Manuscript title: Cost-effectiveness of Sacubitril/valsartan in Germany

Manuscript subtitle: An Application of the Efficiency Frontier

Running title: An Application of the Efficiency Frontier

Concise summary: the cost-effectiveness for sacubitril/valsartan was assessed for German heart failure patients with a reduced ejection fraction, comparing international and German HTA guidelines.

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Highlights

- Using the German HTA guidelines, the ICER is not taken into consideration. Instead, the efficiency frontier was introduced as an alternative, to avoid the use of QALYs and the setting of willingness-to-pay thresholds.
- We conducted the first direct comparison of the German efficiency frontier methodology to the conventional ICER, using sacubitril/valsartan, a new treatment for patients with chronic heart failure with a reduced ejection fraction.
- Sacubitril/valsartan has a favourable ICER in the German setting, comparable to other European countries. However, using the efficiency frontier, the results would inform decision makers that a considerable discount needs to be negotiated.

Abstract

Objectives: To assess the cost-effectiveness of new treatments in Germany, the efficiency frontier (EF) method has been developed. We compared the cost-effectiveness analysis using international standards and the German methodology, using the heart failure drug, sacubitril/valsartan, as an example.

Methods: A previously-developed Markov model was adapted to include four treatment options: no treatment, enalapril, candesartan and sacubitril/valsartan. The internationally-used incremental cost-effectiveness ratio (ICER) was calculated, as well as cost-effectiveness acceptability curves (CEAC). Additionally, EFs, net monetary benefits (NMBs) and price-acceptability curves were created according to German guidelines. All analyses were performed from the perspective of the German Statutory Health Insurance.

Results: The base-case ICER for sacubitril/valsartan compared to enalapril, is €19,300/QALY. On the CEAC, sacubitril/valsartan is most likely to be cost-effective, out of all included comparators, from a hypothetical willingness-to-pay threshold of €18,250/QALY onwards. No EF could be constructed for the base case. Taking the uncertainty of the input parameters in account for the probabilistic sensitivity analysis, a NMB of around –€14.000 was calculated, depending on the outcome considered, with the NMB being zero at a daily price for sacubitril/valsartan ranging from €1.52 to €1.67.

Conclusions: We calculated an ICER for Germany, comparable to previously published cost-effectiveness analyses for Europe, which widely concluded sacubitril/valsartan to be cost-effective. Using the German EF approach, a considerable discount needs to be applied before sacubitril/valsartan can be considered cost-effective.

Introduction

In Germany, pharmaceutical companies do not need to perform a cost-effectiveness analysis for new drugs to gain market authorization. Instead prices are negotiated between the statutory health insurance funds and the pharmaceutical companies.[1,2] An economic evaluation is merely one of the tools that can be used to negotiate a reimbursement price, but is seldom used.[1,3] If an economic evaluation is commissioned in this process, the *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (IQWIG) is responsible for its assessment; it has developed the concept of the efficiency frontier (EF) as a method to compare the cost-effectiveness of interventions.[1,2,4,5] The benefits and pitfalls of this approach, compared to the more internationally-common cost-effectiveness/-utility analysis, has been debated internationally.[6–9]

Internationally, Incremental Cost-Effectiveness Ratios (ICERs) are commonly used as outcomes of cost-effectiveness analyses, which is the costs per Quality-Adjusted Life Year (QALY) gained. This outcome has the advantage that it enables transferability of cost-effectiveness analyses between different diseases.[10,11] The methods to create an ICER also have some challenges, such as difficulties in assessing disease-specific outcomes with general instruments; differences in health-related quality of life assessment between informants such as patients and the public; and the choice of a willingness-to-pay threshold to decide on the cost-effectiveness of an intervention.[6,12] Using the EF as an outcome to decide whether a new intervention is cost-effective, circumvents these challenges.[5,13] As an alternative to QALYs, disease-specific, health-related outcomes can be used and the threshold, created from the various alternatives for a specific disease, can be used to assess the cost-effectiveness.[5,13] This however, comes at a major disadvantage: different disease areas cannot be compared.[8] Additionally, the costs of the existing

interventions in a certain disease field have a profound effect on the possible costs of an innovative intervention.[7]

Chronic Heart Failure (CHF) has a prevalence of around 1.7% and a one-year all-cause mortality of 23% among newly diagnosed CHF patients.[14] CHF has a large impact on the German healthcare budget: the costs per patient are estimated to be €2100-€9100, with 45-72% of the costs originating from hospitalizations.[15] In 2017, over 460,000 hospitalizations were caused by HF (over 2% of total hospitalizations) and the total costs of HF were over €5.2 billion in 2015 (over 1.5% of total healthcare expenditure).[16,17]

In 2015, sacubitril/valsartan (Entresto™, previously known as LCZ696), a new drug for the treatment of CHF with a reduced ejection fraction (HF-REF), was approved by the European Medicines Agency (EMA).[18] In the PARADIGM-HF trial, reduced mortality and hospitalization rates in addition to an improved quality of life were found for sacubitril/valsartan as compared to enalapril .[19] Subsequent to the approval of sacubitril/valsartan by the EMA, pharmacoeconomic evaluations have been published for many other European countries.[20–24] In a previous study from the Dutch perspective, we concluded that sacubitril/valsartan was cost-effective.[20] To date, one analysis for Germany has been published, reporting an ICER of €23,401 per life-year gained.[25] However, the article by Gandjour and Ostwald does not include a comparison to the EF.[25]

We aim to assess the use of the EF for sacubitril/valsartan, an intervention, which replaces the broadly available generic drug classes: angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). This includes the assessment of the cost-effectiveness of sacubitril/valsartan in Germany, using a previously developed model, adapted to incorporate the EF, according to German guidelines.[4,5,20] Additionally, we perform a cost-utility analysis using

globally-used guidelines, including the calculation of an ICER using QALYs, enabling the comparison with results from other countries. We then compare the conclusions decision makers could draw based on the German methodology, using the EF, and the international health technology assessment standards, using the ICER as an outcome.[4,5,26,27]

Methods

Model design

A Markov model, previously published for the Netherlands, which primarily incorporated data from the PARADIGM-HF trial, was adapted to the German market.[19,20] Monthly cycles were used for a time horizon of 30 years. The following four health states were incorporated (Figure 1):

- Outpatient treated HF-REF;
- Hospital admissions to a general ward;
- Hospital admissions including a stay at the ICU; and
- Death.

All patients started in the outpatient HF-REF state and were admitted to hospital, using the time-dependent rates as reported in the PARADIGM-HF trial.[19] The duration of stay of the PARADIGM-HF trial was used as reported by Packer et al. and 10% of hospital admissions included ICU treatment.[28,29] In the outpatient setting, the mortality rates were calculated using the rates reported in the PARADIGM-HF trial for the death from heart disease and the general German population parameters for other causes of mortality.[19,30] Mortality and hospitalization data from the PARADIGM-HF trial were used, as reported in our analysis for the Netherlands.[20] For the inpatient setting, data published for the CHF population by Corrao et al. were used for both mortality and hospitalizations, since the 30-day hospital deaths from PARADIGM-HF were not publicly available.[31] Rehospitalization rates as published by Desai et al. were used.[32] All transition probabilities are displayed in supplementary table 1 and all treatment effects are displayed in supplementary table 2. Scenario analyses for patients at a starting age of 55 and 75 years were also included.

The model was developed using Microsoft Excel® 2016 (Redmond, WA, USA, available from https://www.office.com/ [accessed August 31, 2018]).

Figure 1. Schematic representation of the chronic heart failure Markov model. ICU, intensive care unit.

Target population

HF-REF patients, as described in PARADIGM-HF, were followed through the Markov model.[19] At the time of writing, sacubitril/valsartan is only registered for use within this group.[18] The starting age was the mean age of the trial: 64 years, with scenarios for patients with a starting age of 55 and 75 years.[19] If no data were available for the HF-REF group or a specific age category, data for the general CHF population were used.

Comparators

Primarily, sacubitril/valsartan was compared to enalapril, an ACEi, as in the PARADIGM-HF trial.[19] German guidelines recommend the prescription of an ACEi to all HF-REF patients. If an ACEi is not tolerated, an angiotensin receptor blocker (ARB) can be used, such as valsartan or candesartan.[33] The cost-effectiveness of sacubitril/valsartan was assessed using the German EF approach, which was constructed using three mutually-exclusive treatment options: placebo (no treatment); enalapril, representing the group of ACEis; and candesartan, representing the group of ARBs.[4,5,34–36] For the base case, we included the differences in effects and costs of the four treatment options for the full time horizon. As no head-to-head trials were available for candesartan vs. sacubitril/valsartan placebo vs. sacubitril/valsartan and enalapril vs. candesartan, adjusted, indirect comparisons were performed.[37,38] In supplementary figure 1 and supplementary table 3 further details are provided on the relative risks of all direct and indirect comparisons. Regarding ICU admissions, only comparative data on enalapril vs. sacubitril/valsartan was

found; patients on placebo and candesartan were assumed to have the same risk of an ICU admission as placebo.[28]

Costs

The costs in the model were taken from the perspective of the Statutory Health Insurance (SHI).[4] The exact input parameters can be found in supplementary table 4. The price of sacubitril/valsartan was used from the appraisal dossier for Germany: €6.66 per day.[41] Other drug costs were taken from the German institute of medical documentation and information (dimdi) or the site of the SHI.[42] Hospitalization costs were based on the German diagnosis related group (G-DRG) system and the method previously used by Schmidt et al.[43,44] One-day, general and ICU hospitalization costs were determined by their respective DRG codes, considering the length-of-stay of PARADIGM-HF as reported by Packer et al., multiplied by the average German lumpsum (*Landesbasisfallwerte*).[28,43,45] Outpatient care costs were added monthly to all patients in the model and consisted of both general practitioner and cardiologist costs, visited on average 1.8 times annually, distributed equally.[46,47] Sickness allowance (*Krankengeld*) was not included in the model, as the starting age in the model is higher than the effective age of labour market exit, and were therefore assumed to be negligible.[4,48] All costs were converted into 2018 euros.[49]

Health outcomes and utilities

The health outcomes considered in the model were: hospitalizations averted in the first 42 modelled months, 42-months survival, life-years gained and QALYs gained. The 42-month follow-up period for survival and hospitalizations was selected as this corresponds to the total follow-up of PARADIGM-HF.[19] For the QALY calculations, EQ-5D utility values from PARADIGM-HF were used, since no German-specific utilities were found in the literature.[50,51]

The baseline utility value was 0.78, a disutility value of 0.21 was used for hospitalized patients and for sacubitril/valsartan treatment a utility benefit of 0.011 was incorporated.[50,51]

Time horizon and discounting

A 30-year time horizon was used to approach a lifetime horizon, with a starting age of 64. Both costs and effects were discounted at 3%, with 0% and 5% used in scenarios, in line with the German guidelines.[4]

Model outcomes

Incremental cost-effectiveness ratio, sensitivity analyses and scenario analyses

ICERs were constructed for placebo, enalapril and candesartan compared to sacubitril/valsartan, with the main outcome considered being enalapril compared to sacubitril/valsartan, enabling us to compare our outcomes to other cost-utility analyses. The increase in costs was divided by the increase in quality adjusted life years (QALYs). The ICERs reported are rounded to the nearest hundreds of euros. To study the uncertainty in the model, a probabilistic sensitivity analysis (PSA) was performed using 10,000 replications, leading to a conventional cost-effectiveness (CE) plane and a cost-effectiveness acceptability curve (CEAC), incorporating placebo, enalapril, candesartan and sacubitril/valsartan. For the univariate sensitivity analysis, a Tornado diagram was created to display the effects of the uncertainty of specific values, using the 80%-120% interval of the means, recording the corresponding effects on the ICER of sacubitril/valsartan compared to enalapril.

To account for potential changes in drug costs, various price points were included in the scenario analyses: for sacubitril/valsartan the daily costs of €3 and €10 were included. For enalapril and candesartan a price point of €1 per day was included. To see the effects of the extrapolation of costs and effects of sacubitril/valsartan, a scenario was included where the benefits and added

costs of sacubitril/valsartan were only included for the follow-up of the PARADIGM-HF trial: 42 months. Additionally, the discount rates were varied to 0% and 5%. The starting ages of the cohort were also varied, by including 55 year-old an 75 year-old cohorts.

Efficiency frontier

As mentioned, the IQWIG guidelines recommend an alternative method to perform health technology assessment.[4,5] The EF is drawn on an inverted CE plane between the non-dominated alternative current treatment options, the new intervention is then compared with respect to this (linearly extrapolated) frontier.[4] Although the use of QALYs is not ruled out, their use are not mandated in Germany, as opposed to many other countries.[3,4] The EF method was developed with the use of direct, disease-specific and clinical outcomes in mind, without the need to use QALYs.[5] To create a usable EF, at least two non-dominated alternatives should be available next to the novel treatment that is considered for reimbursement. We designed an EF with placebo, enalapril, candesartan and sacubitril/valsartan. The uncertainty of the EF was considered by constructing a price-acceptability curve and calculating the net monetary benefit (NMB).[10,52] The price-acceptability curve was plotted by calculating the daily price where sacubitril/valsartan would be situated precisely on the EF, and thus be cost-effective, for all replications of the Monte Carlo analysis. The median NMB and interquartile range for the introduction price of sacubitril/valsartan (€6.66 /day) was calculated, as well as the median daily price where the NMB was equal to zero, this being the highest price where sacubitril/valsartan could be considered cost-efficient (i.e. it is situated on the EF). Model replications where no EF could be constructed, were excluded from the NMB analysis.

Results

Base case results

The base case results are displayed in table 1. Sacubitril/valsartan costs more than enalapril, but both life years and QALYs are gained. In the sacubitril/valsartan group, over 2,000 hospitalizations are prevented in the 30-year time horizon compared to the enalapril group. The base case ICER is €19,300/QALY for sacubitril/valsartan versus enalapril; enalapril and candesartan are cost-saving compared to placebo, mainly due to the decrease in the number of hospitalizations.

No EF can be created for the base case, regardless of the considered outcome: enalapril dominates all other comparator treatment options, resulting in the inability to assess the efficiency of sacubitril/valsartan. Inverted base-case cost-effectiveness planes are displayed in supplementary figure 2.

CE plane and CEAC

Figure 2 displays CE planes, showing the results of the probabilistic sensitivity analysis. Compared to placebo, most iterations show additional costs for sacubitril/valsartan and savings for enalapril and candesartan. Enalapril and candesartan have similar costs and effects. The CEAC is displayed in Figure 3. If the willingness to pay is equal to the base-case ICER (€19,300/QALY), sacubitril/valsartan is the most likely treatment to be considered cost-effective, with a probability of 41%.

Figure 2. Cost-effectiveness planes of enalapril, candesartan and sacubitril/valsartan compared to placebo; and sacubitril/valsartan compared to enalapril

Figure 3. Cost-effectiveness acceptability curves

Efficiency frontier

Although no EF could be constructed for the base case, this was possible in the probabilistic analysis. Table 2 shows that this was possible for 77.5% of model replications, when survival, life-years gained or QALYs were considered as outcomes of the analysis and for 31.4% of replications if reduced hospitalizations were considered. The median NMB for sacubitril/valsartan at its introduction price in Germany is similar for all included outcomes: around -€14,000. The median calculated daily price of sacubitril/valsartan where the NMB is equal to zero, ranges from €1.52 to €1.67, depending on the outcome considered. The price-acceptability curves (Figure 4), display the probability of sacubitril/valsartan being cost-effective at different price points (costs are per day) for the included outcomes.

Figure 4. Price-acceptability curves of the cost-effectiveness of sacubitril/valsartan

Univariate sensitivity analysis and scenario analyses

The univariate sensitivity analysis, displayed as a tornado diagram, with the ICER of sacubitril/valsartan compared to enalapril as the considered outcome, is displayed in supplementary figure 4. The ICER is mainly impacted by the effect of sacubitril/valsartan on the mortality, the costs of this drug and the utilities of HF patients in the home setting.

The results of the impact on the ICERs of the various included scenario analyses are shown in supplementary table 5. Sacubitril/valsartan, enalapril and candesartan drug costs have a major impact on the results. As long as the daily price of enalapril and candesartan are not increased, these drugs will dominate placebo.

Discussion

At €6.66 per day for sacubitril/valsartan, the ICER compared to the current treatment enalapril is €19.300/QALY. To reach a probability of 90% of being cost-effective, a willingness-to-pay threshold of €45,000/QALY would have to be considered (figure 3). Using the EF approach, the base case does not result in interpretable results; as enalapril, the cheapest alternative considered, is dominating placebo and candesartan, resulting in the inability to draw an EF using the available treatment options. The median daily price of sacubitril/valsartan where the NMB is equal to zero (i.e. it is situated on the EF), ranges from €1.52 to €1.67.

The CE plane (figure 2) displays the incremental costs and effects of enalapril, candesartan and sacubitril/valsartan as compared to placebo. Enalapril and candesartan are overlapping on the plane, due to their very similar costs and effects. However, the uncertainty surrounding candesartan is greater, mainly due to the method its effects are modelled: there was no direct comparison with enalapril available. Compared to the other interventions, sacubitril/valsartan is more effective and more expensive. The univariate sensitivity analysis shows that the impact on mortality of sacubitril/valsartan is the main driver of the cost-effectiveness, followed by its costs, the quality-of-life measurements in the outpatient setting and the reduction in hospitalizations caused by sacubitril/valsartan.

Using the EF approach, sacubitril/valsartan could not be considered cost-effective in more than 5% of model replications, at a daily price of €6.66, independent of the outcome considered. The different outcomes considered do not influence our results to a large degree. The outcomes used to construct the EF based on gained life years (42-month survival, total life years gained and QALYs gained) provided comparable results: the cost-effectiveness planes are very similar, the price-acceptability curves are overlapping and an EF could be constructed in almost 80% of

model replications. Using the decrease in hospitalizations to construct the EF gives a similar shaped price-acceptability curve, although a EF could only be constructed in about 30% of replications, moving the vertical intercept down. The interquartile range of the NMB is also considerably wider compared to the other outcomes considered. This difference can be explained by the larger benefit of enalapril on hospitalizations than on mortality, compared to candesartan (see also supplementary table 3).[34,35]

As compared to our previously-reported results for the Netherlands, the base-case ICER is approximately the same (both around €19,000/QALY). Compared to previously-published ICERs for European countries, which range from €17,600 to €23,401 with an average of €20,676, our ICER for Germany is within this range.[20–25] For Germany, Gandjour and Ostwald calculated an ICER of €23,401, a small difference when regarding their very different model design: the included discounts on sacubitril/valsartan, their inclusion of indirect medical costs and their adjustments to the PARADIGM-HF mortality rates, based on Germany-specific data.[25]

This analysis has a number of limitations, first of all, for the inclusion of candesartan and placebo, we focused on the model parameters with the largest impact on the results: mortality and hospitalizations, as data on the other inputs were not available in scientific literature. This also limited the number of clinical outcomes we could consider for the EF. The comparison between sacubitril/valsartan and placebo or candesartan is indirect, as no clinical trials have been performed with these comparators; the same holds true for candesartan vs. enalapril – of course, this has been considered for the PSA. The selection of comparators has a major impact on the construction of the EF: next to placebo, we included two comparable and mutually-exclusive drugs, representing two large classes of drugs (ACEis and ARBs).[5] These will however not be used as monotherapy in most patients and be combined with several other drugs, such as

diuretics and beta blockers, and possibly other treatments, such as a pacemaker or cardiac resynchronization therapy; these treatments cannot really be considered true alternatives in the context of the EF and were therefore not included as comparators to sacubitril/valsartan.[5,19,33,36,53] In addition to the EF analysis, IQWIG guidelines detail the calculation of the budget impact, that can also be used in the decision-making process.[4] Notably, we considered the budget impact outside of the scope of this research, however, Gandjour and Ostwald previously reported a maximum annual increase of the German healthcare budget of €88 million, which corresponds to less than 0.04% of total SHI expenditure.[25]

The median daily price where sacubitril/valsartan is situated on the EF (NMB=0) ranges from €1.52 to €1.67. Using the price indicated by the EF, the introduction price of sacubitril/valsartan would warrant negotiations by German decision makers, to further approach this price point. If the ICER would instead be used to assess the cost-effectiveness of sacubitril/valsartan in the German context, it would most likely be deemed cost-effective at market entry, as reported for other European countries.[20–24]

This comparison marks a major difference in conclusions decision makers would draw using either the ICER or EF approach. If we consider a fixed budget for CHF alone, the EF may provide more relevant information for decision makers: the health gains per euro will not decrease as long as the treatment is on or above the frontier. However, if we accept that patented drugs are more expensive, due to the coverage of development costs, the EF approach is not very useful in this case, since currently there is no method to determine an acceptable price point for innovative drugs replacing generic drugs. The latter issue was also raised by Sculpher and Claxton: a disease area with a concentration of generics, will have a low acceptable price point for innovative drugs.[7] Using both approaches (ICER and EF) simultaneously, which are not

mutually exclusive, as this research shows, may have benefits in the decision making process. If a new product has an ICER that is regarded cost-effective, but the efficiency, as determined using the EF is low, the results could still be used to negotiate a discount. This might be especially relevant for innovations with a potentially large budget impact. Additionally, the EF's ability to consider various outcomes may be helpful if alternative outcomes, such as patient-reported outcomes, are generated by clinical trials.[54] We think it may be useful to perform similar comparisons in various other fields, where patented drugs reflect important treatment modalities, such as oncology.

Currently, sacubitril/valsartan is only registered for the use in HF-REF patients, although this model partly uses data for the general CHF population. German guidelines advice to only treat patients with the new drug if patients still are symptomatic under enalapril.[53] New data could improve knowledge regarding the long-term effects of the new drug and the certainty of its cost-effectiveness. Additionally, the results of the PARAGON-HF trial, which is expected to be completed in 2019, can indicate whether sacubitril/valsartan improves clinical outcomes for CHF patients with a preserved ejection fraction.[55,56] A Post-hoc analysis from PARADIGM-HF indicates that sacubitril/valsartan might improve glycaemic control, which could improve the cost-effectiveness considering a diabetes is a common comorbidity in this patient population.[57,58] As this outcome was not routinely assessed, this aspect could not be considered in our analysis and further research would be useful from a clinical point of view, as well as from an economic perspective.[59]

In conclusion, our model shows that sacubitril/valsartan can be considered cost-effective, at its introduction price in Germany, when using globally-used methods to perform the economic

evaluation.[10] In contrast, using the EF approach, a discount of around 75% for sacubitril/valsartan should be targeted to make it cost-effective.

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Tables

Table 1. Base case results, per 10,000 patients

	Placebo	***Enalapril***	***Candesartan***	***Sacubitril/valsartan***
Costs	*€ 83,261,040*	*€ 73,298,835*	*€ 74,111,116*	*€ 231,145,386*
Hospitalizations (30 years)	13,915	10,192	10,531	*8,121*
Hospitalizations (42 months)	6,367	4,141	4,350	2,930
Percentage of patients surviving after 42 months	59%	65%	64%	70%
Life years	54,527	63,037	61,825	72,450
QALYs	42,323	49,020	48,069	57,192
ICER (/QALY, compared to placebo)	-	Dominating	Dominating	€9,900

ICER (/QALY, compared to enalapril)	Dominated	-	Dominated	€19,300

ICER values rounded to the nearest hundreds of euros

QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio

Table 2. Probabilistic results of efficiency frontier approach

Outcome	Hospitalizations averted (compared to placebo, first 42 months)	42-month survival	Average total life years	Average total QALYs
Number of model replications where an EF could be constructed	31.4%	77.5%	77.5%	77.5%
Median NMB at introduction price of sacubitril/valsartan [IQR]	-€14,300 [-€11,600 − -€16,200]	-€14,100 [-€12,300 − -€15,400]	-€14,000 [-€12,200 − -€15,300]	-€13,800 [-€12,000 − -€15,200]
Median daily price sacubitril/valsartan with NMB=0 [IQR]	€1.52 [€0.67 − €2.57]	€1.57 [€0.95 − €2.31]	€1.61 [€0.99 − €2.37]	€1.67 [€1.03 − €2.43]

NMBs are rounded to the nearest hundreds of euros

QALY: quality-adjusted life-year; EF: efficiency frontier; NMB: net monetary benefit; IQR: interquartile range

Figure 1

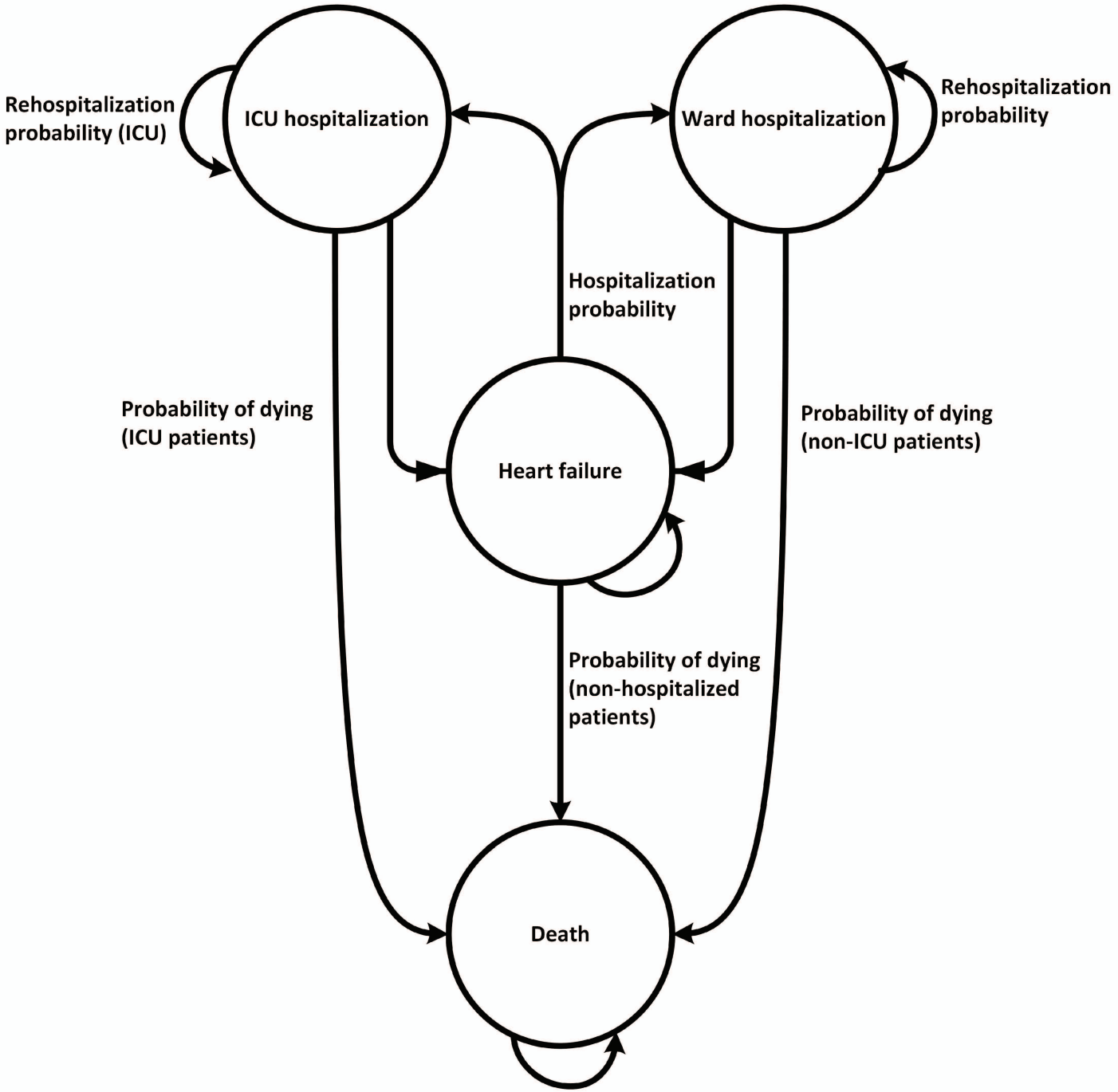

Rehospitalization probability (ICU)
ICU hospitalization
Ward hospitalization
Rehospitalization probability
Hospitalization probability
Probability of dying (ICU patients)
Heart failure
Probability of dying (non-ICU patients)
Probability of dying (non-hospitalized patients)
Death

Figure 2

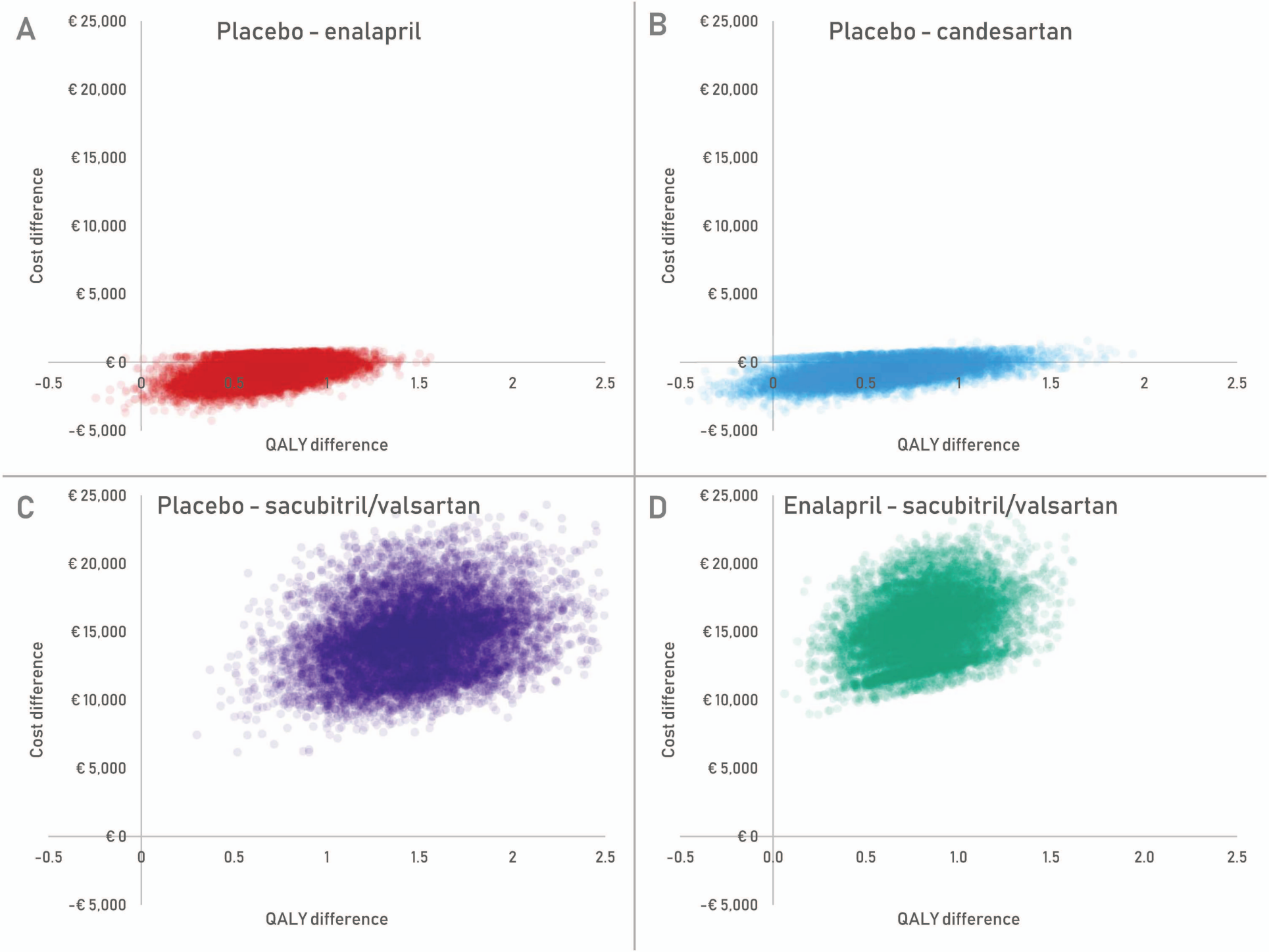

A
Placebo - enalapril
B
Placebo - candesartan
C
Placebo - sacubitril/valsartan
D
Enalapril - sacubitril/valsartan
Cost difference
QALY difference
€ 25,000
€ 20,000
€ 15,000
€ 10,000
€ 5,000
€ 0
-€ 5,000
-0.5
0
0.5
1
1.5
2
2.5

Figure 3

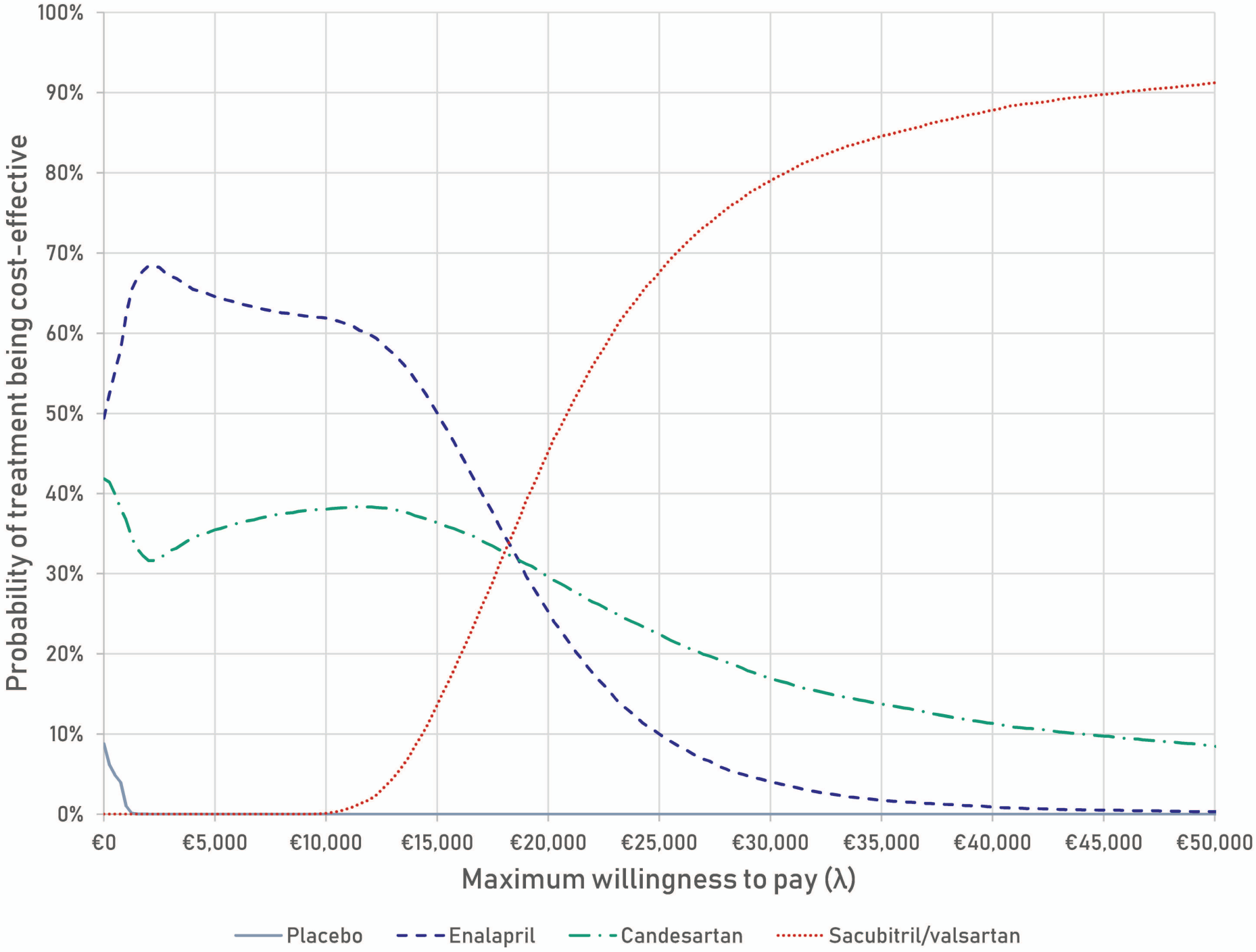
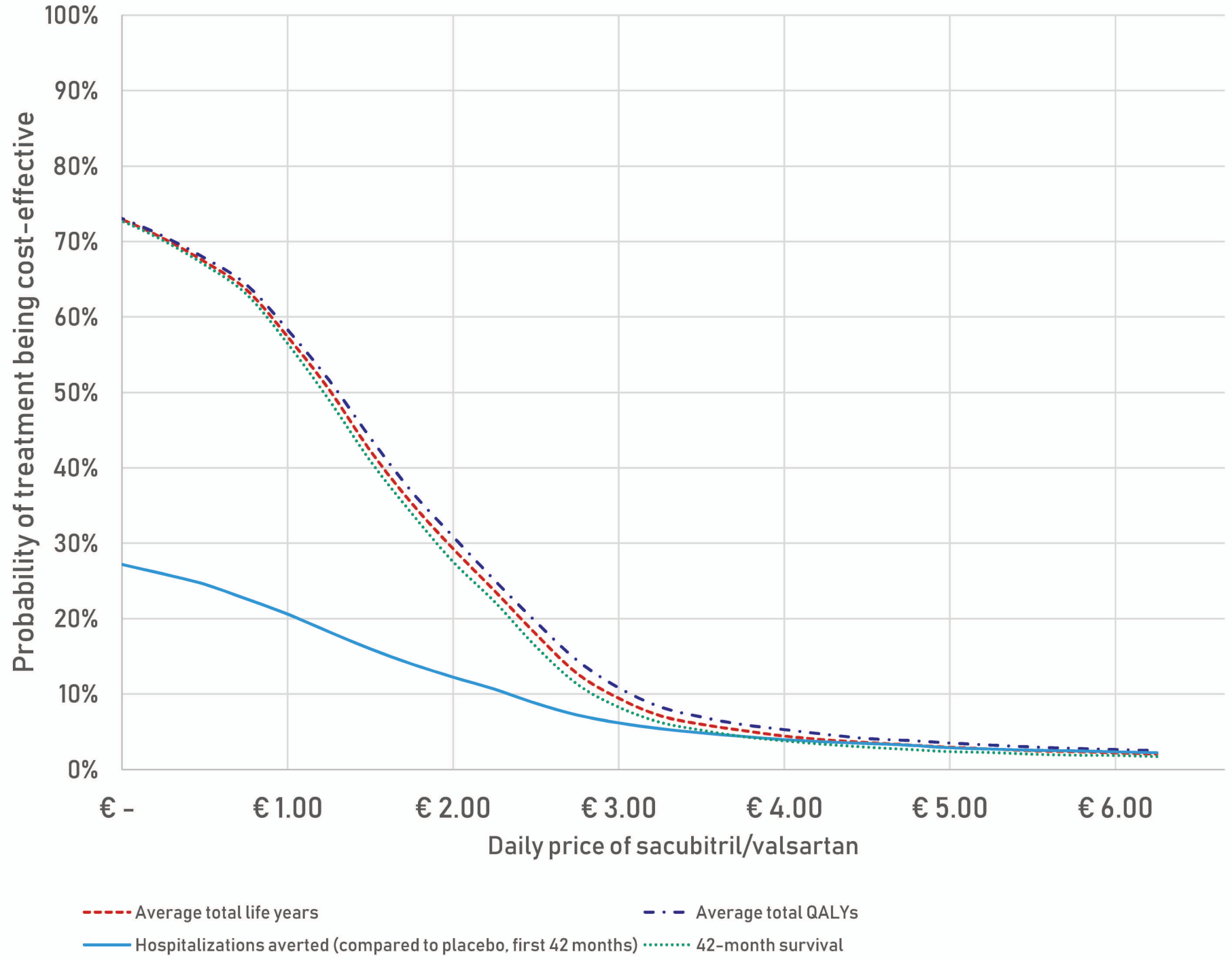

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability of treatment being cost-effective
€0
€5,000
€10,000
€15,000
€20,000
€25,000
€30,000
€35,000
€40,000
€45,000
€50,000
Maximum willingness to pay (λ)
Placebo
Enalapril
Candesartan
Sacubitril/valsartan

Figure 4


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability of treatment being cost-effective
€ -
€ 1.00
€ 2.00
€ 3.00
€ 4.00
€ 5.00
€ 6.00
Daily price of sacubitril/valsartan
Average total life years
Average total QALYs
Hospitalizations averted (compared to placebo, first 42 months)
42-month survival

Supplementary appendix

Cost-effectiveness of Sacubitril/valsartan in Germany: An Application of the Efficiency Frontier

Simon van der Pol, PharmD; Lisa A. de Jong, PharmD; Pepijn Vemer, PhD; Danielle E.M.C. Jansen, PhD; Maarten J. Postma, PhD

Contents

Supplementary table 1 - transition probabilities used in the Markov model

Transition	Probability (monthly)	References
Outpatient - death (cardiovascular)	0.0089	1
Background mortality		2
Age 55-59	0.00041	
Age 60-64	0.00064	
Age 65-69	0.00090	
Age 70-74	0.0015	
Age 75-79	0.0021	
Age ≥80	0.0020	
Mortality during ward hospitalization		3
Age 50-73	0.037	
Age 74-80	0.074	
Age 81-85	0.10	
Age ≥ 86	0.20	
Mortality during ICU hospitalization	0.11	4
Hospitalization		5
Month 1	0.012	
Month 100	0.0086	
Month 200	0.0082	
Month 300	0.0080	
Rehospitalization	Enalapril and candesartan: 0.199	6
	Sacubitril/valsartan: 0.088	6
	Placebo: 0.251	7

Supplementary table 2 - Treatment Effects, including uncertainty used for probabilistic sensitivity analysis

Treatment effects	Risk ratio [95% CI]	Distribution	References
Sacubitril/valsartan (relative to enalapril)	All-cause Mortality: 0.84 [0.76-0.93] Hospitalization: 0.77 [0.67-0.89] ICU admission: 0.82 [0.72-0.94]	Lognormal Lognormal Lognormal	1 5 5
Placebo (relative to enalapril)	All-cause Mortality: 1.18 [1.03-1.33] Hospitalization: 1.56 [1.37-1.82] ICU admission: 1	Lognormal Lognormal	8 8 Assumed
Candesartan (relative to placebo)	Mortality: 0.87 [0.74-1.03] Hospitalization: 0.68 [0.57-0.81] ICU admission: 1	Lognormal Lognormal	9 9 Assumed

Supplementary table 3 – average direct and indirect relative risks

Hospitalization risk

	Placebo	Enalapril	Candesartan	Sacubitril/valsartan
Placebo	-	0.85[8]	0.87[9]	0.72*
Enalapril	1.18[8]	-	1.02*	0.84[1]
Candesartan	1.15[9]	0.98*	-	0.83*
Sacubitril/valsartan	1.39*	1.19[1]	1.21*	-

*indirect comparison

Mortality

	Placebo	Enalapril	Candesartan	Sacubitril/valsartan
Placebo	-	0.64[8]	0.68[9]	0.51*
Enalapril	1.56[8]	-	1.07*	0.77[1]
Candesartan	1.47[9]	0.94*	-	0.75*
Sacubitril/valsartan	1.96*	1.30[1]	1.33*	-

*indirect comparison

Supplementary table 4 - cost input parameters

Description	Monthly costs (2018 euros)	Reference
Enalapril treatment	€9.07^	10
Sacubitril/valsartan treatment	€199.8*	11
Candesartan treatment	€8.46^	10
Other CHF drugs⁺ treatment	€12.36	1,10
Costs of outpatient CHF care (general practitioner and cardiologist)	€7.87	12,13
Hospitalization length of stay	**Additional costs: general ward | ICU (2018 euros)**	14,15
0 days	€794.01	
1 day	€2420.18 | €3543.58	
2 days	€3550.52 | €5013.72	
3 days	€4200.63 | €6483.85	
4 days	€4850.75 | €7953.99	
5 days	€5500.87 | €9424.12	
6 days	€5500.87 | €10894.26	
>6 days	€5500.87 | €10894.26	

^scenario analysis for €3 per day is included; *scenario analyses for €3 and €10 per day are included; ⁺hydrochlorothiazide, digoxin, spironolactone and metoprolol, using the usage data from PARADIGM-HF and German reference pricing

CHF: Chronic Heart Failure; ICU: Intensive Care Unit; LOS: length of stay

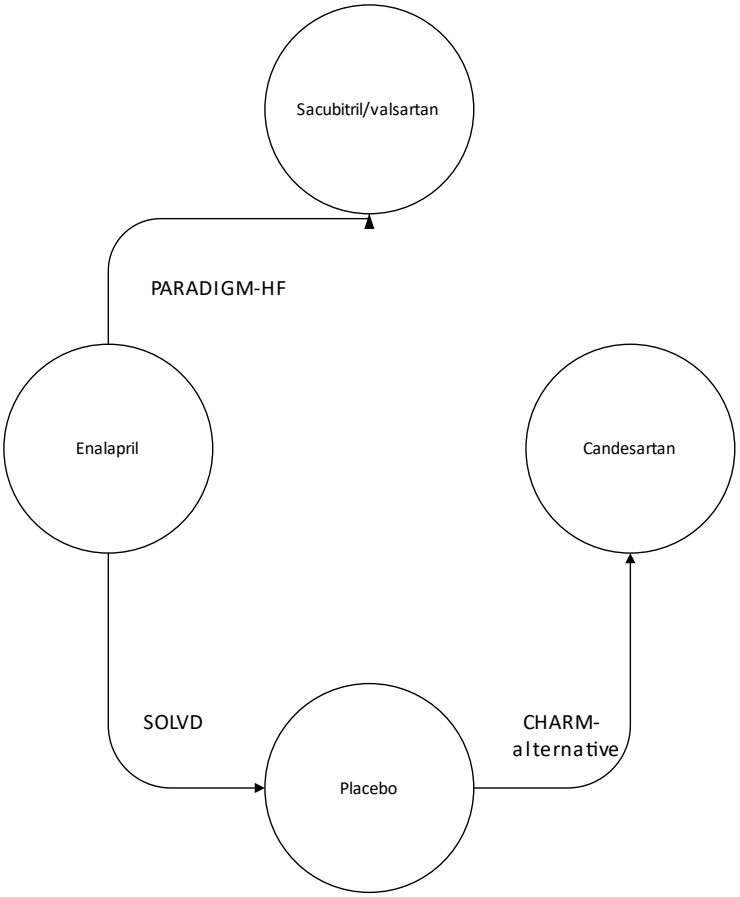
Supplementary table 5 - scenario analyses

Scenario	ICER (sacubitril/valsartan vs. enalapril, /QALY)	ICER (enalapril vs. placebo, /QALY)	ICER (candesartan vs. placebo, /QALY)
Base case	€19,300	Dominating	Dominating
0% discounting rate	€17,000	Dominating	Dominating
5% discounting rate	€20,900	Dominating	Dominating
€3 per day for sacubitril/valsartan	€7,600	Dominating	Dominating
€10 per day for sacubitril/valsartan	€30,000	Dominating	Dominating
€1 per day for enalapril and candesartan	€17,400	€900	€1,200
No extrapolation of effects beyond 42 months	€17,000	Dominating	Dominating
Starting age: 55 years	€19,600	Dominating	Dominating
Starting age: 75 years	€18,800	Dominating	Dominating

ICER values rounded to the nearest hundreds of euros

ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year

Supplementary figure 1 - flowchart of included trials

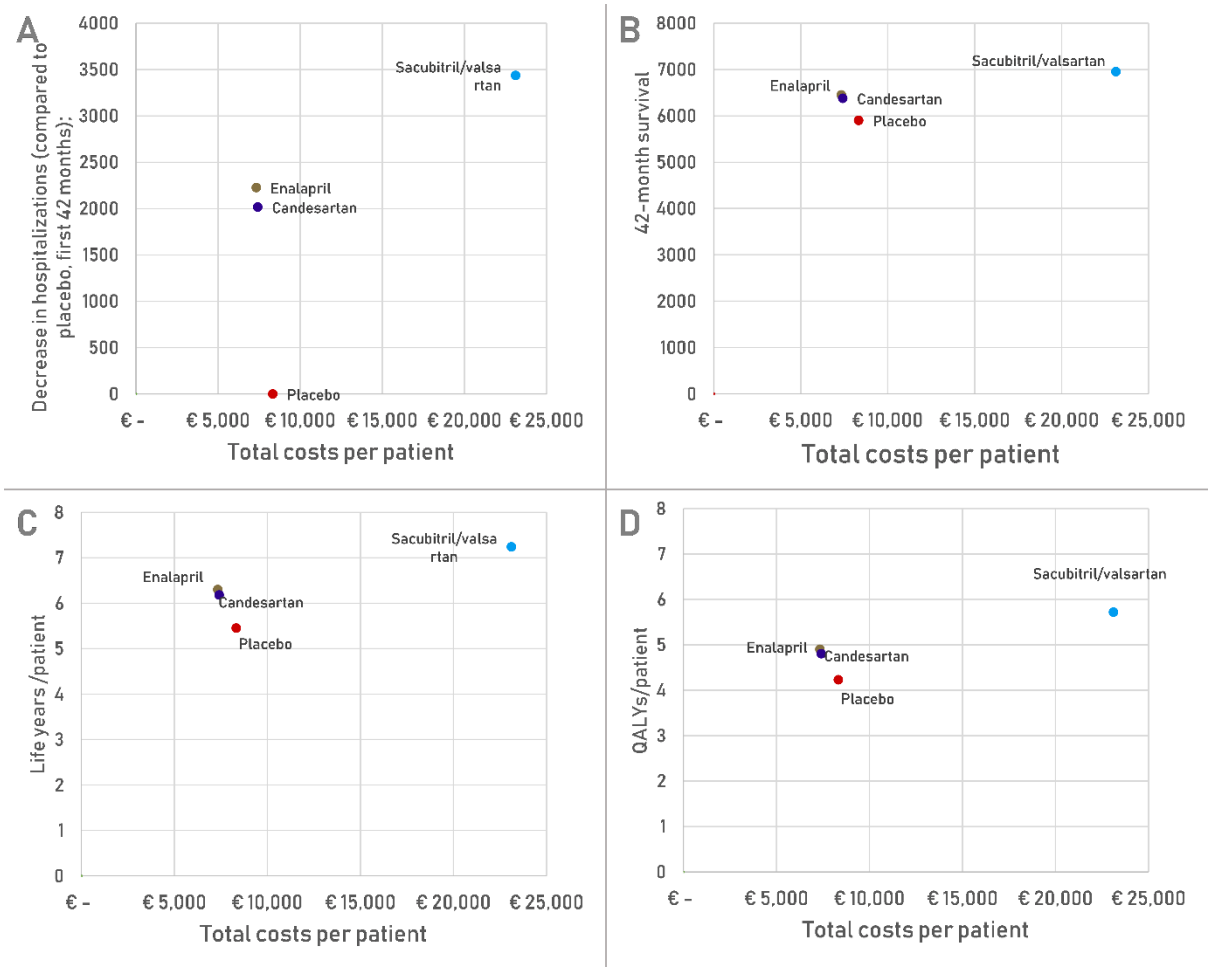


SOLVD: Studies Of Left Ventricular Dysfunction[8]

CHARM-alternative: Candesartan in Heart failure: Assessment ofReduction in Mortality and morbidity-Alternative[9]

PARADIGM-HF: Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial[1]

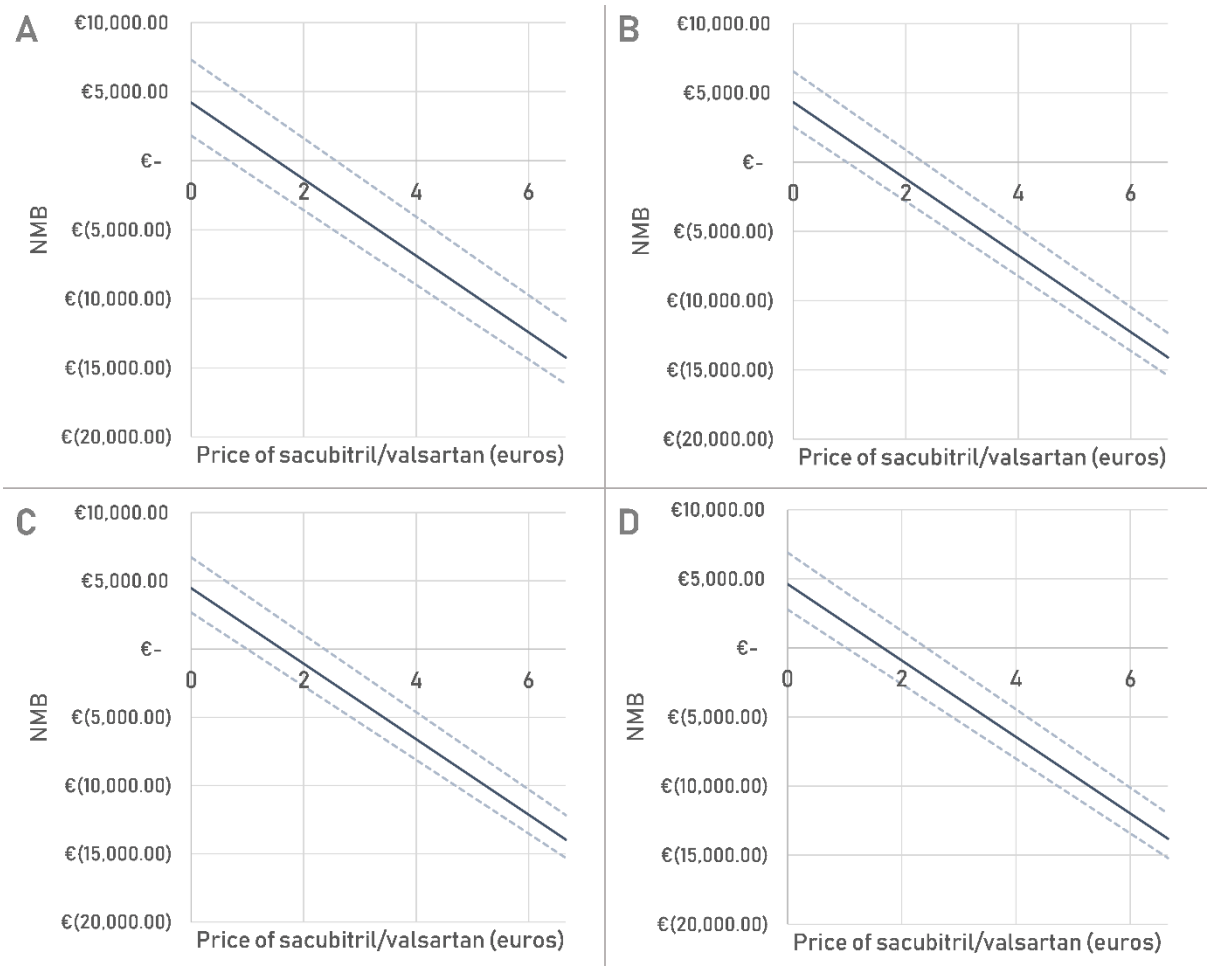
Supplementary figure 2 - base-case inverted cost-effectiveness planes for various outcomes



A: Decrease in hospitalizations (compared to placebo, first 42 months); B: 42-month survival; C: Average total life years; D: Average total QALYs

QALY: Quality-adjusted life year

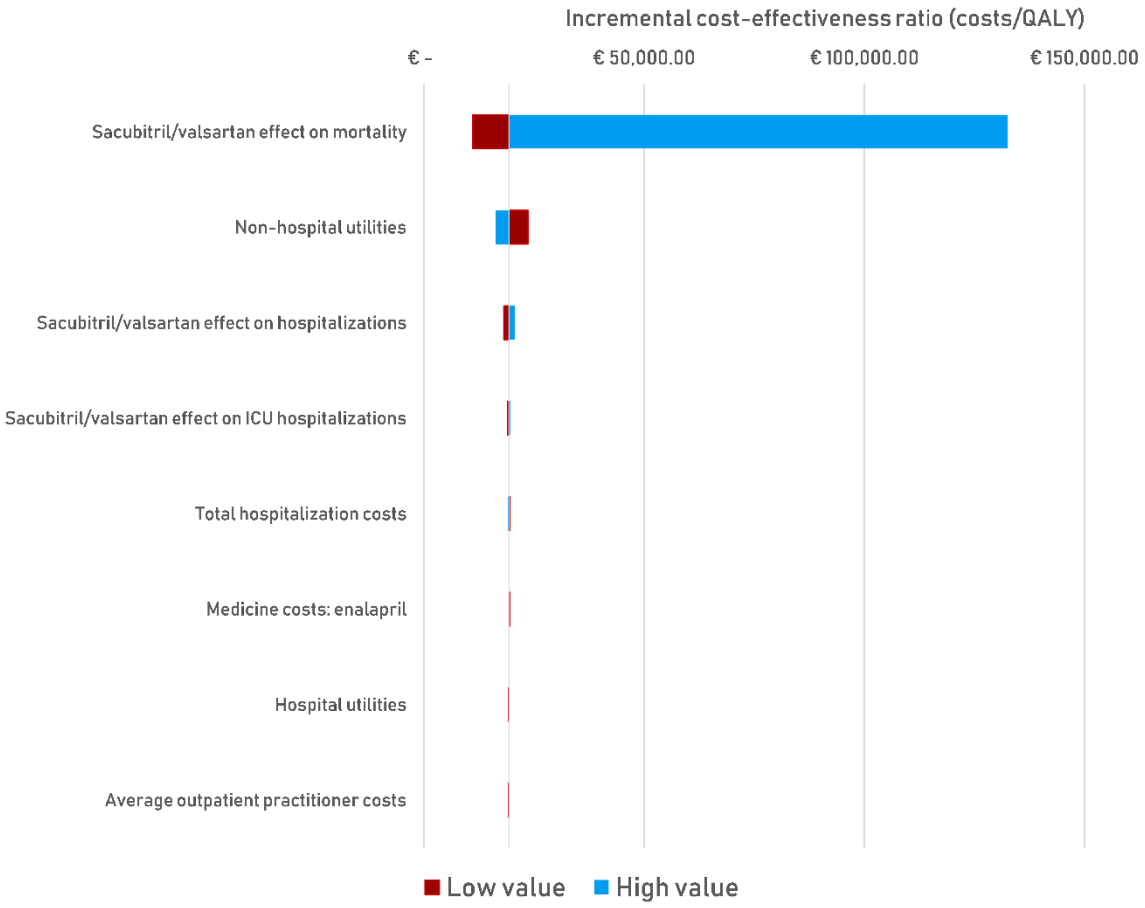
Supplementary figure 3 - NMB for a range of daily prices of sacubitril/valsartan the various outcomes, including the interquartile range (dotted line)



A: Decrease in hospitalizations (compared to placebo, first 42 months); B: 42-month survival; C: Average total life years; D: Average total QALYs

NMB: Net Monetary Benefit

Supplementary figure 4 - tornado diagram of the univariate sensitivity analysis of the ICER of sacubitril/valsartan compared to enalapril



QALY: Quality-Adjusted Life Year

ICU: Intensive Care Unit

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