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Cost Effectiveness of the Angiotensin Receptor Neprilysin Inhibitor Sacubitril/Valsartan for Patients with Chronic Heart Failure and Reduced Ejection Fraction in the Netherlands: A Country Adaptation Analysis Under the Former and Current Dutch Pharmacoeconomic Guidelines

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ABSTRACT

Objectives: To describe the adaptation of a global health economic model to determine whether treatment with the angiotensin receptor neprilysin inhibitor LCZ696 is cost effective compared with the angiotensin-converting enzyme inhibitor enalapril in adult patients with chronic heart failure with reduced left ventricular ejection fraction in the Netherlands; and to explore the effect of performing the cost-effectiveness analyses according to the new pharmacoeconomic Dutch guidelines (updated during the submission process of LCZ696), which require a value-of-information analysis and the inclusion of indirect medical costs of life-years gained. **Methods:** We adapted a UK model to reflect the societal perspective in the Netherlands by including travel expenses, productivity loss, informal care costs, and indirect medical costs during the life-years gained and performed a preliminary value-of-information analysis. **Results:** The incremental cost-effectiveness ratio obtained was €17,600 per quality-adjusted life-year (QALY) gained. This was robust to changes in most structural assumptions and across different subgroups of patients. Probability sensitivity analysis results showed that the probability that LCZ696 is cost-effective at a €50,000 per QALY threshold is 99.8%, with a population expected value of perfect information of €297,128. On including indirect medical costs of life-years gained, the incremental cost-effectiveness ratio was €26,491 per QALY gained, and LCZ696 was 99.46% cost effective at €50,000 per QALY, with a population expected value of perfect information of €2,849,647. **Conclusions:** LCZ696 is cost effective compared with enalapril under the former and current Dutch guidelines. However, the (monetary) consequences of making a wrong decision were considerably different in both scenarios.

Keywords: heart failure, ACE inhibitor, cost-effectiveness analysis, productivity costs.

Introduction

Chronic heart failure (HF) is a clinical condition involving the circulatory ability of the heart to meet the body's demands. HF is characterized by symptoms such as fatigue, breathlessness, edema, and arrhythmias [1]. Patients with HF have poor survival rates [2] (around 50% of patients with HF are expected to die within 5 years of diagnosis) and a substantial loss of quality of life [3]. Approximately 50% of the total HF population suffers from HF with reduced ejection fraction, characterized by impaired contractility, or HF with preserved ejection fraction, characterized by impaired relaxation of the heart.

It is estimated that HF affects approximately 23 million individuals worldwide and that one-fifth of people aged 40 years will develop HF during their lifetime [4]. In the Netherlands, approximately 140,000 individuals had HF in 2011 [5]. HF is not very prevalent in Dutch younger men and women: in the age category between 15 and 64 years, 1.9 men per 1000 and 1.6 women per 1000, respectively. However, in men and women older than 65 years, the prevalence is 44.7 and 49.1 per 1000 individuals, respectively, whereas the prevalence is very high in individuals older than 85 years: 153.9 (men) and 149.3 (women) per 1000 individuals. In 2012, 2.625 men and 4.136 women died of a primary diagnosis of HF in the Netherlands [5].

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Most patients with chronic symptomatic HF with reduced ejection fraction are treated according to current guidelines with angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers. Furthermore, patients also receive mineralocorticoid receptor antagonists where appropriate. When ACEI are not tolerated, patients may receive angiotensin receptor blockers (ARB) [1,6]. However, if patients remain symptomatic despite this combination of medications, ACEI should be replaced by the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (LCZ696), which is stated as a class I recommendation ("evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective") in the recent European Society of Cardiology guidelines [1]. In addition, patients could receive ivabradine or cardiac resynchronization therapy if symptoms persist despite treatment with beta-blockers, ACEI (or ARB), and a mineralocorticoid receptor antagonist [1].

Upon ingestion, LCZ696 dissociates into two components in the body: sacubitril and the ARB valsartan [7]. Valsartan blocks the angiotensin II type 1 receptor and ameliorates the adverse effects of a chronically activated renin-angiotensin-aldosterone system, while simultaneously sacubitrilate (the active metabolite of sacubitril) decreases neprilysin, which is also referred to as neutral endopeptidase. Neutral endopeptidase breaks down, for example, natriuretic peptides, which are the endogenous counterparts of vasoconstrictive hormones such as angiotensin II. The reduction of this breakdown with sacubitril results in accumulation of natriuretic peptides, which is of benefit.

The efficacy of the ARNI LCZ696, compared with the ACEI enalapril, was studied in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial [8], a phase III prospective double-blind randomized controlled trial, in which differences in morbidity and mortality between LCZ696 and enalapril in a population with chronic HF and reduced ejection fraction were compared. The results of the trial were recently published, and showed that LCZ696 was superior to enalapril in reducing cardiovascular mortality and HF morbidity [9]. The main findings from the PARADIGM-HF trial are summarized in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.013. A global health economic model was developed alongside the PARADIGM-HF trial to assess the cost effectiveness of LCZ696 compared with enalapril in patients with chronic HF [10].

The Dutch guidelines for cost-effectiveness research have several distinguishing features compared with other jurisdictions, most notably the adoption of a societal perspective, the requirement to calculate productivity losses using the friction cost-method, differential discounting, and the inclusion of caregiver burden on the cost side of the economic evaluation [11]. The Dutch guidelines were updated during the submission process of LCZ696 [12]. These new guidelines also require a value-of-information (VOI) analysis [13–15], when there is any decision uncertainty, and the inclusion of indirect medical costs of life-years gained, a cost category that is explicitly of importance in life-extending interventions.

The objective of this article was twofold. We first describe the adaptation of the global health economic model to the Dutch setting to determine whether treatment with the ARNI LCZ696 is cost effective compared with the ACEI enalapril in the Netherlands. After that, we explore the effect on the incremental cost-effectiveness ratio (ICER) and the associated reimbursement decision should the cost-effectiveness analysis be performed according to the new Dutch guidelines [12]. In May 2016, the Dutch National Health Care Institute (Zorginstituut Nederland) provided the Ministry of Health with a positive advice for the ARNI LCZ696 [16], concluding that LCZ696 is a cost-effective therapy, with a valid and proven cost-effectiveness analysis. The advice made was largely based on the cost-effectiveness analysis presented in this article. LCZ696 is fully reimbursed per June 1, 2016, in the Netherlands, as decided by the Ministry of Health [17].

Methods

We explored the cost effectiveness of the ARNI LCZ696 compared with the ACEI enalapril in adult patients with chronic HF with reduced left ventricular ejection fraction in the Netherlands.

Study Population

The population included in the model was that considered by the PARADIGM-HF trial. On average, patients were aged 63.8 years, 21% were women, and most patients were in New York Heart Association (NYHA) class II. Consulted experts considered some baseline characteristics of the subgroup of Western-European patients more representative for the Dutch patient population. Therefore, the base-case analysis was conducted using the baseline characteristics from the Western-European patients in the PARADIGM-HF trial. Following the advice of the Dutch National Health Care Institute experts, the mean age observed of these patients in the trial (66.7 years) was replaced by 75 years, because 66.7 years was considered too low for the Dutch population [18]. Complete baseline characteristics are presented in Table 1.

Intervention and Comparator

The intervention considered is the ARNI sacubitril/valsartan (LCZ696). The daily target dose in the PARADIGM-HF trial (200 mg twice a day, which corresponds with sacubitril/valsartan 97 mg/103 mg twice a day) was used in the base case. The ACEI enalapril was chosen as the comparator in the base-case analysis because this was also the comparator in the PARADIGM-HF trial and because it is the best studied ACEI in HF [19–22]. The daily target dose of 10 mg twice a day (20 mg daily) for enalapril in the PARADIGM-HF trial was selected for the base case.

Outcomes

The main outcome of our analysis was incremental costs per quality-adjusted life-year (QALY) gained, expressed as the ICER. Secondary outcomes included the number of hospitalizations and adverse events. Discontinuation from treatment was also included in the analysis.

Country Adaptation

We performed a country adaptation of the global pharmacoeconomic model that was developed to assess the cost effectiveness of the ARNI LCZ696 compared with the ACEI enalapril in the United Kingdom and the United States [10,23]. Performing a country adaptation of a cost-effectiveness model implies that it is important to use national guidelines and clinical expert opinion to determine whether clinical practice and patient population are transferable. Seven cardiologists were asked to participate voluntarily in this study. Six of them were willing to participate; one was not available. We developed a questionnaire seeking information on current treatment practice in the Netherlands. This included questions regarding the transferability of the population of the PARADIGM-HF trial, medication usage, procedures performed during a hospitalization, resource use on adverse events, proportion of patients working and absence from paid work per NYHA class, and treatment discontinuation. The questionnaire was sent by email to the experts and then we had one individual phone interview with each expert where all the questions were then answered. In case of no consensus, we followed the most frequently provided answer (the mode in statistical terminology). Experts were asked if they agreed with

Table 1 – Baseline characteristics: PARADIGM-HF trial.

Baseline demographic characteristics	Western Europe (N = 2051)	All patients (N = 8399)
Mean age (y)	66.71	63.80
Sex: female (%)	19	22
Region (%)		
North America	0	7
Latin America	0	17
Western Europe	100	24
Central Europe	0	34
Other	0	18
Race (%)		
White	88	66
Black	7	5
Asian	2	18
Other	3	11
Baseline measurements		
% NYHA I	5	5
% NYHA II	76	71
% NYHA III	19	24
% NYHA IV	0	1
Mean LVEF (%)	29	29
Mean SBP (mm Hg)	121.4	121.4
Mean heart rate (bpm)	70.0	72.4
Mean eGFR (ml/min/1.73 m^2)	64.6	67.7
Mean NT-proBNP (pg/ml)	2559	2891
Mean sodium (mmol/l)	141.7	141.5
Mean potassium (mmol/l)	4.5	4.5
Mean QRS duration (ms)	125.6	117.4
Mean BMI (kg/m^2)	28.9	28.2
Comorbidities at baseline		
% Diabetes	36	34
% Hypertension	64	71
Previous HF medication		
% Prior ACEI use	82	78
% Prior ARB use	18	23
Background therapy at baseline		
% Beta-blocker use	93	93
% MRA use	47	56
% Digoxin use	19	30
% Lipid-lowering medication use	65	56
% Allopurinol use	9	5
Medical history		
Time since HF diagnosis		
% ≤1 y	25	30
% 1–5 y	35	38
% >5 y	40	31
% Ischemic etiology	58	60
% Prior stroke	9	9
% Prior atrial fibrillation/ flutter	40	37
% Prior angina	0	0
% Prior cancer	6	4
% Current smoker	16	14
% Previously hospitalized for heart failure	59	63

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; bpm, beats per minute; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; SBP, systolic blood pressure.

the final assumptions, which, in any case, were analyzed in different scenarios to test the robustness of the model results. The complete questionnaire can be found in Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.013. The structure of the global model was deemed appropriate for use in the Netherlands by clinical and health economic experts, provided that a societal perspective on costs was incorporated. This implied that direct (traveling expenses) and indirect (productivity costs and informal care costs) non-medical costs were included in the model. Main modeling assumptions and all input parameters used in the model are described in Appendixes 3 and 4, respectively, in Supplemental

Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.013. Below we describe the main differences encountered in the Dutch model.

Dutch cost-effectiveness threshold

The cost-effectiveness threshold in the Netherlands depends on the burden of disease as expressed by the proportion of normal quality-adjusted life expectancy lost because of the condition (proportional shortfall) related to the disease as currently treated in daily practice [24]. The appropriate cost-effectiveness threshold in the Netherlands can be calculated using input from the economic model and the Institute for Medical Technology Assessment Disease Burden Calculator [25]. The Institute for Medical Technology Assessment Disease Burden Calculator calculates normal QALY expectancy, corrected for age and sex using Dutch mortality [26] and three-level EuroQol five-dimensional questionnaire utility data from the general population [27]. The proportional shortfall is obtained by dividing the QALYs while treated with the comparator (i.e., standard of care before the new treatment) in the economic model by the normal QALY expectancy.

Costs related to productivity losses

The mean age of the patient population considered in the base-case analysis was 75 years. For these patients, we assumed that they do not incur productivity costs (they are older than 65 years and therefore, retired). However, we included productivity costs in the model because the average age in the PARADIGM-HF trial was 63.8 years, and the trial population (and so this age) was used in the sensitivity analyses.

The implementation of productivity costs implied major changes in the structure of the global model. We included the productivity losses due to hospitalizations for patients who were considered working at baseline. Expert opinion was sought to estimate the proportion of patients who would be working per NYHA class, because data on employment status were lacking (cf. Appendix 4, Tables 19 and 20). We assumed that patients who were not working at baseline were also not working in the 23 weeks before (friction period). Therefore, long-term productivity costs were not included in the model. The probability that a patient was working was based on the baseline NYHA class and age. In addition, this probability was adjusted with an age-sex–specific net-participation rate [28] because not all patients who are able to work are actually working. Furthermore, we assumed that all the patients who work are working partially (50%), independent of their NYHA class. The median length of stay during a hospitalization for a patient with HF is 10.5 days [29]. When a patient with a paid job was hospitalized, it was assumed that this patient incurs productivity costs for 1 month, including the length of stay, because it is likely that after a hospitalization the patient is not able to work immediately. The number of friction hours per day is estimated by dividing the average number of hours working per week in the Dutch population by the days working in a week (5). Because it is unknown on which day of the week patients are admitted to the hospital, a correction for unproductive hours, such as holidays or sick leave, should not be applied. Therefore, 7 days per week (instead of 5) were assumed when calculating the number of productive hours per day. An age-sex–specific cost per hour [30] was multiplied with the total friction hours per day to obtain a total cost per day (see Appendix 4, Tables 19 and 20). As an example, the productivity costs of a 50-year-old man with NYHA class II are presented in Appendix 5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.013.

Informal care costs

We assumed that all patients received informal care. The costs of informal care were reported in the Dutch ivabradine reimbursement dossier from 2013 as €66 per month [31]. This value was sourced from a National Institute for Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu [RIVM]) report on informal care from 2001 [32] and represents an average of all informal caregivers, and it is independent of the severity of the disease. Thus, it is very likely that the costs are in reality higher, because patients with severe HF (NYHA IV) are bedbound. We assumed therefore that the value chosen might underestimate the actual informal care costs. To test the impact of this assumption on the ICER, we performed scenario analyses in which the informal care costs were doubled and halved.

Traveling expenses

Traveling expenses were based on Hakkaart-van Roijen et al. [30] and added to the costs of outpatient visits, emergency room visits, and hospitalizations. The mean distance that patients in the Netherlands travel to a hospital is 7 km (one-way). Costs are €0.22/km, irrespective of the mode of transport. Parking costs are €3.30 per hospital visit. We assumed that 50% of the patients travel by car and 50% travel by public transport, because it is unknown how patients visit the hospital. On average, traveling expenses amount to €4.73 per visit.

Medication costs

Daily costs of all medications, including LCZ696, were based on the Z-index [33] and further calculated applying the following formula from the 2010 Dutch costing manual [30] that was valid at the time the analyses were done: *Medication costs = pharmacists purchase price* (Z-index) − *clawback* (8.3%) + *VAT* (6%) + *pharmacy dispensing fee*. The daily cost of LCZ696 (based on the recommended dose) was €4.95 for 200 mg twice a day (which corresponds with sacubitril/valsartan 97 mg/103 mg twice a day). Applying the formula above, the daily cost of LCZ696 used in the model was €4.83. The daily cost of enalapril (based on the target dose as defined in the PARADIGM-HF trial protocol) was €0.14 for 10 mg twice a day.

Patients included in the PARADIGM-HF trial were supposed to be on an optimal medical regimen of background HF medications, whose costs were also included in the model. The type, proportion, and dosage of background medication were adapted to the Dutch current practice. All medication costs included in the model are summarized in Appendix 4, Table 13.

HF management costs

HF management costs were based on the Effective Cardio report [34] because no data were collected during the PARADIGM-HF trial and current clinical guidelines do not recommend a specific management or follow-up protocol [35]. The Effective Cardio report showed that in 2011 on average Dutch patients with HF visit an outpatient hospital clinic 3.9 times, and have 2.8 telephone consultations. It was assumed that all these appointments were with the cardiologist, resulting in a monthly cost of €36.49.

Hospitalization costs

For every specific type of hospitalization (surgery, interventional procedure, and medical management), the National Health Service reference costs were replaced with Dutch unit costs from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit [NZa]) and OPENDIS databases [36]. The average costs per hospitalization were estimated at €3960 (Appendix 4, Table 16).

Adverse event costs

All the adverse events reported in the PARADIGM-HF trial were considered in our analysis. Assumptions for resource use to treat adverse events were based on Dutch clinical expert opinion. Because the answers of the experts varied, the most likely option

that summarizes the answers of all experts was chosen. Resource use and costs per adverse event are summarized in Appendix 4, Table 17.

Health state utility

The health-related quality of life (HRQOL) data were derived from the PARADIGM-HF trial. For the Netherlands, the Dutch EQ-5D tariff published by Lamers et al. [37] was applied to EQ-5D responses, irrespective of the subject's country of origin, to generate EQ-5D utility values for each subject in the trial. A detailed description of how HRQOL was incorporated in the model can be found in the pharmacoeconomic dossier submitted to the Dutch National Health Care Institute [16, pp. 25–27].

Mortality rates

Cardiovascular (CV) mortality from the PARADIGM-HF trial was combined with non-CV mortality using Dutch all-cause life tables [38]. Overall, LCZ696 was associated with a hazard ratio of 0.806 for CV mortality. The relative effect of LCZ696 on mortality was the same across all patient subgroups (e.g., NYHA I/II vs. NYHA III/IV), which was based on the observations of the primary statistical analysis presented by McMurray et al. [9], reporting a consistent effect of LCZ696 across all prespecified subgroups.

Hospitalization and adverse event rates

Hospitalization and adverse event rates were modeled using PARADIGM-HF data. Therefore, these parameters did not change for the Dutch cost-effectiveness analysis (cf. Appendix 4, Tables 5 and 6).

Requirements according to the new Dutch pharmacoeconomic guidelines

Indirect costs in life-years gained. Costs in life-years gained were calculated by combining the modeled reduction in mortality due to LCZ696 with estimates of per capita health care expenditures by age and sex, excluding those related to HF, which are already incorporated in the model, derived from PAID version 1.1 [39,40].

VOI analysis. The new Dutch guidelines require the calculation of the expected value of perfect information (EVPI) when the probability that the intervention is cost effective at the appropriate cost-effectiveness threshold is lower than 100%. The EVPI is usually interpreted as the maximum amount the decision maker is willing to pay to eliminate all uncertainty in the decision to adopt a new intervention [13–15]. Because the decision is based on current information, the intervention with the maximum expected net monetary benefit is chosen as optimal. The EVPI per patient can be directly calculated from a probabilistic sensitivity analysis (PSA) as the average of the maximum net benefits across all PSA iterations minus the maximum average net benefit for the two interventions considered here. The population EVPI is then calculated by multiplying the per-patient EVPI by the size of the potential population that could benefit from the new intervention summed over the expected lifetime for which the recommendation that results from the VOI analysis is considered applicable, and discounted at 4% per year. A period of 5 years was assumed for the expected lifetime of this recommendation. The estimated number of patients eligible for LCZ696 in the Netherlands in the years 2016-2020 was 37,288, 38,174, 39,089, 40,009, and 40,954, respectively [41–45]. When the population EVPI exceeds the expected costs of additional research, further research might be justified to reduce decision uncertainty. When this happens, the input parameters for which extra data collection is potentially worthwhile can be identified by calculating the expected value of partial perfect information (EVPPI) [46–48].

Description of Base-Case, Sensitivity, and Scenario Analyses

Base-case analysis

The base-case analysis was conducted using the settings for the input parameters described in previous sections. A lifetime time horizon was adopted for the base-case analysis with a cycle length of 1 month. A half-cycle correction was used [49]. Where necessary, costs were adjusted to 2015 using the general price index from the Dutch Central Bureau of Statistics [50]. The economic model uses a discount rate of 4% for costs and a discount rate of 1.5% for effects as recommended by the Dutch pharmacoeconomic guidelines [11].

Subgroup, scenario, and sensitivity analyses

A number of patient subgroups were considered to be of potential economic relevance (age groups, NYHA classes, etc.) and, therefore, were included in the model. These are presented in Appendix 6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.013.

Extensive scenario analyses were performed in which key structural assumptions regarding time horizon, mortality, utilities, treatment effects, discontinuation, costs, and the comparator chosen were varied to estimate the impact of those assumptions on the ICER. A younger patient population (that in the PARADIGM-HF trial) was chosen to demonstrate the impact of incorporating productivity costs. A summary of the performed scenario analyses can be found in Appendix 6.

Parameter uncertainty was first studied using deterministic sensitivity analyses and presented as a tornado diagram [51,52]. Joint parameter uncertainty was explored through PSA [53,54]. The probability distributions used in the PSA are shown in Appendix 4, Table 18. The results of 10,000 Monte-Carlo simulations were plotted on the cost-effectiveness plane [55–57] and a cost-effectiveness acceptability curve was estimated [58].

Results

Appropriate Cost-Effectiveness Threshold

The normal quality-adjusted life expectancy of the population in the model (75 years old, 19% females) is 9.52 QALYs. Expected QALYs with the current standard of care (ACEI enalapril) are 4.31. Hence, 55% of normal QALY expectancy is lost because of the disease [(9.52-4.31)/9.52]. The associated cost-effectiveness threshold at a proportional shortfall between 41% and 70% is €50,000 per QALY.

Base-Case Analysis

Base-case results showed that patients treated with LCZ696 have higher survival probability than do patients treated with enalapril. Median predicted survival was 5.33 and 4.92 years for LCZ696 and enalapril, respectively. Moreover, LCZ696 led to an increase in the mean number of life-years per patient compared with enalapril: 5.67 years versus 5.28 years, respectively. The mean QALY gain was 0.33. Total costs for LCZ696 amounted to €21,840 and to €16,001 for enalapril. The difference was primarily due to the treatment costs of LCZ696. The fact that LCZ696 increased survival led to higher costs of background therapy, adverse events, and HF management. Because LCZ696 patients were less frequently admitted to the hospital (than enalapril patients), they had lower hospitalization and productivity costs. The average annual therapy costs increased but the average annual

Table 2 – Cost-effectiveness results: LCZ696 vs. enalapril.

Results	LCZ696	Enalapril	Incremental
Outcomes			
Heart failure hospitalizations	0.85	0.88	−0.03
Other cardiovascular hospitalizations	1.25	1.29	−0.04
Noncardiovascular hospitalizations	1.26	1.31	−0.04
All-cause hospitalization	3.36	3.48	−0.12
Number of hospitalizations per year	0.59	0.66	−0.07
Life-years	5.67	5.28	0.39
QALYs	4.39	4.06	0.33
Lifetime costs (€)			
Primary therapy	6,413	310	6,104
Background therapy	1,747	1,634	113
Hospitalization	11,229	11,758	− 529
Heart failure management	2,243	2,099	145
Adverse events	155	146	8
Societal (informal care)*	53	54	− 1
Total costs (€)	21,840	16,001	5,839
Annual costs (€)			
Average therapy costs†	1,440	368	1,072
Average nontherapy costs‡	2,405	2,654	− 249
Cost effectiveness			
Total costs	€21,840	€16,001	€5,839
Total QALYs	4.39	4.06	0.33
Incremental cost/incremental QALYs (ICER)	–	–	€17,600

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.
* Societal costs include only informal care costs because the mean age of the patient population in the base case is 75 years. Therefore, costs associated with productivity losses are assumed to be €0.
† (primary therapy + background therapy)/life-years.
‡ (hospitalization + heart failure management + adverse events)/life-years.

nontherapy costs decreased because of LCZ696. Dividing the incremental costs (€5839) by the incremental QALYs (0.33) leads to an ICER of €17,600. Base-case cost-effectiveness results are summarized in Table 2.

Subgroup, Scenario, and Sensitivity Analyses

The results of the subgroup analyses are presented in Appendix 6, Table 1. ICERs exhibited low variation, reflecting the finding of the PARADIGM trial that the treatment effect was similar across subgroups. The greatest difference with the base-case analysis was caused by age. Older age was associated with increased ICERs, because the time in which QALYs may be accrued is reduced as age increases.

Scenario analyses were performed to test the robustness of the structural assumptions. The results for all scenarios are shown in Appendix 6, Table 2. We observed that only those scenario analyses that assumed the LCZ696 treatment effect would be maintained for a short period of time (from 2 up to 5 years), and scenario analyses in which the time horizon was reduced found ICERs exceeding €30,000 per QALY.

The tornado diagram in Figure 1 presents the results of the 10 input parameters that have the largest effect on the ICER when a univariate sensitivity analysis was performed. The most important parameters are those regarding mortality and hospitalization. The highest ICER obtained was €33,393.

The scatter plot of the PSA outcomes in the cost-effectiveness plane shows that all the outcomes produced in the analysis are located in the northeast quadrant of the cost-effectiveness plane (Fig. 2, top). A positive correlation between costs and QALYs can be observed, showing that LCZ696 is more expensive but also provides more QALYs than enalapril. The probabilistic ICER is estimated as €17,648 per QALY gained (95% confidence interval €12,981–€29,934), thus similar to the base-case ICER (€17,600). The cost-effectiveness acceptability curve for LCZ696 is shown in Figure 2, bottom, and it confirms that LCZ696 is likely to be considered cost effective because at a €50,000 threshold the probability that LCZ696 is cost effective is 99.80%.

Application of the New Dutch Guidelines

Indirect costs in life-years gained

The increased longevity due to LCZ696 causes an additional discounted medical consumption, unrelated to HF, of €2950. Expressed in incremental costs per QALY, this increases the ICER with €8891 (€2950/0.33). Given a base-case ICER of €17,600, an ICER including indirect medical costs in life-years gained would sum to €26,491.

VOI analysis

In the base-case scenario, decision uncertainty was small because LCZ696 was 99.80% cost effective at €50,000 per QALY. On including indirect costs in life-years gained, LCZ696 was 99.46% cost effective at €50,000 per QALY. Thus, there was only a 0.34% increase in decision uncertainty. However, the (monetary) consequences of making a wrong decision at a population level were considerably different in both scenarios. In the base-case scenario, the population EVPI at a cost-effectiveness threshold of €50,000 per QALY was €297,128 (€1.71 per patient). Under the new guidelines, this would result in a population EVPI almost 10 times higher: €2,849,647 (€16.40 per patient).

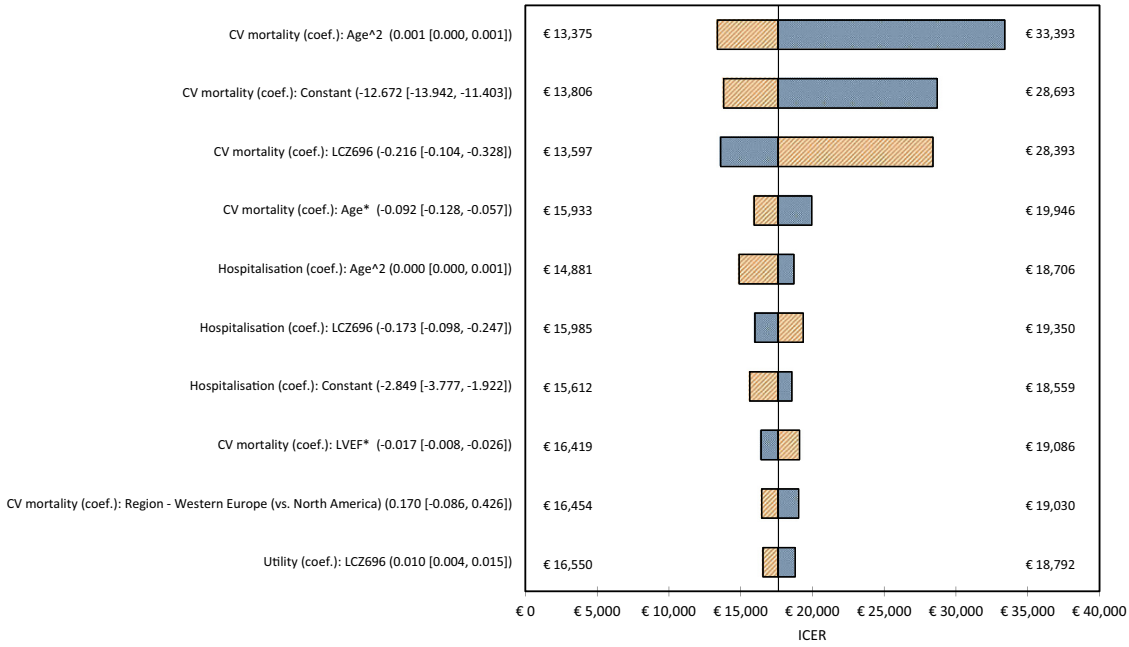

Fig. 1 – Tornado diagram. Coef., coefficient; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LVEF, left ventricular ejection fraction.

Conclusions

The country adaptation presented in this article relies on several distinguishing features of the Dutch pharmacoeconomic guidelines. These include the adoption of a societal perspective, the calculation of productivity losses using the friction cost-method, differential discounting, the inclusion of caregiver burden on the cost side of the economic evaluation, the incorporation of indirect medical costs of life-years gained, and a VOI analysis. Clinical and health economic experts deemed the structure of the global model appropriate for use in the Netherlands. In the absence of specific Dutch data, other adjustments were needed in the cost-effectiveness model to inform the input parameters for which Dutch data were not available. Thus, for our base-case analysis, we used the baseline characteristics from the Western-European patients in the PARADIGM-HF trial, but replacing the mean age observed of these patients (66.7 years) by 75 years. CV mortality (combined with non-CV mortality using Dutch all-cause life tables), hospitalization, and adverse event rates were modeled using PARADIGM-HF data. These adjustments were validated by the consulted experts, who concluded that these were the most representative for the Dutch population. Based on the base-case analysis results, it is concluded that the ARNI sacubitril/valsartan (LCZ696) is cost effective compared with the ACEI enalapril for the treatment of patients with chronic HF and reduced ejection fraction in the Netherlands. The ICER obtained was €17,600 per QALY gained. This result was driven primarily by reductions in mortality, but also by improvements in HRQOL and reductions in hospitalization. These findings were robust to changes in most structural assumptions and across different subgroups of patients. PSA results showed that the probability that LCZ696 is cost effective at a €50,000 per QALY threshold is 99.8%. Thus, despite all the adjustments made, the base-case ICER seemed consistent with previous findings [10,23]. To explore this further, we compared our base-case results with those obtained should the UK settings be applied (e.g., equal discounting and no productivity costs). These are summarized in Appendix 7 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.013. We observed that the ICER under the UK settings is consistently higher (between ~€2000 and €4000) than the ICER under the Dutch settings (without costs in life-years gained). Nevertheless, under a provision like in the United Kingdom, LCZ696 would still be considered cost effective.

Including indirect costs in life-years gained increased the ICER to €26,491. This was expected because LCZ696 is a life-extending treatment. Given a proportional shortfall of 55%, the cost-effectiveness threshold of €50,000 per QALY applies. Thus, under the new guidelines, LCZ696 would still be considered cost effective. However, the population EVPI did show that the inclusion of indirect costs in life-years gained increased the opportunity loss associated with making a wrong decision by approximately a factor of 10 (in life-extending interventions, an increase in population EVPI is expected). In particular, our results show that in the base-case scenario the population EVPI at a cost-effectiveness threshold of €50,000 per QALY was €297,128 and €2,849,647 under the new guidelines. To properly interpret these values, they should be compared with the expected costs of conducting additional research, which consequently should also be estimated. On the basis of 74 project proposals consisting of seven different types of research, all of which were granted by the Netherlands Organisation for Health Research and Development (ZonMw), van Asselt et al. [59] concluded that the median total budget assigned per granted project was €431,000. Taking this estimate as a valid reference for the Dutch setting, the population EVPI in our base-case scenario is lower than the expected costs of additional research. Therefore, the decision uncertainty associated with the base-case scenario should be deemed appropriate for decision making. However, in the scenario under the new guidelines, this does not occur. Whether this population EVPI is large enough to recommend additional research to reduce decision uncertainty is likely to be determined with a more detailed VOI analysis, which identifies the input parameters with the highest EVPPI. This EVPPI estimate should then be compared with the expected costs of additional research on these specific input parameters (the €431,000 above is a total in which all types of research were included). Note finally that the fact that the addition of the costs during life-years gained caused the increase in EVPI does not imply that these costs

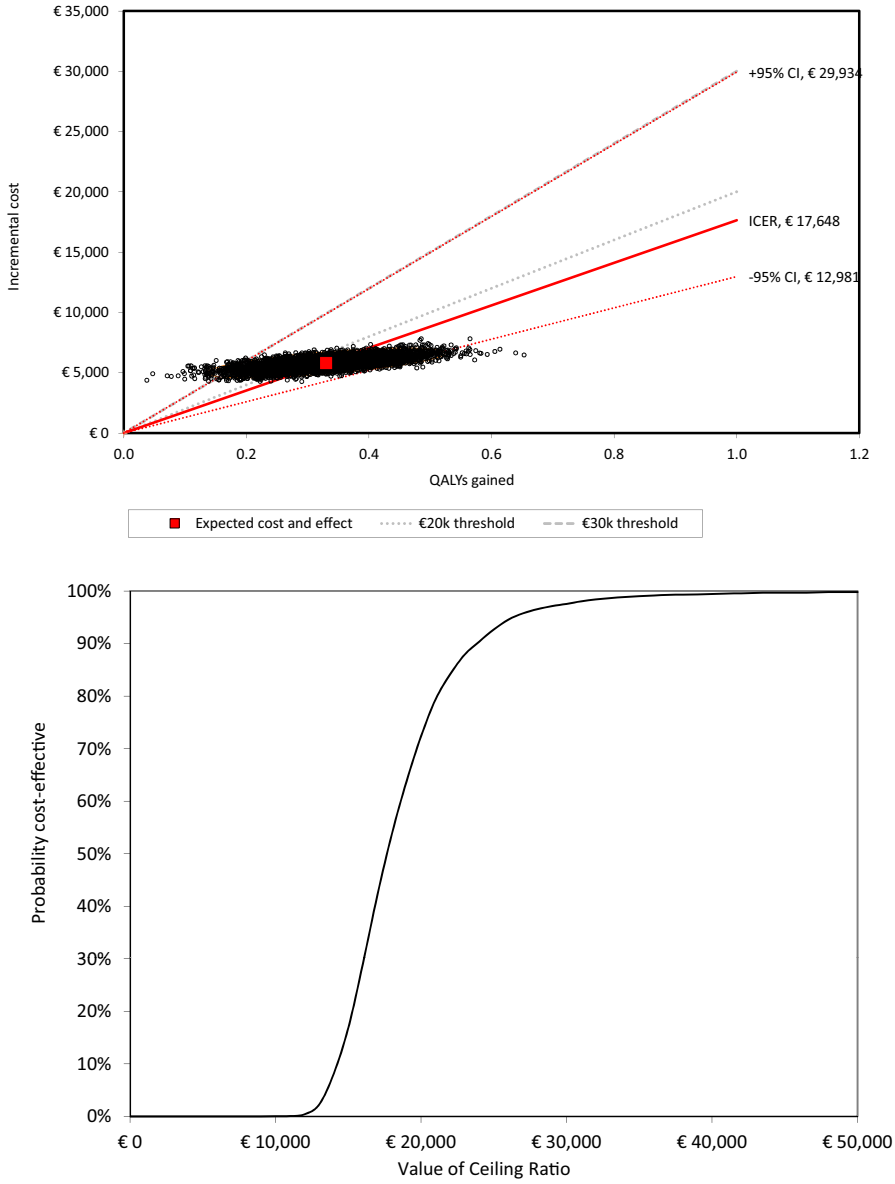

Fig. 2 – CE plane and CEAC. CE, cost effectiveness; CEAC, cost-effectiveness acceptability curve; CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

are the input parameters that require additional research. It is more likely that the addition of these costs increase the EVPPI of survival-related input parameters.

It should be emphasized that our model can run three types of simulations: "Patient-level analysis," "Mean patient characteristics," and "User-defined patient characteristics." The former can be run only with all the individual patients in the PARADIGM-HF trial (i.e., a selection of individual patients is not possible). The latter two options perform the economic evaluation for an "average" patient with the mean characteristics of the PARADIGM-HF trial and user-defined characteristics, respectively. We chose the third type of simulation to ensure that the age of the patient population in the model was representative for the Netherlands. Because the model is not linear, the ICER from a patient-level analysis is not the same as the ICER from an analysis with user-defined patient characteristics. In the base-case analysis presented in the pharmacoeconomic dossier submitted to the Dutch National Health Care Institute (cf. Table 13) [16], the population selected was that in the PARADIGM-HF trial. The model was run in patient-level mode, which produced an ICER of €18,580. When the model was run in user-defined patient characteristics, with the mean characteristics of the PARADIGM-HF trial, the ICER was €16,843. A rough estimate of what a patient-level ICER could be in our base-case scenario could be corrected by using a standard transfer ratio derived by taking the difference between the patient-level ICER and the user- defined ICER, that is, patient-level base-case ICER (€18,580)/user-defined base-case ICER (€16,843) = 1.1031. Applied to the ICER presented in this article, this would give an estimate of what the patient-level mode ICER would be: €19,415 (€17,600 × 1.1031).

The key limitation of this analysis is the requirement to extrapolate beyond the follow-up of the PARADIGM-HF trial (with median follow-up of 27 months). The uncertainty this causes is addressed in various scenario analyses with different time horizons and different methods to extrapolate the treatment benefits beyond the follow-up of the trial. These scenarios

showed that extrapolation of the short-term results (e.g., HRQOL, mortality, and treatment discontinuation) did not influence the cost-effectiveness results. It should be noted however that all analyses were based on the original regression coefficients estimated for all patients. Preferably, the coefficients of the regression models should have been re-estimated for the Western European subgroup separately. However, this was not done because the trial was not powered for such a subgroup analysis. Given that this could not be overcome with the available data, the approach proposed in our article was deemed appropriate by the consulted cardiologists and the experts from the Dutch National Health Care Institute. Thus, the risk reduction on CV mortality of LCZ696 used in our model is the one based on all patients in the PARADIGM-HF trial, which is reported in the form of a hazard ratio equal to 0.806 (see, e.g., Appendix 4, Table 1). A threshold analysis indicates that this hazard ratio could go up to 0.959 and the ICER would still be below €50,000, and therefore, LCZ696 would still be considered cost effective. The effect of age on CV mortality is significant and it certainly has an impact on the ICER as can be seen, for example, in the tornado diagram (Fig. 1). However, we do not have the data to calculate another hazard ratio based on Western European patients. Therefore, whereas it might be the case that a more robust risk reduction in the Dutch analysis could be expected, we believe that in the absence of data to confirm this, such a statement would be speculative.

From the study by Garg and Yusuf [60], a meta-analysis of 34 randomized controlled trials in which eight different types of ACEI were compared, it was concluded that enalapril was clinically representative of all ACEI. Thus, our analysis was meant for a broader purpose, which is to estimate the class effects between ACEI and the ARNI LCZ696. We have found LCZ696 to be a cost-effective option for the treatment of HF when compared with ACEI in the Netherlands. The Dutch National Health Care Institute provided the Ministry of Health with a positive advice for LCZ696 in May 2016 [16]. Based on the cost-effectiveness analysis presented in this article, the Dutch National Health Care Institute concluded that LCZ696 is a cost-effective therapy, with a valid and proven cost-effectiveness analysis. The Ministry of Health decided that LCZ696 is fully reimbursed per June 1, 2016, in the Netherlands. Furthermore, this study shows that LCZ696 is cost effective also when the new 2016 Dutch guidelines are followed.

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Supplemental Materials

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