asian (vs Caucasian)	0.7093	0.1539	1.2648	95% CI	Multivariate normal
All-cause mortality: Race - Other (vs Caucasian)	0.0831	–0.1322	0.2984	95% CI	Multivariate normal
All-cause mortality: NYHA class III/IV (vs I/II)	0.2021	0.0821	0.3221	95% CI	Multivariate normal
All-cause mortality: LVEF*	–0.0138	–0.0220	–0.0056	95% CI	Multivariate normal
All-cause mortality: Heart rate*	0.0055	0.0012	0.0097	95% CI	Multivariate normal
All-cause mortality: log(eGFR)*	–0.2356	–0.4225	–0.0487	95% CI	Multivariate normal
All-cause mortality: log(NT-proBNP)*	0.3866	0.3330	0.4402	95% CI	Multivariate normal
All-cause mortality: Sodium*	–0.0306	–0.0480	–0.0131	95% CI	Multivariate normal
All-cause mortality: QRS duration*	0.0019	0.0007	0.0030	95% CI	Multivariate normal
All-cause mortality: Diabetes	0.2149	0.1084	0.3214	95% CI	Multivariate normal
All-cause mortality: Beta blocker use	–0.2873	–0.4598	–0.1147	95% CI	Multivariate normal
All-cause mortality: Lipid lowering medication use	–0.0860	–0.1970	0.0249	95% CI	Multivariate normal
All-cause mortality: 1-5 years since HF diagnosis (vs ≤1 year)	0.2049	0.0729	0.3368	95% CI	Multivariate normal
All-cause mortality: >5 years since HF diagnosis (vs ≤1 year)	0.2902	0.1482	0.4323	95% CI	Multivariate normal
All-cause mortality: Ischaemic aetiology	0.1857	0.0696	0.3017	95% CI	Multivariate normal
All-cause mortality: Prior stroke	0.1711	0.0088	0.3335	95% CI	Multivariate normal
All-cause mortality: Previously hospitalised for HF	0.1522	0.0438	0.2606	95% CI	Multivariate normal
All-cause mortality: EQ-5D*	–0.5413	–0.7672	–0.3154	95% CI	Multivariate normal
All-cause mortality: Constant	–12.7596	–13.9020	–11.6172	95% CI	Multivariate normal
All-cause mortality: Gamma	0.0004	0.0002	0.0005	95% CI	Multivariate normal
% of deaths with CV cause (Sacubitril/valsartan)	0.7848	0.7527	0.8145	95% CI	Beta
% of deaths with CV cause (ACEi)	0.8299	0.8027	0.8548	95% CI	Beta
Discontinuation: Sacubitril/valsartan	–0.1115	–0.2104	–0.0127	95% CI	Multivariate normal
Discontinuation: Region – Latin America (vs North America)	–0.2855	–0.4783	–0.0927	95% CI	Multivariate normal
Discontinuation: Region – Western Europe (vs North America)	–0.1076	–0.2798	0.0646	95% CI	Multivariate normal

Parameter	Mean value	Lower value for univariate SA	Upper value for univariate SA	Reference for uncertainty	Distribution used in PSA
Discontinuation: Region – Central Europe (vs North America)	–0.4092	–0.5880	–0.2305	95% CI	Multivariate normal
Discontinuation: Region – Other (vs North America)	–0.8739	–1.0988	–0.6491	95% CI	Multivariate normal
Discontinuation: Heart rate*	0.0065	0.0024	0.0107	95% CI	Multivariate normal
Discontinuation: log(eGFR)*	–0.5315	–0.7069	–0.3561	95% CI	Multivariate normal
Discontinuation: log(NT–proBNP)*	0.2045	0.1517	0.2572	95% CI	Multivariate normal
Discontinuation: Sodium*	–0.0164	–0.0338	0.0009	95% CI	Multivariate normal
Discontinuation: Diabetes	0.1546	0.0500	0.2592	95% CI	Multivariate normal
Discontinuation: Beta blocker use	–0.1750	–0.3624	0.0125	95% CI	Multivariate normal
Discontinuation: Lipid lowering medication use	–0.1914	–0.3008	–0.0819	95% CI	Multivariate normal
Discontinuation: 1–5 years since HF diagnosis (vs ≤1 year)	0.1020	–0.0299	0.2340	95% CI	Multivariate normal
Discontinuation: >5 years since HF diagnosis (vs ≤1 year)	0.2879	0.1536	0.4222	95% CI	Multivariate normal
Discontinuation: Ischaemic aetiology	0.1311	0.0186	0.2435	95% CI	Multivariate normal
Discontinuation: EQ–5D*	–0.4726	–0.6869	–0.2583	95% CI	Multivariate normal
Discontinuation: Constant	–7.9937	–8.2645	–7.7228	95% CI	Multivariate normal
Hospitalisation (coef.): Sacubitril/valsartan	–0.1729	–0.2476	–0.0983	95% CI	Multivariate normal
Hospitalisation (coef.): Age*	–0.0553	–0.0816	–0.0291	95% CI	Multivariate normal
Hospitalisation (coef.): Age^2	0.0005	0.0003	0.0007	95% CI	Multivariate normal
Hospitalisation (coef.): Female	–0.2989	–0.3957	–0.2022	95% CI	Multivariate normal
Hospitalisation (coef.): Region – Latin America (vs North America)	–0.3638	–0.5296	–0.1980	95% CI	Multivariate normal
Hospitalisation (coef.): Region – Western Europe (vs North America)	0.0161	–0.1294	0.1616	95% CI	Multivariate normal
Hospitalisation (coef.): Region – Central Europe (vs North America)	–0.3230	–0.4714	–0.1746	95% CI	Multivariate normal
Hospitalisation (coef.): Region – Other (vs North America)	–0.3520	–0.5190	–0.1850	95% CI	Multivariate normal
Hospitalisation (coef.): Heart rate*	0.0070	0.0038	0.0102	95% CI	Multivariate normal
Hospitalisation (coef.): log(eGFR)*	–0.4791	–0.6211	–0.3371	95% CI	Multivariate normal
Hospitalisation (coef.): log(NT–proBNP)*	0.2290	0.1891	0.2688	95% CI	Multivariate normal
Hospitalisation (coef.): Sodium*	–0.0215	–0.0346	–0.0084	95% CI	Multivariate normal
Hospitalisation (coef.): QRS duration*	0.0031	0.0019	0.0042	95% CI	Multivariate normal
Hospitalisation (coef.): Diabetes	0.3340	0.2547	0.4134	95% CI	Multivariate normal
Hospitalisation (coef.): Prior use of ACEi	–0.1043	–0.1962	–0.0124	95% CI	Multivariate normal
Hospitalisation (coef.): Beta blocker use	–0.3320	–0.4747	–0.1893	95% CI	Multivariate normal
Hospitalisation (coef.): Lipid lowering medication use	0.0722	–0.0122	0.1567	95% CI	Multivariate normal
Hospitalisation (coef.): 1–5 years since HF diagnosis (vs ≤1 year)	0.2651	0.1687	0.3616	95% CI	Multivariate normal
Hospitalisation (coef.): >5 years since HF diagnosis (vs ≤1 year)	0.4038	0.3016	0.5061	95% CI	Multivariate normal
Hospitalisation (coef.): Ischaemic aetiology	0.0862	–0.0009	0.1734	95% CI	Multivariate normal
Hospitalisation (coef.): Prior stroke	0.1469	0.0191	0.2746	95% CI	Multivariate normal
Hospitalisation (coef.): Prior atrial fibrillation/ flutter	0.0942	0.0123	0.1761	95% CI	Multivariate normal
Hospitalisation (coef.): Prior cancer	0.1629	–0.0095	0.3353	95% CI	Multivariate normal
Hospitalisation (coef.): Current smoker	0.2119	0.1060	0.3178	95% CI	Multivariate normal
Hospitalisation (coef.): Previously hospitalised for HF	0.3345	0.2548	0.4142	95% CI	Multivariate normal
Hospitalisation (coef.): EQ–5D*	–0.4855	–0.6615	–0.3095	95% CI	Multivariate normal
Hospitalisation (coef.): Constant	–2.8905	–3.8207	–1.9603	95% CI	Multivariate normal
Utility (coef.): Sacubitril/valsartan	0.0106	0.0044	0.0168	95% CI	Multivariate normal
Utility (coef.): Age*	–0.0008	–0.0011	–0.0005	95% CI	Multivariate normal
Utility (coef.): Female	–0.0309	–0.0387	–0.0231	95% CI	Multivariate normal
Utility (coef.): Region – Latin America (vs North America)	0.0412	0.0271	0.0553	95% CI	Multivariate normal
Utility (coef.): Region – Western Europe (vs North America)	0.0126	–0.0007	0.0259	95% CI	Multivariate normal
Utility (coef.): Region – Central Europe (vs North America)	–0.0003	–0.0135	0.0130	95% CI	Multivariate normal
Utility (coef.): Region – Other (vs North America)	0.0410	0.0261	0.0560	95% CI	Multivariate normal
Utility (coef.): NYHA class II (vs I)	–0.0093	–0.0242	0.0057	95% CI	Multivariate normal
Utility (coef.): NYHA class III (vs I)	–0.0509	–0.0674	–0.0344	95% CI	Multivariate normal
Utility (coef.): NYHA class IV (vs I)	–0.0917	–0.1319	–0.0514	95% CI	Multivariate normal
Utility (coef.): Heart rate*	–0.0003	–0.0005	0.0000	95% CI	Multivariate normal
Utility (coef.): log(NT–proBNP)*	–0.0093	–0.0127	–0.0059	95% CI	Multivariate normal
Utility (coef.): Sodium*	0.0010	–0.0001	0.0022	95% CI	Multivariate normal
Utility (coef.): BMI	–0.0020	–0.0026	–0.0013	95% CI	Multivariate normal
Utility (coef.): Diabetes	–0.0140	–0.0208	–0.0072	95% CI	Multivariate normal
Utility (coef.): 1–5 years since HF diagnosis (vs ≤1 year)	–0.0165	–0.0242	–0.0088	95% CI	Multivariate normal
Utility (coef.): >5 years since HF diagnosis (vs ≤1 year)	–0.0226	–0.0309	–0.0143	95% CI	Multivariate normal
Utility (coef.): Ischaemic aetiology	–0.0073	–0.0140	–0.0006	95% CI	Multivariate normal

Parameter	Mean value	Lower value for univariate SA	Upper value for univariate SA	Reference for uncertainty	Distribution used in PSA
Utility (coef.): Prior stroke	–0.0118	–0.0230	–0.0006	95% CI	Multivariate normal
Utility (coef.): Current smoker	–0.0130	–0.0220	–0.0039	95% CI	Multivariate normal
Utility (coef.): EQ–5D*	0.4885	0.4729	0.5041	95% CI	Multivariate normal
Utility (coef.): Hospitalised within previous 30 days	–0.1047	–0.1159	–0.0935	95% CI	Multivariate normal
Utility (coef.): Hospitalised 30–90 days previously	–0.0539	–0.0624	–0.0454	95% CI	Multivariate normal
Utility (coef.): Adverse event – cough	–0.0282	–0.0410	–0.0154	95% CI	Multivariate normal
Utility (coef.): Adverse event – hypotension	–0.0292	–0.0415	–0.0168	95% CI	Multivariate normal
Utility (coef.): Annual change	–0.0079	–0.0097	–0.0061	95% CI	Multivariate normal
Utility (coef.): Constant	0.8224	0.8022	0.8426	95% CI	Multivariate normal
Adverse events: hypotension, annual rate, Sacubitril/valsartan	0.0630	0.0580	0.0680	95% CI	None
Adverse events: hypotension, annual rate, ACEi	0.0420	0.0380	0.0460	95% CI	None
Adverse events: hypotension, mean duration (days)	64.8721	58.8900	70.9000	± 25%	Log
Adverse events: cough, annual rate, Sacubitril/valsartan	0.0510	0.0460	0.0560	95% CI	Log
Adverse events: cough, annual rate, ACEi	0.0650	0.0600	0.0700	95% CI	Log
Adverse events: cough, mean duration (days)	73.3328	66.0200	80.6500	± 25%	Log
Adverse events: angio-oedema, annual rate, Sacubitril/valsartan	0.0020	0.0010	0.0030	95% CI	None
Adverse events: angio-oedema, annual rate, ACEi	0.0010	0.0000	0.0020	95% CI	None
Adverse events: elevated serum creatinine, annual rate, Sacubitril/valsartan	0.0150	0.0120	0.0170	95% CI	Log
Adverse events: elevated serum creatinine, annual rate, ACEi	0.0200	0.0170	0.0230	95% CI	Log
Adverse events: elevated serum potassium, annual rate, Sacubitril/valsartan	0.0730	0.0670	0.0780	95% CI	Log
Adverse events: elevated serum potassium, annual rate, ACEi	0.0790	0.0730	0.0850	95% CI	Log
Costs, primary therapy, enalapril, cost per pack: 5	7.32	5.49	9.15	± 25%	None
Costs, primary therapy, enalapril, cost per pack: 10	9.43	7.07	11.79	± 25%	None
Costs, background therapy, carvedilol, cost per pack: 3.125	6.95	5.21	8.69	± 25%	None
Costs, background therapy, carvedilol, cost per pack: 6.25	7.45	5.59	9.31	± 25%	None
Costs, background therapy, carvedilol, cost per pack: 12.5	17.80	13.35	22.25	± 25%	None
Costs, background therapy, carvedilol, cost per pack: 25	26.63	19.97	33.28	± 25%	None
Costs, background therapy, bisoprolol, cost per pack: 5	15.90	11.93	19.88	± 25%	None
Costs, background therapy, bisoprolol, cost per pack: 10	26.05	19.54	32.56	± 25%	None
Costs, background therapy, spironolactone, cost per pack: 25	7.85	5.89	9.81	± 25%	None
Costs, background therapy, spironolactone, cost per pack: 50	15.50	11.63	19.38	± 25%	None
Costs, background therapy, spironolactone, cost per pack: 100	35.85	26.89	44.81	± 25%	None
Costs, background therapy, digoxin, cost per pack: 125	7.10	5.33	8.88	± 25%	None
Costs, background therapy, digoxin, cost per pack: 250	8.80	6.60	11.00	± 25%	None
Costs, background therapy, atorvastatin, cost per pack: 10	28.20	21.15	35.25	± 25%	None
Costs, background therapy, atorvastatin, cost per pack: 20	28.20	21.15	35.25	± 25%	None
Costs, background therapy, atorvastatin, cost per pack: 40	28.20	21.15	35.25	± 25%	None
Costs, background therapy, atorvastatin, cost per pack: 80	28.29	21.22	35.36	± 25%	None
Costs, background therapy, simvastatin, cost per pack: 20	37.35	28.01	46.69	± 25%	None
Costs, background therapy, simvastatin, cost per pack: 40	37.35	28.01	46.69	± 25%	None
Costs, background therapy, simvastatin, cost per pack: 80	37.35	28.01	46.69	± 25%	None
Costs, background therapy, furosemide, cost per pack: 40	4.85	3.64	6.06	± 25%	None
Costs, background therapy, aspirin, cost per pack: 100	6.60	4.95	8.25	± 25%	None
Costs, background therapy, warfarin, cost per pack: 3	7.65	5.74	9.56	± 25%	None
Costs, background therapy, clopidogrel, cost per pack: 75	44.98	33.74	56.23	± 25%	None
Beta blockers, % of patients	0.9300	0.9200	0.9400	95% CI	Beta
Mineralocorticoid receptor antagonist, % of patients	0.5561	0.5500	0.5700	95% CI	Beta
Digoxin, % of patients	0.3023	0.2900	0.3100	95% CI	Beta
Lipid lowering medications, % of patients	0.5630	0.5500	0.5700	95% CI	Beta
Diuretics, % of patients	0.8022	0.7900	0.8100	95% CI	Beta
Aspirin, % of patients	0.5178	0.5100	0.5300	95% CI	Beta
Anticoagulants, % of patients	0.3197	0.3100	0.3300	95% CI	Beta
ADP antagonists, % of patients	0.1500	0.1400	0.1600	95% CI	Beta
Costs, monthly cost of HF management	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – hypotension, cost per PCP visit	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – hypotension, number of PCP visits required	2.00	1.50	2.50	± 25%	Log
Costs, adverse events – elevated serum creatinine, cost per PCP visit	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – elevated serum creatinine, number of PCP visits required	2.00	1.50	2.50	± 25%	Log

Parameter	Mean value	Lower value for univariate SA	Upper value for univariate SA	Reference for uncertainty	Distribution used in PSA
Costs, adverse events – elevated serum creatinine, cost per lab test	8.00	6.00	10.00	± 25%	Log
Costs, adverse events – elevated serum potassium, cost per PCP visit	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – elevated serum potassium, number of PCP visits required	2.00	1.50	2.50	± 25%	Log
Costs, adverse events – elevated serum potassium, cost per lab test	8.00	6.00	10.00	± 25%	Log
Costs, adverse events – cough, cost per PCP visit	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – cough, number of PCP visits required	2.00	1.50	2.50	± 25%	Log
Costs, adverse events – cough, cost per lab test	8.00	6.00	10.00	± 25%	Log
Costs, adverse events – angio-oedema, % with milder angio-oedema	0.60	60%	60%	± 25%	Beta
Costs, adverse events – angio-oedema, cost per outpatient contact	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – angio-oedema, no. of outpatient visits required	2.00	1.50	2.50	not varied	Log
Costs, adverse events – angio-oedema, daily cost of antihistamines	0.77	0.77	0.77	± 25%	None
Costs, adverse events – angio-oedema, no. of days on antihistamines	14.00	10.50	17.50	± 25%	Log
Costs, adverse events – angio-oedema, cost per ER visit	492.00	369.00	615.00	± 25%	Log
Costs, adverse events – angio-oedema, cost per PCP visit	110.30	82.73	137.88	± 25%	Log
Costs, adverse events – angio-oedema,no. of PCP visits required	1.00	1.00	1.00	not varied	Log
Costs, adverse events – angio-oedema, daily cost of glucocorticoids	1.42	1.42	1.42	± 25%	None
Costs, adverse events – angio-oedema, no. of days on glucocorticoids	5.00	3.75	6.25	± 25%	Log
Costs, titration, cost per PCP visit	110.30	82.73	137.88	± 25%	Log
Costs, titration, number of PCP visits required (titration)	2.00	1.50	2.50	± 25%	Log
Costs, titration, NT–proBNP testing	70.00	52.50	87.50	± 25%	Log
Costs, titration, number of outpatient visits required (NT–proBNP testing)	1.00	0.75	1.25	± 25%	Log
Costs, titration, cost per outpatient contact	132.02	99.02	165.03	± 25%	Log

Table S13: Results of subgroup analyses.

Subgroup	Δ Costs	Δ QALYs	ICER	% change from base-case
Full analysis set	CHF 10 926	0.425	CHF 25 684	0%
Baseline age <65 years	CHF 11 707	0.444	CHF 26 375	3%
Baseline age ≥65 years	CHF 10 115	0.406	CHF 24 900	–3%
Baseline age <75 years	CHF 11 396	0.437	CHF 26 089	2%
Baseline age ≥75 years	CHF 8872	0.376	CHF 23 624	–8%
Region - North America	CHF 9697	0.418	CHF 23 194	–10%
Region - Latin America	CHF 10 766	0.428	CHF 25 164	–2%
Region - Western Europe	CHF 10 771	0.445	CHF 24 229	–6%
Region - Central Europe	CHF 11 153	0.396	CHF 28 132	10%
Region - Other	CHF 11 359	0.455	CHF 24 990	–3%
Baseline NYHA class I/II	CHF 11 409	0.451	CHF 25 317	–1%
Baseline NYHA III/IV	CHF 9456	0.349	CHF 27 128	6%
Baseline LVEF ≤ median	CHF 10 377	0.420	CHF 24,698	–4%
Baseline LVEF > median	CHF 11 565	0.432	CHF 26 801	4%
Baseline SBP ≤ median	CHF 10 792	0.429	CHF 25 127	–2%
Baseline SBP > median	CHF 11 088	0.420	CHF 26 373	3%
Baseline eGFR <60	CHF 9394	0.397	CHF 23 642	–8%
Baseline eGFR ≥60	CHF 11 805	0.441	CHF 26 738	4%
Baseline NT-proBNP ≤ median	CHF 12 841	0.465	CHF 27 589	7%
Baseline NT-proBNP > median	CHF 8863	0.382	CHF 23 186	–10%
Diabetes at baseline	CHF 9477	0.399	CHF 23 762	–7%
No diabetes at baseline	CHF 11 689	0.439	CHF 26 602	4%
Hypertension at baseline	CHF 10 744	0.416	CHF 25 801	0%
No hypertension at baseline	CHF 11 366	0.447	CHF 25 421	–1%
Prior use of ACEI	CHF 11 005	0.426	CHF 25 855	1%
Prior use of ARB	CHF 10 642	0.425	CHF 25 067	–2%
Use of beta-blocker at baseline	CHF 11 075	0.428	CHF 25 879	1%
No use of beta-blocker at baseline	CHF 8944	0.391	CHF 22 856	–11%
Use of aldosterone antagonist at baseline	CHF 10 845	0.422	CHF 25 720	0%
No use of aldosterone antagonist at baseline	CHF 11 027	0.430	CHF 25 640	0%
≤1 year since diagnosis of HF	CHF 12 887	0.466	CHF 27 674	8%
1–5 years since diagnosis of HF	CHF 10 536	0.414	CHF 25 464	–1%
>5 years since diagnosis of HF	CHF 9532	0.401	CHF 23 758	–8%
Ischaemic aetiology	CHF 10 501	0.413	CHF 25 434	–1%
Non-ischaemic aetiology	CHF 11 563	0.444	CHF 26 033	1%
Prior atrial fibrillation at baseline	CHF 10 089	0.404	CHF 24 990	–3%
No prior atrial fibrillation at baseline	CHF 11 414	0.438	CHF 26 057	1%
Prior HF hospitalisation	CHF 10 306	0.416	CHF 24 786	–3%
No prior HF hospitalisation	CHF 11 973	0.442	CHF 27 111	6%

MRA = mineralocorticoid receptor antagonist; AF = atrial fibrillation; BB = beta-blocker; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate; NT-proBNP = N terminal pro-brain natriuretic peptide; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HF = heart failure.