# Cost-effectiveness analysis of LVADs as destination therapy compared to bridge-to-transplantation or heart transplantation for end-stage heart failure patients in the Netherlands

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**Abstract**

**Introduction:** Heart failure (HF) is a major public health problem, affecting nearly two percent of the Dutch population, with end-stage heart failure (ESHF) being a critical form of the disease. ESHF patients experience severe symptoms despite optimal medical treatment, often resulting in a reduced quality of life. While heart transplantation (HTx) is the preferred treatment, long waiting times and limited donor availability create significant challenges. Left Ventricular Assist Devices (LVADs) have become a valuable alternative, initially used as a bridge to transplantation (BTT), but increasingly used as destination therapy (DT) for patients who are ineligible for a transplant. However, the high cost of LVADs raises questions about their cost-effectiveness. This study aims to assess the cost-effectiveness of LVADs as DT compared to BTT and HTx for ESHF patients in the Netherlands.

**Methods:** This study is a model-based cost-effectiveness analysis (CEA) comparing LVAD as DT to usual care, which is a Combined strategy of LVAD as BTT and HTx, in the context of Dutch healthcare. A cohort Markov model was developed with health states: pharmaceutical management (PM), LVAD as BTT, LVAD as DT, HTx, and death. Transition probabilities, costs, and utilities were used as input for the model. The cohort consists of ESHF patients on the transplant waiting list, and the model simulates transitions over a lifetime horizon with starting age 40, with monthly cycles. Several strategies were evaluated, including LVAD as DT, LVAD as BTT, HTx, and a Combined strategy, to assess the cost-effectiveness of LVAD as DT compared to other options. Extrapolated survival curves, fitted using the Weibull distribution, were developed based on Kaplan-Meier (KM) curves to model the transitions to death. A probabilistic sensitivity analysis (PSA), one-way sensitivity analysis (OWSA) and scenario analyses were performed to assess the impact of uncertainty on results.

**Results:** In the deterministic model, the HTx and Combined strategies were more cost-effective than the LVAD as DT strategy. LVAD as BTT was dominated by HTx and the Combined strategy. Although LVAD as DT has low costs, it is associated with low quality adjusted life-years (QALYs), making the other strategies more favorable. PSA results confirmed the robustness of the model. OWSA showed that transition probabilities for PM to LVAD as BTT or HTx, costs of LVAD as BTT and HTx, and utility of HTx have the greatest impact on the model. One scenario analysis showed decreased costs and QALYs for health states including HTx, when the model takes into account the limited availability of heart donors. Another scenario analysis showed slightly better cost-effectiveness for the LVAD strategies when the cost of the device decreased.

**Conclusion:** This CEA found that LVAD as DT is not cost-effective compared to usual care for ESHF patients in the Netherlands, as its lower costs are balanced by lower QALYs. The lower survival rate of LVAD as DT and limited patient eligibility contribute to its lack of cost-effectiveness. While reducing LVAD device costs or limiting heart transplants could help, improvements in survival and quality of life are needed for LVAD as DT to become cost-effective.

# 1 Acknowledgment

In front of you is my master thesis for the Master Health Sciences, which I conducted from September 2024 till February 2025. The thesis has been performed at the Health Technology and Service Research of the University of Twente, in which I researched the cost-effectiveness of left-ventricular assist devices as destination therapy, compared with the usual care pathway, which consists of a left-ventricular assist device as bridge-to-transplant and a heart transplant.

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I wish you a lot of pleasure reading this thesis!

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# 2 Introduction

## *2.1 Background*

Heart failure (HF) is a critical public health problem worldwide [1]. In the Netherlands, almost two percent of the population has the diagnosis heart failure [2]. A critical form of heart failure, is end stage heart failure (ESHF). ESHF patients show severe symptoms of heart failure, either at rest or with minimal physical activity, despite receiving the highest level of pharmaceutical treatment [1]. Within the New York Heart Association (NYHA) functional classification, ESHF patients fall into the III-IV class, with class I being the least progressed HF and class IV being the most progressed HF. As HF progresses, quality of life of patients decreases [3]. Symptoms that ESHF patients experience include shortness of breath even at rest or with minimal physical effort, fatigue and abdominal discomfort, which can be a burden during everyday activities [4].

Heart failure can develop at a young age, though it is more commonly seen in older adults. In the Netherlands, incidence rates rise sharply from approximately 1 per 1000 person-years for those under 60 to nearly 50 per 1000 person-years among individuals aged 90 and above [5]. Gender also influences risk, with men having a slightly higher likelihood of developing heart failure than women—33 percent compared to 28 percent [6]. Heart failure patients often experience comorbidities, which may include both cardiovascular and non-vascular conditions such as coronary artery disease, hypertension, anemia, obesity, and chronic kidney disease [7]. These comorbidities significantly impact heart failure outcomes and can substantially affect quality of life. Patients with ESHF have a poor prognosis, with a one-year mortality rate of approximately 50% despite pharmaceutical management [1].

There are several treatment options for patients who develop heart failure. The first options would be lifestyle changes, pharmaceutical treatment or surgical treatment [8]. Lifestyle changes include losing weight, restricting sodium and fluid intake, and quitting smoking [8]. First-line pharmaceutical treatment of ESFH patients consists of angiotensin converting enzyme (ACE) inhibitors, to lower blood pressure [1]. If ACE inhibitors are not tolerated by the patient or do not relieve symptoms, angiotensin II type I receptor blockers (ARBs) are prescribed as an alternative or on top of the ACE inhibitors, to further decrease blood pressure and to prevent damage to kidney and heart [9]. Because of fluid retention in ESHF patients, diuretics should also be considered [1]. Patients with stable ESHF should be using $\beta$ - adrenergic receptor blockers, which also decrease blood pressure and make the heart pump less intensively [10]. In case patients get more advanced ESHF, they are recommended to get aldosterone receptor antagonists on top of the before mentioned medication, which again lower blood pressure [11]. It is also possible to perform surgical procedures in ESHF patients. An example of a possible surgical procedure is ventricular restoration to decrease the volume of the left ventricle and increase its function [8].

When the above mentioned treatments have not shown enough symptom relief, the next best possible treatment option is heart transplantation [12]. In the Netherlands, there are three transplant centers that together perform 40-50 heart transplants each year, while there are 120 patients on the waiting list each year [13]. The heart transplant centres are the Erasmus Medical Centre in Rotterdam, Universitair Medisch Centrum Utrecht (UMCU) and Universitair Medisch Centrum Groningen (UMCG) [14]. Only patients who are likely to benefit significantly from a transplant, and who have manageable risk factors are placed on the waiting list. Patients must have severe, ESHF that does not improve with optimal medical and device therapies. Patients should pass three diagnostic items which are: assessment of physical capacity, prognostic scores and pulmonary hemodynamic assessment. Lastly, existing comorbidities should be manageable and patients must demonstrate the ability to adhere to a complex post-transplant regimen [13]. Even though there are selection criteria, the waiting list is long which results in a waiting time for a donor heart of approximately three years. Because patients with ESHF have a 1-year mortality rate of 50 percent, they can not wait three years in order to receive a donor heart [1].

At the end of the last century, the first continuous flow mechanical cardiac support devices, also known as ventricular assist devices (VADs) were introduced. In the last decades, these VADs have been progressing, resulting in worldwide usage [8, 15]. VADs are mechanical pumps that help the heart by taking over some or all of its pumping function. They are used to assist blood circulation and ensure

that organs receive enough blood. A VAD can support either the left side of the heart (LVAD), the right side (RVAD), or both sides simultaneously (BiVAD) [8]. This research will focus exclusively on LVADs, as they represent the most commonly used type of VAD, accounting for 90 percent of all VAD implants [16, 17] Additionally, LVADs are more commonly used because the left ventricle pumps blood to the entire body, whereas the right ventricle supplies only the lungs, reducing the need for RVADs [18]. In the Netherlands, LVADs are implanted in the three heart transplantation centres, and in the Leids Universitair Medisch Centrum (LUMC) [19].

LVAD placement is an invasive procedure in which a mechanical device is implanted in the heart's left ventricle. The device is powered via a driveline connected to external batteries and a controller, requiring patients to carry this in an external bag or pocket [20, 19].While the LVAD allows patients to remain at home and not be confined to a hospital bed, it can reduce quality of life due to the stress of managing the device, concerns about body image, and limitations on activities such as driving and swimming [20].

Since the introduction of VAD therapy, multiple devices have been developed. First generation devices were pulsatile volume-displacement pumps [21, 15]. Due to the large size and high chance of infection these devices are rarely used anymore. The second-generation devices are continuous flow devices, which are smaller and more durable than first-generation devices because the only moving part is the rotor. Lastly, third-generation devices are continuous flow centrifugal pumps, which are mostly used nowadays due to their small size, ease to implement and durability [21]. This research will focus on second- and third generation devices as these are most commonly used.

Originally LVADs are used as a bridge to transplantation (BTT), meaning that patients receive an LVAD for a short time, while still being on the transplant waiting list [12]. BTT is used to get through the waiting period for a transplant, avoid further decline in health, and potentially enhance the function of other organs. According to the the International Thoracic Organ Transplant (ISHLT) Registry, already 50 percent of heart transplants are now performed with an LVAD as a bridge to transplant [13][8]. Even though LVADs were traditionally meant as BTT, they are more frequently being used as destination therapy (DT). LVADs used as DT can be used long-term for those who are not candidates for a transplant [22]. Therefore, LVADs are implanted with the goal of remaining in place for the rest of the patient's life, which is possible with follow-up care and replacement of technical parts [15].

Within the group of patients that get an LVAD as DT, there is a distinction between unintentional DT and and intentional DT. Intentional DT refers to patients who receive an LVAD as a long-term solution because they are deemed ineligible for a heart transplant or no heart donor is available. These patients rely on the LVAD for the rest of their lives, leading to lower overall survival rates compared to those eligible for transplant. In contrast, unintentional DT occurs when patients initially implanted with an LVAD as BTT do not receive a donor heart in time. Although the original intent was to bridge them to a transplant, they remain dependent on the LVAD indefinitely, without successfully transitioning to transplantation. These patients are essentially in a DT-like situation but with better initial health conditions, which may lead to differences in survival compared to intentional DT patients.

Even though LVADs have shown increased survival and quality of life in patients with end-stage heart failure, it is inevitable that LVADs are costly devices. Prices for LVAD vary between €58,000 and €95,000, depending on the device type and country of implantation [12] [23]. In the research by Neyt et al. in 2013, a cost-effectiveness analysis has been performed for LVADs as DT compared to optimal pharmaceutical treatment in the Netherlands [23]. The motivation for this research was a statement by the "Zorginstituut Nederland", which said that LVADs as DT would not be reimbursed by Dutch health insurances in patients with end-stage heart failure [24]. The researchers wanted to find out whether LVADs as DT would be cost-effective and should therefore be reimbursed. They concluded that in the most ideal situation, the incremental cost-effectiveness ratio (ICER) would be above €100.000 euros per quality adjusted life-year (QALY), which is still high. This research has been performed 11 years ago, and in the meantime there have been new technological advances for LVADs, which could improve outcome measures, such as survival and QALYs, resulting in a more optimistic ICER and therefore a better cost-effectiveness [25]. Therefore this research will look into the cost-effectiveness of LVADs as DT for patients with ESHF in the Netherlands, preferably including most recent data available.

### *2.2 Research question and aim*

The research question is as follows: "Are Left Ventricular Assist Devices as destination therapy cost-effective compared to bridge-to-transplantation or heart transplantation for end-stage heart failure patients on the heart transplant waiting list in the Netherlands?"

The aim of this research is to investigate the cost-effectiveness of Left Ventricular Assist Devices (LVADs) as destination therapy (DT) compared to bridge-to-transplantation (BTT) or heart transplantation (HTx) for ESHF patients that are on the heart transplant waiting in the Netherlands, based on the most current available data. As already 50 percent of heart transplants are performed using LVADs as BTT, both treatment options are considered usual care [13]. So, it is either possible to get a direct transplant or by first receiving an LVAD. Furthermore, the study will assess both costs, quality-adjusted life years (QALYs) and survival to determine the economic and clinical feasibility of LVADs as DT compared to usual care within the Dutch healthcare system.

## 3 Method

### *3.1 Study design*

This research is a model-based cost-effectiveness analysis (CEA). In this CEA, the use of an LVAD as DT is compared with using LVAD's as BTT and HTx, which is considered usual care. This analysis is done in the perspective of the Dutch healthcare system. Therefore, the aim was to use literature and data from Dutch sources and registries when possible. Otherwise, data from comparable countries to the Netherlands were used.

Patients can transition between the health states on a monthly basis, so the model's cycle length is one month. This is chosen to capture the rapid changes in health status common among ESHF patients [26]. The model uses a lifetime horizon to ensure that all associated costs and health outcomes are captured, continuing until all patients have transitioned to the "death" state.

### *3.2 Model structure*

The model is structured as a Markov model, with the following health states: *Pharmaceutical management* (PM), *LVAD as bridge-to-transplantation* (BTT), *LVAD as destination therapy* (DT), *heart transplantation* (HTx) and *death*, which is shown in Figure 1. This Markov model is build by using the software R, version 4.4.0 [27]. A Time-Dependent Cohort State-Transition Model by Alarid-Escudero et al. has been used as a template to build this CEA upon [28].

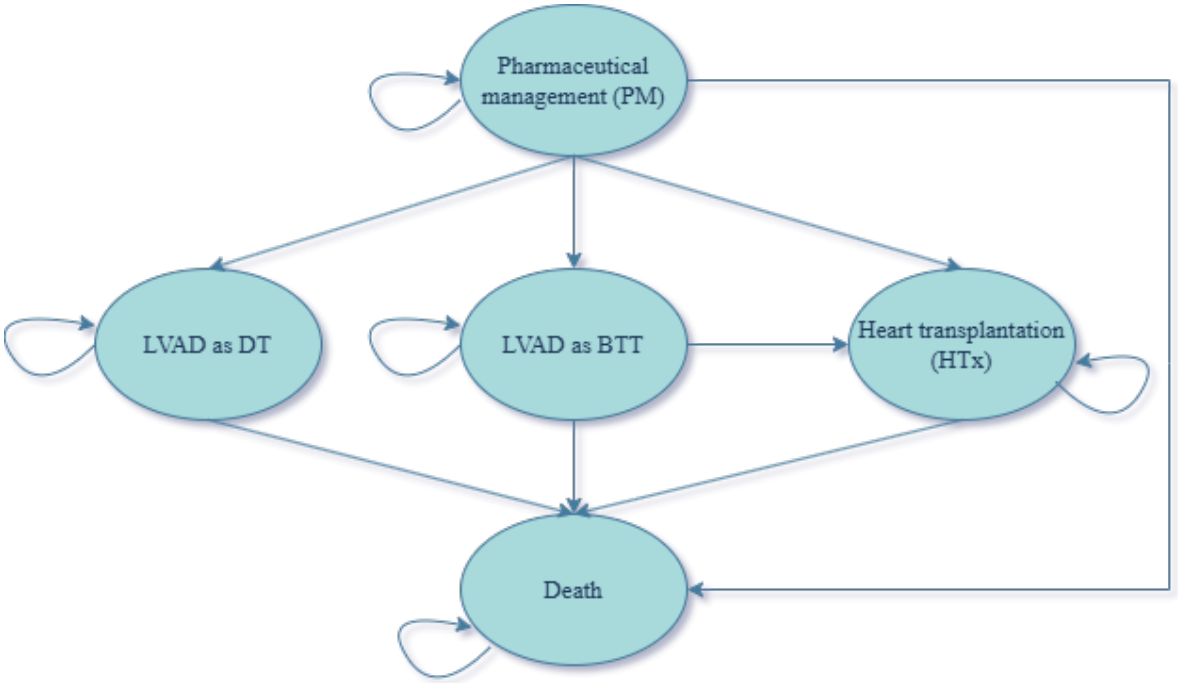


Figure 1: Markov Model structure

### 3.2.1 Cohort description

The cohort consists of ESHF patients, who receive pharmaceutical treatment according to the "Nederlandse Huisartsen Genootschap" (NHG) guidelines, including ACE inhibitors, ARBs, diuretics, $\beta$-blockers, and aldosterone receptor antagonists to manage symptoms and improve heart function [29]. Heart failure patients are considered end-stage when they are classified as NYHA class III or IV, meaning all patients in this cohort have at least a class III classification or higher [1]. All patients in the cohort meet the selection criteria of getting a heart transplant, and are therefore all on the transplant waiting list. Data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), covering the period from 2006 to 2021, reveals that the majority of patients fall into the 40-59 (41%) and 60-79 (46%) age groups, with 78% being male [30]. The INTERMACS includes 766 primary LVAD patients from North American hospitals. Common comorbidities in this cohort include pulmonary hypertension (21%), a history of atrial arrhythmia (20%), and severe diabetes (10%) [30]. The largest part of the ESHF patients is 40 years or older, so therefore the starting age of this cohort is 40 years old. The ending age of the model is 80 years old. This was chosen because the majority of patients with ESHF will have reached the terminal stage of their disease by this age. While both treatments can extend survival, studies indicate that the median survival with long-term LVAD support is 4.5 years [31], compared to 12 years for heart transplantation [32]. Extending the time horizon beyond 80 years would likely have minimal impact on cost-effectiveness results, as the number of surviving patients would be very small.

### 3.2.2 Health state transitions

All patients in the cohort start in the PM health state. As stated earlier, these patients are eligible for either an LVAD or heart transplant and are therefore on the waiting list of getting a heart transplant. From the PM health state, patients can transition to LVAD as DT, LVAD as BTT, HTx and death. Patients can stay in each health state, which is illustrated by the continuous arrow. Patients can transition to death from all states. The death state is an absorbing state, meaning that there are no transitions out of this state.

There is no arrow from LVAD as BTT to LVAD as DT, as patients that do not get an available donor heart in time will transition to the death state. This is because of the concept of intentional and unintentional DT patients. Unintentional DT patients are actually patients in the LVAD as BTT state who transition to death before they can transition to the HTx state. However, within the this model

this distinction is not explicitly made, because of simplicity. It is very hard to determine which patients get an intentional or unintentional LVAD as DT, as there is no data available.

#### 3.2.3 Strategies

Based on the health states and model structure outlined above, several strategies were chosen for analysis. A strategy can be interpreted as a pathway. From the PM state, there are different pathways that can be followed. These pathways are designed to ultimately determine whether LVADs as DT are cost-effective in comparison to LVADs as BTT or HTx. The four strategies are:

- LVAD as DT: from PM, patients can only transition to LVAD as DT or death.
- LVAD as BTT: from PM, patients can only transition to LVAD as BTT or death. From LVAD as BTT, patients can also transition to HTx.
- HTx: from PM, patients can only transition to HTx or death.
- Combined: from PM, patients can transition to LVAD as BTT, HTx or death. Subsequently, patients can transition from LVAD as BTT to HTx. This is considered usual care.

There are four strategies, but the most important ones are LVAD as DT and the Combined strategy, as they are compared in this analysis. However, for completeness the other two strategies have also been simulated. The other two strategies are also possible pathways for ESHF patients, and therefore give a clear overview of the situation.

### *3.3 Model input*

The input variables transition probabilities, costs and utilities have been collected and will be described below.

#### 3.3.1 Transition probabilities

In the model, there is a total of eight transitions, as shown in Figure 1. The first transitions are from the PM health state to LVAD as DT, LVAD as BTT, HTx or death. Consequently there are death transitions from these health states. From LVAD as BTT there is also a transition to HTx. The non-death transitions are assumed, constant values. These assumptions have been made based upon clinical outcomes of LVAD implantation in the Netherlands and clinical expert opinion (Dr. Olivier Manintveld, Erasmus Medical Center, personal communication, 13 December 2024) [33]. The annual probability to get an LVAD as DT is 20%, to get an LVAD as BTT is 40%, to get a heart transplant is 40% and to get a heart transplant after bridging by an LVAD is 75%. These annual probabilities have been transformed to monthly probabilities to reflect the monthly cycles in the model. The corresponding values can be found in Table 1.

In order to perform a probabilistic sensitivity analysis (PSA), distributions for the input parameters needed to be chosen. For the non-death transition probabilities a beta distribution has been chosen, as these are constant values between 0 and 1 [34]. The alpha and beta parameter of the beta distribution were calculated using a formula that incorporates the transition probability mean and sample size (100). In the absence of actual patient-level data, the sample size parameter of 100 was chosen to provide a moderate level of certainty around the estimated transition probability without making it too restrictive. A 95 percent confidence interval was used, with lower and upper bounds at 2.5% and 97.5%, respectively. The parameters and confidence intervals were derived using the Beta distribution's quantile function, to ultimately provide a realistic variability in the transition probabilities. The alpha and beta parameters can also be found in Table 1.

The death transitions are represented in the model in a time-dependent vector. To retrieve these vectors, Kaplan-Meier (KM) survival curves were digitized from published sources, using the Engauge Digitizer [35]. This step was necessary because the original data was only available in graphical form, not in a usable numerical format. Engauge was used to extract time points and corresponding survival probabilities directly from the KM curves. For PM, a KM survival curve from an RCT comparing

LVADs to optimal medical therapy has been used and digitized [36]. This study was performed in 2001, including 129 North-American ESHF patients who were ineligible for a HTx. However, the mean age of the patient group on optimal medical therapy was 68 years old and all patients had at least NYHA class IV. The cohort used in this CEA is 40 years or older and has NYHA class III or IV, meaning that the data from the RCT is too pessimistic for this CEA. Therefore a hazard ratio of 0.4 has been used on the extrapolated survival curve, to get a better representation of the cohort in this CEA.

For LVAD as BTT and DT, KM survival curves from INTERMACS have been used [30]. And lastly, for HTx a KM curve from the Special Report for death/retransplant among primary, deceased donor transplant recipients from the International Society for Heart and Lung Transplantation (ISHLT) has been used [37]. The ISHLT registry includes patients who have undergone heart and/or lung transplantation, primarily from the United States, Europe, Canada, Australia and New Zealand. The used KM curve covers data for heart transplants from 1992 to 2017, including 97,140 patients.

The digitized KM curves were fitted to parametric survival distributions, including Gompertz, Gamma, Weibull, Exponential, and Lognormal models. The fit of each distribution was evaluated visually by comparing the fitted curves to the reconstructed KM curve and quantitatively using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The model with the lowest AIC and BIC values was identified as the best fit. By plotting these parametric survival curves and choosing the best fit to the data, the data could be extrapolated beyond the observed time points, ensuring that the full time horizon of the model was captured.

For the death transitions, a multivariate normal distribution (rmvnorm) was used, as these transitions are modeled using time-dependent vectors [38]. The rmvnorm distribution takes two inputs: the mean vector and the covariance matrix. The mean vector represents the expected mortality probabilities for each transition, derived from the shape and scale parameters of the chosen parametric distribution. The covariance matrix captures the uncertainty in these probabilities, reflecting the relationships between different mortality probabilities based on the model fit. The shape and scale parameters used to generate the mean vector are provided in Table 1, while the corresponding covariance matrices are presented in Figure 2.

| **Parameter** | **Base Case Value (monthly)** | **Beta/rmvnorm parameters** | | **Min and max values** | | **Source** |
|---|---|---|---|---|---|---|
| | | $\boldsymbol{\alpha}$ | $\boldsymbol{\beta}$ | **Low** | **High** | |
| PM to DT | 0.02 | 1.82 | 97.18 | $0.02 \times 10^{-2}$ | 0.096 | Assumption |
| PM to BTT | 0.04 | 4.13 | 94.87 | $0.04 \times 10^{-1}$ | 0.15 | Assumption |
| PM to HTx | 0.04 | 4.13 | 94.87 | $0.02 \times 10^{-1}$ | 0.14 | Assumption |
| BTT to HTx | 0.11 | 10.80 | 88.20 | 0.03 | 0.26 | Assumption |
| | | **Shape** | **Scale** | | | |
| PM to death | NA | 0.03 | 2.07 | NA | NA | [36] |
| DT to death | NA | -0.11 | 4.22 | NA | NA | [30] |
| BTT to death | NA | -0.02 | 4.51 | NA | NA | [30] |
| HTx to death | NA | -0.01 | 2.65 | NA | NA | [37] |

Table 1: Parameter input table transition probabilities

$$\Sigma_{\text{PM to death}} = \begin{bmatrix} 6.36 \times 10^{-5} & 2.55 \times 10^{-5} \\ 2.55 \times 10^{-5} & 1.05 \times 10^{-4} \end{bmatrix} \quad \Sigma_{\text{DT to death}} = \begin{bmatrix} 1.40 \times 10^{-4} & -5.30 \times 10^{-5} \\ -5.30 \times 10^{-5} & 2.32 \times 10^{-4} \end{bmatrix}$$

$$\Sigma_{\text{BTT to death}} = \begin{bmatrix} 1.77 \times 10^{-4} & -1.02 \times 10^{-4} \\ -1.02 \times 10^{-4} & 2.71 \times 10^{-4} \end{bmatrix} \quad \Sigma_{\text{HTx to death}} = \begin{bmatrix} 1.01 \times 10^{-4} & 1.10 \times 10^{-6} \\ 1.10 \times 10^{-6} & 1.32 \times 10^{-4} \end{bmatrix}$$

Figure 2: Covariance matrices for the death transitions

#### 3.3.2 Costs

The cost input parameters have been gathered from databases, registries, and literature. Each health state's cost comprises several components, for example device costs, hospitalization costs (e.g., days spent in the hospital), and screening costs. Below these components are explained in more detail for each health state. These components are summed to calculate the total cost per health state, as shown in Table 2 as the base case value. These costs have been converted to Euros and to the year 2024, so they all refer back to the same price year [39]. In this CEA, discount rates of 3 percent for the costs and 1.5 percent for effects have been used, accordingly to the Dutch Guideline for health economic evaluations in healthcare [40].

For each health state, costs are categorized into two time frames: the first month, and the period after the first month. This distinction accounts for the significant cost difference immediately following implant of an LVAD or heart transplant compared to the subsequent months [41]. Implantation or transplantation itself is expensive, but also the hospitalization accounts for a large part of the costs. However, after patients get out of the hospital, monthly costs are significantly lower, which is why a distinction in these time frames has been made. Additionally, it is assumed, for simplicity, that costs remain constant after the first month. The distinction into month one and the subsequent months does not apply to the PM health state, as there is no implantation or transplantation. The costs therefore stay the same over all months. In the following paragraphs the costs for each health state are described in detail. The specific costs can be found in Table 2 and appendices B and C.

**1. PM**: Patients staying in the PM health state need medication, for which the costs have been calculated based on the treatment plan for chronic heart failure in the NHG guidelines [29]. For each step in the treatment plan, the average cost for the prescribed medicine(s) per month has been taken from 'Farmaceutisch Kompas', and this has been summed to get to the total amount of €75 per month [42]. A more detailed description of the costs of the medication is in appendix B. Next to pharmaceutical treatment, a large part of the costs comes from hospitalization when complications occur and patients need to be admitted to the hospital. On average, patients in the final years of their life are admitted 12 days per year to the hospital, so per month it is assumed that this would be one day [43]. Therefore the cost of one day of care in the hospital of €644 is used, according to the Dutch costing manual [44].

**2. LVAD as DT:** For the first month of getting an LVAD as DT, the largest part of the costs consists of the device cost. On average, the device costed €70,000 in 2010, which is up to €94,000 in 2024 [23]. Other costs are those of days of (intensive) care, minutes spent in the operating room, and screening costs. The costs for days in (intensive) care and minutes spent in the operating room are taken from the Dutch costing manual [44]. The screening tests and its costs are retrieved from the price list of the Erasmus Medical Centre (Dr. Olivier Manintveld, Erasmus Medical Center, personal communication, 13 December 2024), [45]. After one month, the costs consists of a check up at the hospital every three months, visits to the thrombosis service, and readmission costs when complications occur regarding the implantation of the LVAD [46, 47].

**3. LVAD as BTT:** The costs of getting an LVAD as BTT are the same as the costs for getting an LVAD as DT for the first month, because the implantation process is the same. However, there is a slight difference between the costs after the first month. This difference stems from the difference in check up at the cardiologists, which is every two months for LVAD as BTT instead of three months for

LVAD as DT (€65 versus €40 per month). The other components of the costs are assumed to be the same.

**4. HTx:** Just like the implantation of an LVAD, a heart transplant is a costly procedure. It consists of the costs for screening to test whether the patient can receive a donor heart, support during the whole process of heart transplantation, the procedure itself and the aftercare. This process can take a few months, up to years, depending on the waiting time for a donor heart. These prices have been taken from the price list of the Erasmus Medical Center and are confirmed by a cardiologist of the Erasmus Medical Center [45]. After one month it is assumed that the costs only consists of immunosuppression medication that patients will have to take their whole life. These costs were determined by retrieving a list of the maintenance immunosuppressive therapies for heart transplantation, defined by Söderlund et al. [48]. The specific costs were then retrieved from 'Farmacotherapeutisch Kompas' and summed [42]. A more detailed description of the costs of the medication is in appendix B.

Lastly, there are costs associated with going into the death state. During the last phase of illness before death, also called end of life care, healthcare costs increase [49]. This is also the case for ESHF patients, where the highest expenses are recorded during the final six months of life, with the main costs driver being hospitalization costs [50]. To reflect the increasing costs associated with transitioning to the death state, a transition cost has been integrated into the model. A day of care in the hospital is €644, which is multiplied by seven days, because the assumption has been made that patients remain in the hospital in their final week of life [44].

For the costs, a gamma distribution has been chosen, because the costs can vary a lot due to individual differences in, for example, length of hospital stay. This distribution can account for the skewness in the costs and the fact that the costs are non-negative [44, 34]. The shape and scale parameters of the gamma distribution are calculated using the mean cost and an assumed coefficient of variation of 20 percent, which reflects a moderate variability in costs. These parameters can be seen in Table 2.

| **Parameter** | **Base Case Value** | **Gamma parameters** | | **Min and max values** | | **Source** |
|---|---|---|---|---|---|---|
| | | **Shape** | **Scale** | **Low** | **High** | |
| PM (month 1) | €774 | 25 | 298.97 | €337 | €1376 | [44, 42] |
| PM (month 2+) | €774 | 25 | 298.97 | €337 | €1376 | [44, 42] |
| LVAD as DT (month 1) | €137,088 | 25 | 5483.52 | €61,092 | €248,993 | [44, 23, 47, 45] |
| LVAD as DT (month 2+) | €263 | 25 | 10.53 | €115 | €468 | [44, 46, 47] |
| LVAD as BTT (month 1) | €137,088 | 25 | 5483.52 | €59,451 | €238,099 | [44, 23, 47, 45] |
| LVAD as BTT (month 2+) | €284 | 25 | 11.40 | €106 | €527 | [44, 46, 47] |
| HTx (month 1) | €120,562 | 25 | 4822.51 | €57,220 | €211,777 | [45] |
| HTx (month 2+) | €600 | 25 | 24 | €288 | €1111 | [44] |
| Transtion costs when dying | €4508 | 25 | 180.32 | €2034 | €8136 | [44, 50] |

Table 2: Parameter input table costs

### 3.3.3 Utilities

In this CEA, QALYs were used to evaluate treatment effectiveness. QALYs are determined by multiplying the utility value (which reflects quality of life) by the life years in each health state. Utility values are constant for each health state and are measured on a scale from zero (death) to one (perfect health) [51]. The utility values for this CEA are provided in Table 3.

For the PM and LVAD health states, utility values are derived from the INTERMACS. These values were obtained from published quality assurance reports, based on the EQ-5D index, for primary LVAD patients [30]. In the reports by INTERMACS, no distinction has been made between LVAD as DT and LVAD as BTT. However, a cost-effectiveness study by Silvestry et al. suggests that utility values for LVAD as DT are slightly higher than those for LVAD as BTT [52]. This may be because DT patients undergo only one surgery instead of two and can adapt to life with their LVAD rather than facing prolonged uncertainty while waiting for a donor heart. Therefore, in this CEA, LVAD as BTT is assumed to have a 0.02 smaller utility value than LVAD as DT, to reflect this difference. Utility values for heart transplantation were derived from taking the mean utility value for post heart transplant of three cost-effectiveness studies [53, 54, 55]. The patient populations in these studies are comparable to the cohort in this study in terms of mean age, gender and NYHA class, but only the study by Ouwens et al. is from the Netherlands, both Sutcliffe et al. and Clegg et al. are from the United Kingdom.

Just like the transition probabilities, utility values fall between 0 and 1, so a beta distribution is used here as well [34]. The same steps as for the transition probabilities were taken to calculate the beta distribution parameters to account for the variability in the utilities. The alpha and beta parameters can be found in Table 3.

| **Parameter** | **Base Case Value** | **Beta parameters** | | **Min and max values** | | **Source** |
|---|---|---|---|---|---|---|
| | | $\boldsymbol{\alpha}$ | $\boldsymbol{\beta}$ | **Low** | **High** | |
| PM | 0.60 | 59.40 | 39.60 | 0.43 | 0.77 | [30] |
| LVAD as DT | 0.80 | 79.20 | 19.80 | 0.65 | 0.91 | [30] |
| LVAD as BTT | 0.78 | 77.22 | 21.78 | 0.56 | 0.89 | [30] |
| HTx | 0.83 | 82.17 | 16.83 | 0.68 | 0.93 | [53, 54, 55] |

Table 3: Parameter input table utilities

#### 3.3.4 Willingness-to-pay threshold

To make conclusions about the cost-effectiveness of one of the strategies in this CEA, an appropriate willingness-to-pay (WTP) threshold needs to be considered. In the Netherlands, Zorginstituut Nederland (ZIN) advises the Ministry of Health, Welfare, and Sport (VWS) on healthcare reimbursement decisions, including recommendations regarding the WTP threshold [56]. This threshold varies based on the severity of the disease, with three different levels: €20,000 per QALY gained, €50,000 per QALY gained, and €80,000 per QALY gained. The severity of the disease is determined by the proportional shortfall (PS), which reflects the average health loss experienced by a patient. Given that end-stage heart failure significantly reduces quality of life and is classified as a severe condition, it is likely to have a high PS score [4]. Consequently, a WTP threshold of €80,000 per QALY gained is assumed appropriate for this CEA.

### *3.4 Sensitivity analysis*

In this CEA, various assumptions were made, which introduced uncertainty into the model. To evaluate the impact of this uncertainty, sensitivity analyses were performed [57].

To capture overall uncertainty, a PSA was conducted using Monte Carlo simulations. This generated an incremental cost-effectiveness plane, where each point represents a possible outcome based on the uncertainty across all input parameters, with appropriate distributions assigned to each input. As described in the model input section, the transition probabilities and utilities have a beta distribution, while the costs have a gamma distribution. In this PSA, 2000 simulations were run, to make sure the results were stable and accurate. While 1000 simulations are usually enough for the results to settle, 2000 simulations are commonly used in health economics to give a reliable view of uncertainty in cost-effectiveness results without using too many computational resources [58]. This resulted in an ICER table, incremental cost-effectiveness plane, efficiency frontier and a cost-effectiveness acceptability curve (CEAC).

In addition to the PSA, a One-Way Sensitivity Analysis (OWSA) was conducted on the PSA results to explore the impact of individual input parameters on the Net Monetary Benefit (NMB), which is

another way to express cost-effectiveness [59]. The formula for the NMB is given by:

$$\text{NMB} = (\text{Effectiveness} \times \text{WTP}) - \text{Costs}$$

All model input parameters, including transition probabilities, costs, and utilities were used in this OWSA. The OWSA was performed on a PSA object, in which a polynomial regression metamodel was used to investigate the parameters that most significantly affect the model's results [60]. Since the PSA object was used, the ranges in the OWSA are identical to those in the PSA. In the OWSA, each parameter was tested at its lower and upper bound within this range to determine how uncertainty in each parameter affects the model's outcomes. The specific high and low values for transition probabilities, costs, and utilities used in the OWSA are provided in Tables 1, 2, and 3. Each strategy was compared to the reference strategy: LVAD as DT. The OWSA produced tornado plots for each comparison, illustrating how uncertainty in the input parameters influences cost-effectiveness.

### *3.5 Scenario analysis*

Two scenario analyses were conducted to evaluate the impact of different assumptions. The current model assumes that a donor heart is always available, as seen in the relatively high transition probabilities from the PM state to HTx and from LVAD as BTT to HTx. To assess the impact of donor scarcity, a scenario analysis was conducted in which the transition probability to HTx was reduced. In this exploratory scenario analysis, the annual transition probability from the PM and BTT health states to the HTX health states were halved. The annual probability of moving from PM to HTx changed to 20% and from BTT to HTx changed to 37.5%. This adjustment lowers the likelihood of receiving a heart transplant, ultimately resulting in fewer patients undergoing transplantation. This analysis helps evaluate how real-world donor shortages affect the cost-effectiveness of LVADs.

Scenario 2 was designed to evaluate the impact of the price of an LVAD. As mentioned earlier, LVADs are costly devices and therefore have a great impact on the cost-effectiveness of the strategies. For this analysis, the cost was manually reduced by €54,000 (almost half of its original price) to explore how a substantial price reduction could affect the outcomes. While it's unclear if such a reduction is realistic, this value represents a significant change that can provide insights into how the cost of the LVAD might influence the cost-effectiveness of the strategies.

## 4 Results

### *4.1 Survival curves*

Extrapolated survival curves were developed using KM curves obtained from the literature, by fitting a statistical distribution. Among the tested distributions, the Weibull distribution came out as the best fit for all four death transitions, based on both visual inspection and the lowest AIC and BIC values. This choice has also been verified by expert opinion (Dr. Olivier Manintveld, Erasmus Medical Centre, personal communication, 17 January 2025). The extrapolated survival curves have been added to appendix D.

### *4.2 Cohort traces*

Figure 3 presents the cohort traces for each strategy, illustrating how the cohort transitions through different health states over time. In these cohort traces, the full time horizon is shown (480 months). Across all strategies, the cohort begins in the PM state and quickly transitions to other states depending on the strategy.

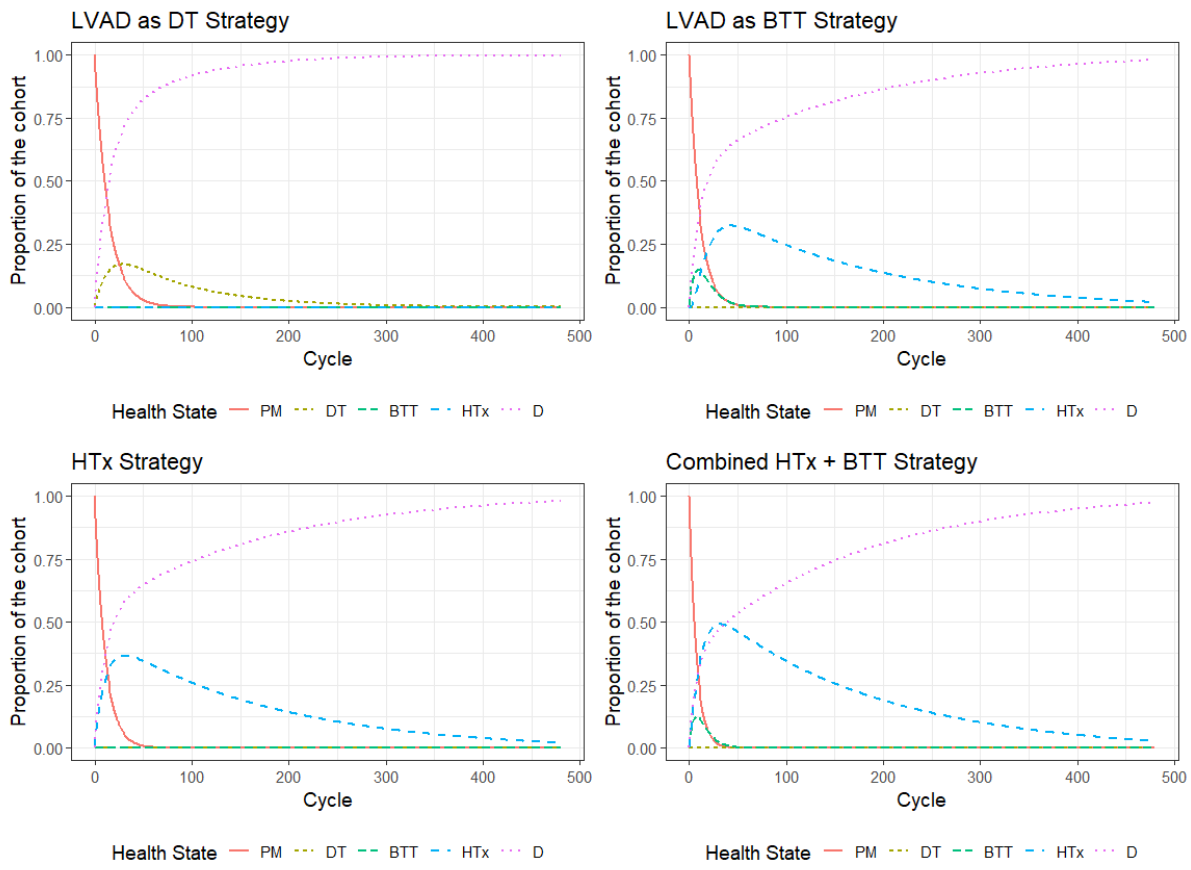


Figure 3: Cohort traces

### *4.3 Deterministic model*

Table 4 shows the ICER table of the deterministic model. The effects are represented as QALYs and life-years. The life-years reflect the survival, without considering the quality of life. LVAD as DT is seen as the reference strategy in this ICER table. This strategy has the lowest cost and lowest QALYs, which makes it easy to compare the other strategies to this strategy. HTx has higher costs, but also higher QALYs. The ICER for HTx is €7,151 per QALY gained, meaning that getting one extra QALY, in comparison to LVAD as DT, costs €7,151. For the Combined strategy one extra QALY would cost €31,057 and for LVAD as BTT it would cost €28,881.07.

| **Strategy** | **Cost (€)** | **Effect (QALYs)** | **Effect (life-years)** | **Incremental cost** | **Incremental effect (QALYs)** | **ICER (QALYs)** |
|---|---|---|---|---|---|---|
| LVAD as DT | 38,957.27 | 1.76 | 2.48 | NA | NA | NA |
| HTx | 58,013.56 | 4.44 | 5.56 | 19,056.29 | 2.66 | 7,150.67 |
| Combined | 162,563.96 | 5.74 | 7.06 | 123,606.69 | 3.98 | 31,056.96 |
| LVAD as BTT | 110,582.33 | 4.25 | 5.35 | 71,625.06 | 2.48 | 28,881.07 |

Table 4: ICER deterministic model (LVAD as DT as reference strategy)

## *4.4 Sensitivity analysis*

### 4.4.1 Probabilistic Sensitivity Analysis

In Table 5, the ICER table of the PSA is shown. In the table, the mean values from the PSA are presented. Again, LVAD as DT is the reference strategy. The results are similar to the deterministic ICER table, meaning that the average results from the PSA come close to the deterministic results. In other words, the uncertainty of the parameters which was captured in the PSA does not drastically change the results. This highlights the robustness of the deterministic model.

| **Strategy** | **Mean cost (€)** | **Mean effect (QALYs)** | **Mean effect (life-years)** | **Mean incremental cost (€)** | **Mean incremental effect (QALYs)** | **Mean ICER (€/QALY)** |
|---|---|---|---|---|---|---|
| LVAD as DT | 45,749.66 | 1.70 | 2.39 | NA | NA | NA |
| HTx | 62,971.66 | 4.27 | 5.35 | 17,222 | 2.57 | 6,690.47 |
| Combined | 165,254.50 | 5.61 | 6.90 | 119,504.84 | 3.91 | 30,563.90 |
| LVAD as BTT | 115,328.19 | 4.06 | 5.12 | 69,578.53 | 2.36 | 29,455.99 |

Table 5: ICER PSA (LVAD as DT as reference strategy)

Figure 4, 5, 6 and 7 show the results of the PSA in graphical format. Figure 4 shows the total costs and QALYs of every strategy from the ICER table, with the uncertainty around it. The BTT, HTx and Combined strategy have great uncertainty (great ellipses), while LVAD as DT shows little uncertainty (smallest ellipse). Notably, the cost of LVAD as DT varies little compared to other strategies, possibly because HTx has greater cost fluctuations than LVAD strategies, as it is the only strategy that does not include HTx. In Figure 5 the incremental cost-effectiveness is shown, with strategy LVAD as DT as reference. In this figure the WTP threshold is also shown, which is set at €80,000. Strategies that are below this line are considered cost-effective compared to LVAD as DT. HTx is the most cost-effective, often dominating by being less costly and more effective. LVAD as BTT and the Combined strategy are costlier but still cost-effective as their points lie below the WTP threshold.

Figure 6 shows the CEAC curve, with the percentage of the cost-effectiveness on the Y-axis and the WTP threshold on the X-axis. At a WTP of €7,000 or lower, LVAD as DT is most cost-effective, at a WTP between €7,000 and €53,000 HTx is most cost-effective and at a WTP of €53,000 or higher the Combined strategy is most cost-effective. Figure 7, the CEA frontier, clearly shows that LVAD as BTT is being dominated by the other three strategies.

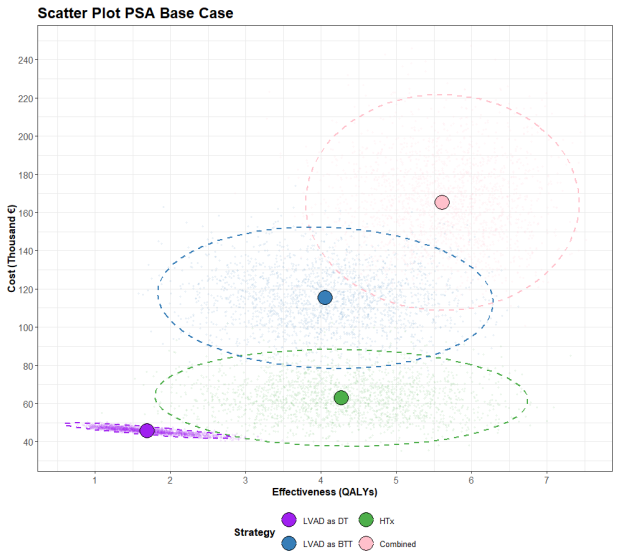


Figure 4: PSA Scatter Plot

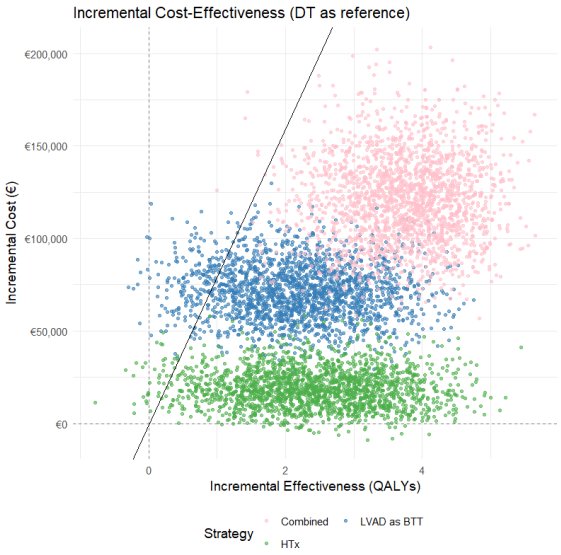


Figure 5: Incremental Cost-Effectiveness

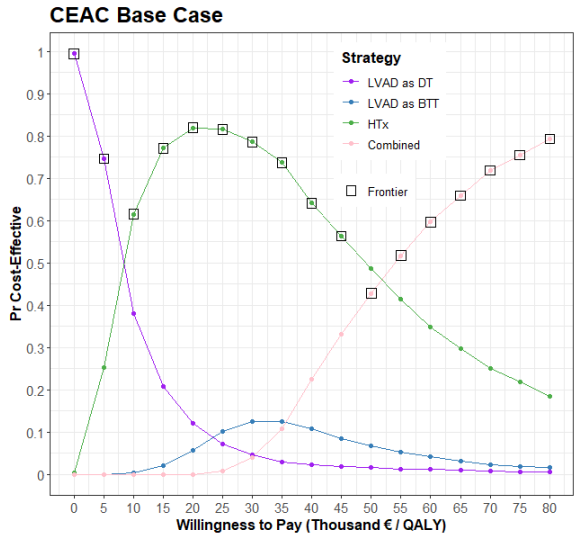


Figure 6: Cost-Effectiveness Acceptability Curve

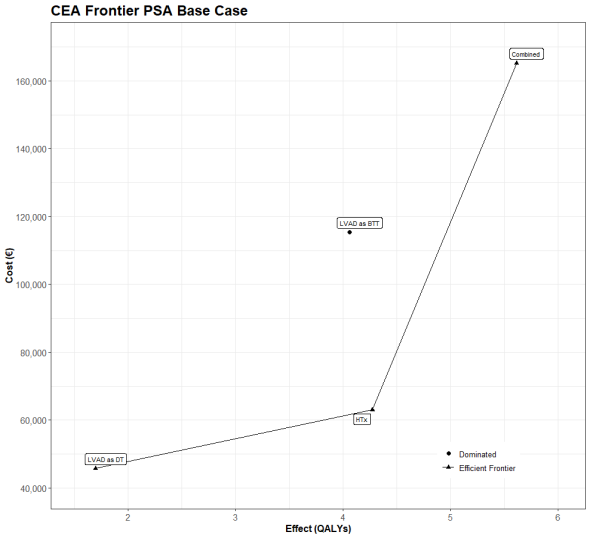


Figure 7: CEA Frontier PSA

### 4.4.2 One-Way Sensitivity Analysis

Figure 8, 9 and 10 show the tornado plots after performing the OWSA, for each strategy compared to the reference strategy LVAD as DT. The vertical axis is based on the NMB of the reference strategy minus the NMB of the comparator strategy. The parameters with the greatest influence (most uncertainty) on the model are positioned at the top of the plot, while the least influential (least uncertainty) are at the bottom. Longer bars indicate a larger impact of uncertainty on the cost-effectiveness comparison. Bars extending to the left indicate that changes in that parameter make LVAD as DT more cost-effective than the comparator, while bars extending to the right suggest that the comparator strategy becomes more cost-effective.

From Figure 8, 9 and 10 it is evident that the transition probabilities for the PM health state to LVAD as BTT and HTx are the most influential parameters to the model. Additionally, changes in the costs of LVAD as BTT and HTx, as well as the utility of HTx, significantly impact the model's outcomes. These parameters are at the top of the graph in all three tornado plots. Some bars in the tornado plots, such as those for the transitions from PM to BTT and PM to HTx, only extend to the left, corresponding to the low value of the parameter (light grey bars). This indicates that the model is only sensitive to the low value. In this case, a lower transition probability makes LVAD as DT more cost-effective than its comparator. In contrast, a dark grey bar that only extends to the right means that the model is only sensitive to the high value of that parameter.

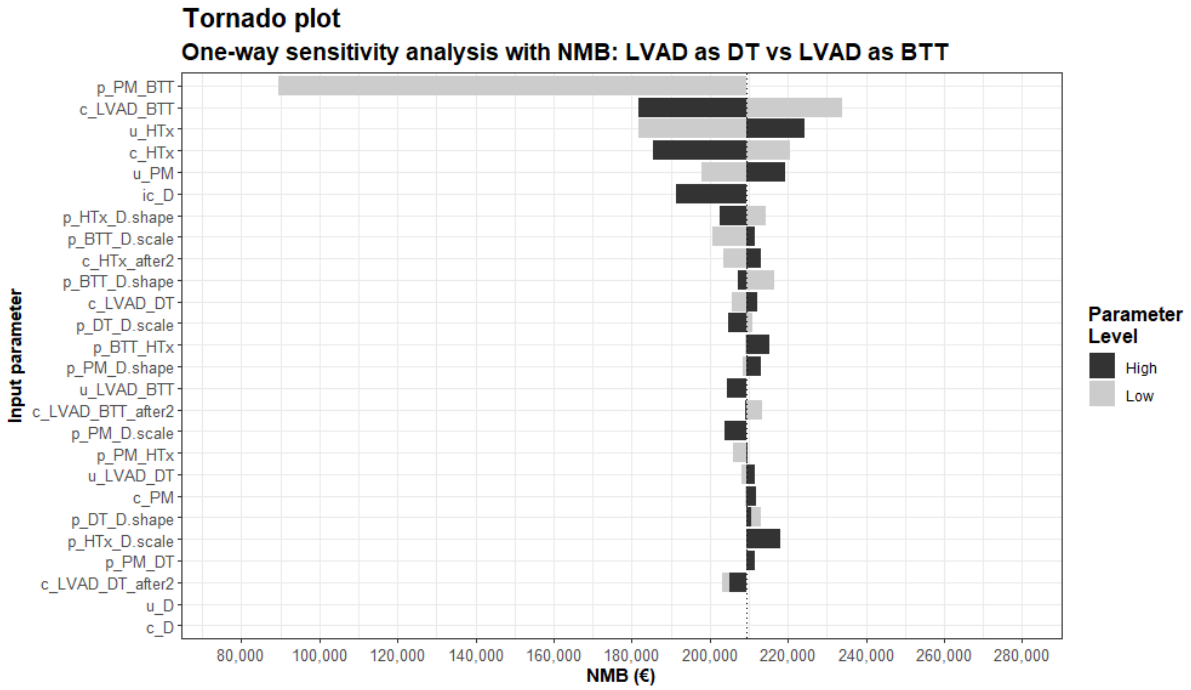


Figure 8: Tornado plot: LVAD as DT vs LVAD as BTT

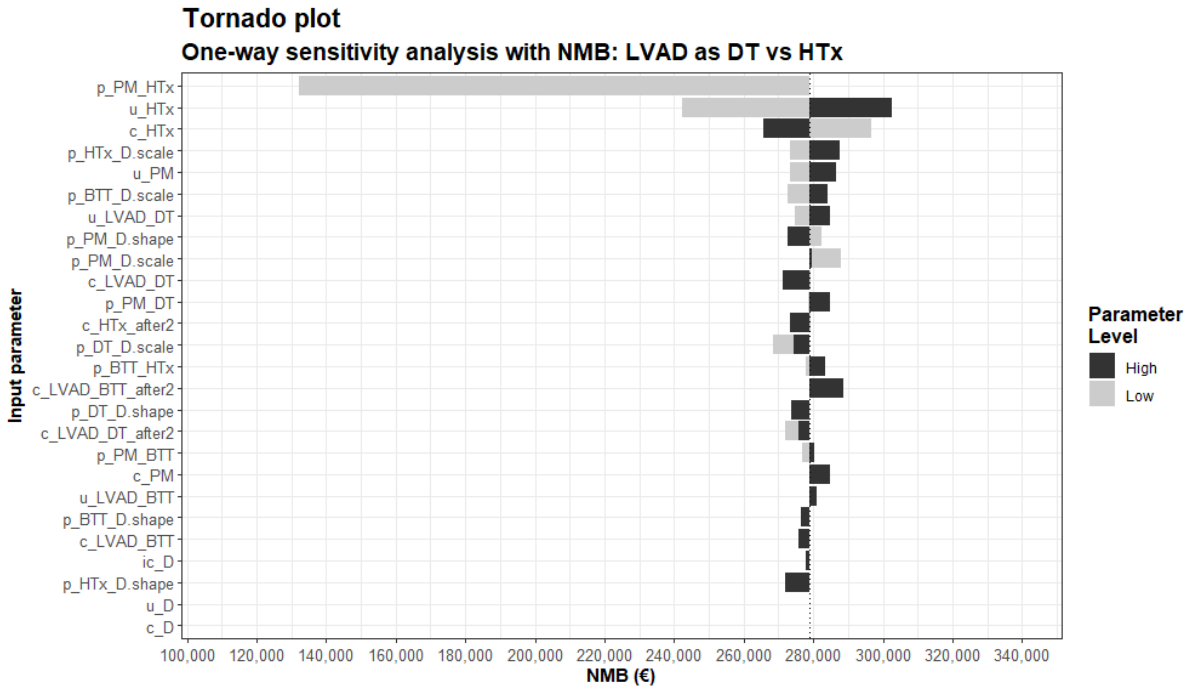


Figure 9: Tornado plot: LVAD as DT vs HTx

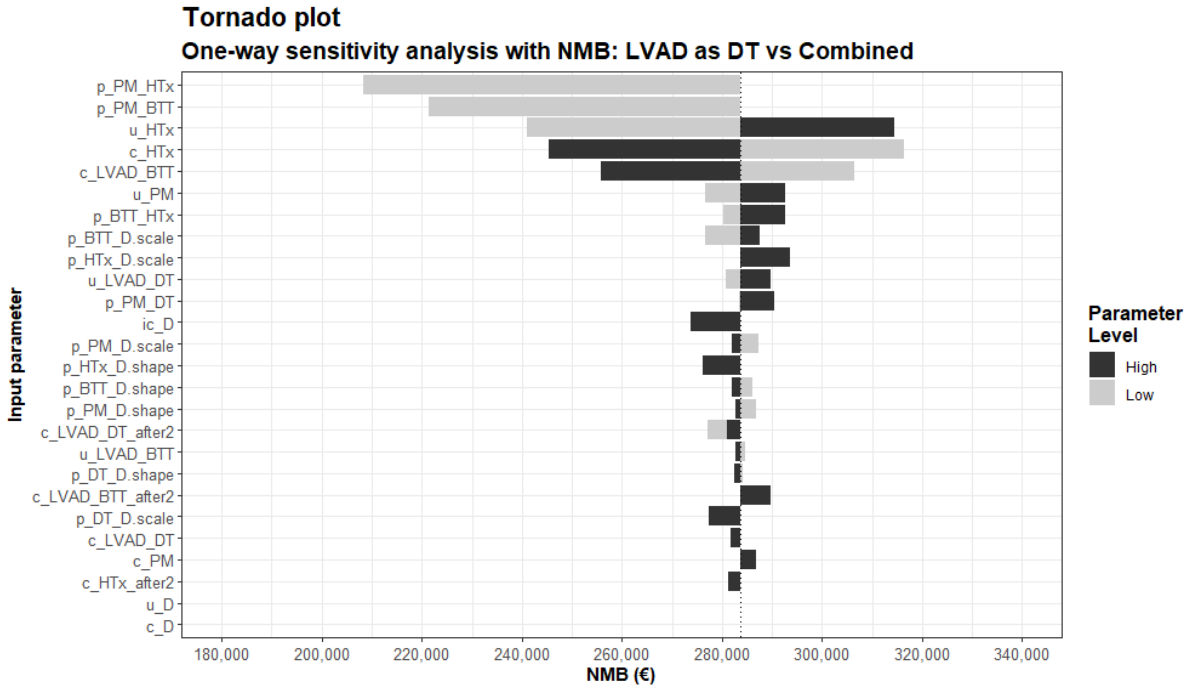


Figure 10: Tornado plot: LVAD as DT vs Combined

## *4.5 Scenario analyses*

### 4.5.1 Scenario 1: Donor heart scarcity

As can be seen in Table 6 and in the CEA frontier in Figure 11, HTx becomes the strategy with the lowest cost in this scenario. HTx now dominates LVAD as DT, which is why no ICER has been calculated.

Next to that, costs of the Combined strategy and LVAD as BTT decreased, which is also noticeable in the incremental cost-effectiveness plane of Figure 12. The QALYs and life-years for the strategies with HTx included have also decreased slightly in comparison to the base case.

| **Strategy** | **Cost (€)** | **Effect (QALYs)** | **Effect (life-years)** | **Incremental cost (€)** | **Incremental effect (QALYs)** | **ICER (€/QALY)** |
|---|---|---|---|---|---|---|
| LVAD as DT | 45,767.97 | 1.69 | 2.39 | NA | NA | NA |
| HTx | 42,664.31 | 2.75 | 3.61 | -3,103.66 | 1.05 | Dominates |
| LVAD as BTT | 107,232.23 | 3.77 | 4.81 | 61,464.26 | 2.08 | 29,607.48 |
| Combined | 136,201.74 | 4.62 | 5.78 | 90,433.77 | 2.92 | 30,925.36 |

Table 6: ICER PSA Scenario 1 (LVAD as DT as reference strategy)

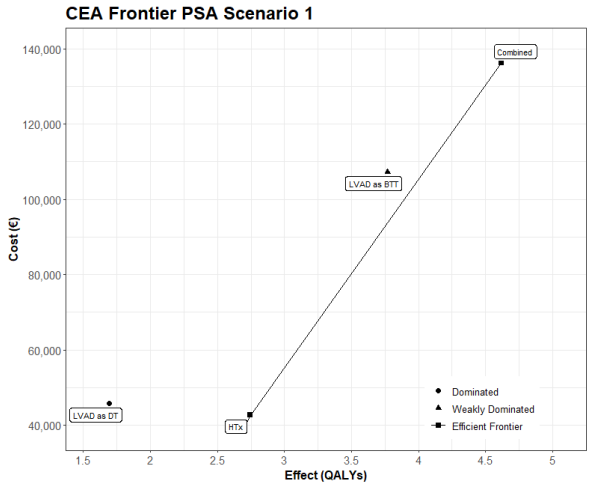


Figure 11: CEA Frontier Scenario 1

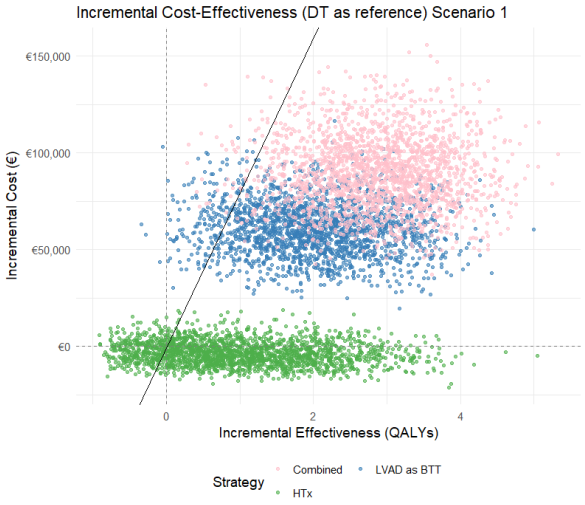


Figure 12: Incremental Cost-Effectiveness Scenario 1

### 4.5.2 Scenario 2: Decreased LVAD costs

Figures 13 and 14 present the CEA frontier and the incremental cost-effectiveness plane for Scenario 2. This scenario shows a decrease in the costs for the LVAD strategies, while their QALYs remained the same, which is shown in Table 7. Therefore the ICER for DT, BTT, and Combined strategy decreased. The CEA frontier in Figure 13 shows that LVAD as BTT is still being dominated. The incremental cost-effectiveness plot in Figure 14 shows a slight upward shift in incremental costs for BTT, HTx, and Combined. Despite HTx's absolute costs and QALYs remaining unchanged, its ICER increased due to the lower cost of the reference strategy.

| Strategy | Cost (€) | Effect (QALYs) | Effect (life-years) | Incremental cost (€) | Incremental effect (QALYs) | ICER (€/QALY) |
|---|---|---|---|---|---|---|
| LVAD as DT | 32,401.92 | 1.70 | 2.39 | NA | NA | NA |
| HTx | 62,971.66 | 4.27 | 5.35 | 30,569.74 | 2.57 | 11,875.86 |
| Combined | 142,246.42 | 5.61 | 6.90 | 109,844.50 | 3.91 | 27,668.64 |
| LVAD as BTT | 92,320.11 | 4.06 | 5.12 | 59,918.19 | 2.36 | 25,391.69 |

Table 7: ICER PSA Scenario 2 (LVAD as DT as reference strategy)

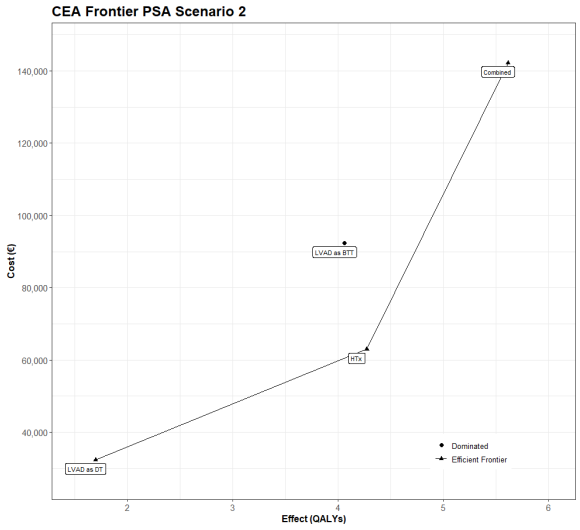


Figure 13: CEA Frontier Scenario 2

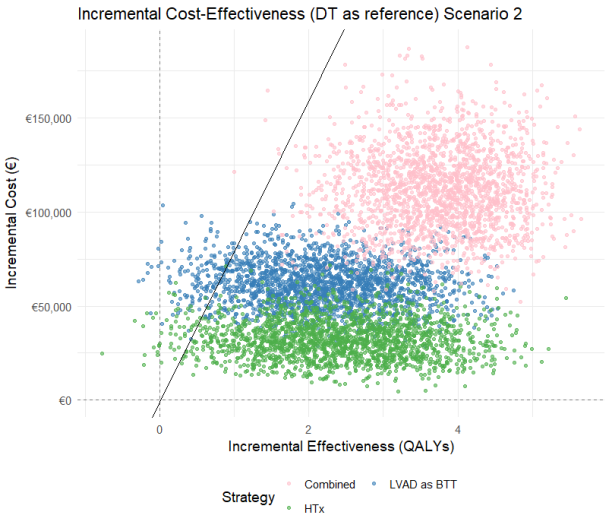


Figure 14: Incremental Cost-Effectiveness Scenario 2

# 5 Discussion

## *5.1 Key findings*

In the CEA, the deterministic and probabilistic sensitivity analyses indicate that DT is not cost-effective at a WTP of €80,000. While its costs are low, the QALYs are also low. This may be because DT patients generally have lower survival rates compared to BTT and HTx patients, partly due to being less physically stable at the time of LVAD implantation. These lower survival rate keeps the associated costs low but limits its overall effectiveness.

HTx comes out as the most cost-effective option, offering higher QALYs at reasonable costs. While BTT and the Combined strategy achieve higher QALYs than DT, their significantly higher costs make them less cost-effective. The Combined strategy's high costs are largely due to the double intervention it requires: first an LVAD implantation, followed by a heart transplant. Nevertheless, due to the high QALYs this strategy achieves, the ICER is nearly the same as for the LVAD as BTT strategy. Therefore these strategies are comparable in terms of cost-effectiveness.

The results of the OWSA provide valuable insights into the key factors influencing the cost-effectiveness of the strategies. From the tornado plot, it is evident that the probabilities for transitioning from PM to HTx and from PM to BTT, along with the costs and utility associated with HTx and the cost of LVAD as BTT, are the most influential parameters. A lower probability of transitioning from PM to LVAD as BTT or HTx, a lower utility for HTx, and higher costs for LVAD as BTT or HTx all increase the cost-effectiveness of LVAD as DT. Interestingly, the most influential parameters are related to the LVAD as BTT and HTx health states. In contrast, changing parameters related to LVAD as DT have less

influence on the model. This suggests that if the goal is to alter the cost-effectiveness of the LVAD as DT strategy, adjustments to the parameters affecting the LVAD as BTT or HTx strategies would likely have a greater effect. In clinical practice, this means that reducing the number of patients receiving LVAD as BTT, whether due to stricter selection criteria or changes in treatment guidelines, could make LVAD as DT more cost-effective. This is because fewer patients getting an LVAD as BTT would lead to fewer costly interventions, altering the overall cost-effectiveness balance in favor of DT. Similarly, policies that increase the costs of BTT or HTx, such as higher hospitalization costs or increased transplant-related costs, could also indirectly make DT more favorable.

The scenario analysis in which the transition probabilities to HTx were reduced highlights the impact of donor heart scarcity on cost-effectiveness outcomes. As shown in the results, HTx has now become the least costly strategy, leading to dominance over LVAD as DT. This means that HTx is both less expensive and more effective than LVAD as DT in this scenario, making LVAD as DT a strictly inferior option when donor scarcity is considered. Additionally, both the Combined strategy and LVAD as BTT have lower total costs in comparison to the base case. This cost reduction is likely due to the prolonged time patients spend in earlier health states, PM or LVAD as BTT, rather than moving to HTx. However, this cost-saving effect comes at the expense of a slight decrease in QALYs and life-years across strategies involving HTx. HTx has the best survival and quality of life in comparison to the other strategies, so less transitions to this state leads to decreased QALYs and life-years. Importantly, the cost-effectiveness of LVAD as DT becomes worse in this scenario. In the base case, LVAD as DT was already less effective than HTx, but in this scenario, it also becomes more expensive relative to HTx. Since HTx dominates LVAD as DT, this suggests that in a setting where donor hearts are scarce, LVAD as DT is not a cost-effective option. This result is counterintuitive because, in clinical practice, donor heart scarcity could indicate an increase in patients receiving LVAD as DT. But even though this would be logical in a clinical setting, the results from this scenario analysis show that donor heart scarcity makes LVAD as DT less cost-effective.

The high cost of LVADs remains a key barrier to cost-effectiveness. In Scenario 2, LVAD costs were significantly reduced to assess their impact on outcomes. The results show that lowering LVAD costs improved the cost-effectiveness of LVAD-based strategies (DT, BTT, and Combined) by reducing their ICER. Since effectiveness in terms of QALYs and life years remained unchanged, the decrease in costs directly translated into better cost-effectiveness for these strategies. However, despite no changes in absolute costs or QALYs for HTx, its ICER increased due to the lower cost of the reference strategy (DT), which raised its relative incremental cost. This explains the noticeable upward shift of the HTx strategy in the incremental cost-effectiveness plane. These findings suggest that reducing LVAD costs could make LVAD-based strategies more competitive alternatives to HTx, potentially influencing future healthcare decision-making. For LVAD as DT specifically, significant cost reductions could improve its cost-effectiveness, but achieving true cost-effectiveness would also require an increase in QALYs.

### *5.2 Strengths of the study*

This CEA has several key strengths that enhance its reliability. First, to the author's knowledge, this is the first CEA in the Netherlands to specifically compare the use of LVADs as DT with usual care for patients with ESHF. While other studies have explored the use of LVADs in the Netherlands, such as the study by Neyt et al., these have primarily compared LVADs to optimal medical therapy rather than to usual care [23]. By addressing this gap, this CEA provides valuable insights into the feasibility of using LVADs as a long-term treatment option, offering a more direct comparison to current usual care.

Second, this CEA includes a detailed analysis of extrapolated survival curves. Since the KM curves from the literature did not extend to the required time horizon, survival curves were generated, fitted with appropriate distributions, and extrapolated. This ensured that long-term survival estimates were more accurately represented, allowing the model to better estimate real-life patient outcomes and provide a more reliable assessment of cost-effectiveness over time.

Third, the analysis includes a detailed sensitivity assessment to test how robust the model is. A PSA was performed to account for uncertainty in the input parameters, giving a better idea of how likely each strategy is to be cost-effective. Consequently, an OWSA was performed to assess the impact of uncertainty on all input parameters. On top of that, two scenario analyses were done to see how changes

in key parameters, like transition probabilities or the cost of LVADs, affect the outcomes. These extra steps help to show how reliable the results are under different conditions.

Finally, four different strategies were included in the analysis. This wide range of options gives a full view of the situation, instead of focusing on just two strategies. It helps to compare all the possible approaches in the right context and understand their strengths and weaknesses.

### *5.3 Comparison to other studies*

Within the field of LVADs, multiple other CEA studies have been performed. Within the Dutch context, Neyt et. al performed a CEA in 2013 in which they compared LVADs as DT to optimal medical therapy, which has been previously mentioned [23]. This study concluded that LVAD as DT has an ICER of €107,600 per QALY in comparison with optimal medical therapy, which is above the WTP threshold of €80,000. There is a better survival and quality of life after LVAD treatment, but the implantation costs and repeat hospitalization costs remain high. Although a direct comparison to this CEA is not possible due to differences in the study population, model input, and comparator arms, some insights can still be drawn. Neyt et al. also concluded that while LVAD therapies are effective, their costs are too high to be truly cost-effective.

Another study, by Sutcliffe et al. in 2013, explored the cost-effectiveness of LVAD as BTT to optimal medical therapy, and subsequently the cost-effectiveness of LVAD as BTT to LVAD as DT in the United Kingdom (UK) [53]. In general, the ICER of LVAD as BTT compared to optimal medical therapy is higher than the WTP threshold in the UK. One interesting finding they highlight is that LVAD as DT has lower costs and lower QALYs than LVAD as BTT, which is in line with the findings of this study.

Lastly, a more recent CEA by Schueler et al. (2021) examined the cost-effectiveness of LVADs as DT in the UK [22]. The study found that, compared to optimal medical therapy, LVADs as DT are cost-effective under the UK's WTP threshold of £50,000 per QALY. LVADs as DT had higher costs compared to the optimal medical therapy group but provided greater survival and improved quality of life, leading to a deterministic ICER of £46,207 per QALY. In contrast to the study by Neyt et al., Schueler et al. found that LVAD as DT can be cost-effective compared to optimal medical therapy, suggesting its potential cost-effectiveness, at least within the UK context.

### *5.4 Limitations of the study*

The model used in this analysis is a simplified version of reality and does not fully capture the uncertainties present in real-world situations. This simplified version is based on some assumptions. The majority of the assumptions had to be made because of the lack of available data. One key assumption concerns the transition probability from the PM state to death, where a hazard ratio (HR) of 0.4 was applied. The reason for this was because no other data was available about the transition from PM to death. The HR was used to counteract the pessimistic nature of the KM curve which was taken from an RCT by Rose et al. [36]. The choice for the hazard ratio of 0.4 was based upon the results of the cohort traces, in which the goal was to reflect the 1-year mortality for PM patients, which lies approximately between 25% and 50% [36, 1]. With a hazard rate of 0.4, the cohort traces showed that after 12 months, approximately 35% of individuals were in the death state, aligning more closely with real-world expectations compared to the scenario without the hazard rate.

Another limitation is that the total costs and utilities for each health state were estimated using data from the literature and registries, which may not always reflect real-world scenarios accurately. While the goal was to use data from the Netherlands, some sources, such as the INTERMACS registry, were from outside the country, specifically North America. Differences in healthcare systems, patient populations, and treatment protocols may affect the applicability of these data to the Dutch context. Additionally, the INTERMACS registry introduces potential bias, as it only includes patients who survived LVAD implantation, excluding those who did not survive the procedure. This exclusion may lead to an overestimation of both survival rates and the overall effectiveness of LVAD treatments in this CEA, as the survival curves and utility values for the LVAD states were based on INTERMACS data.

In addition to survival and utility estimates, cost parameters also required simplifications due to data

limitations. Assumptions were made regarding the length of hospital stays, the duration of surgeries, and the frequency of visits to the thrombosis service. Furthermore, the choice to make a distinction between the first month and the subsequent months was an assumption and is a simpler version of reality. The model also assumes that the costs for each patient per month are the same, because it is a cohort model. But in healthcare, it is known that costs are very dependent on the specific needs of a patient.

Beyond cost-related assumptions, the model also simplifies how patients progress through different health states. One such simplification is the omission of the bridge to candidacy (BTC) state. In clinical practice, some patients who are initially ineligible for heart transplantation may later become eligible if their condition improves while they are on an LVAD [61]. For simplicity, the BTC health state was not included, although it is a relevant stage in the real-world patient pathway. This could not be incorporated into the cohort model, as it is designed to use aggregated data rather than individual patient-level data. Additionally, due to the structure of the cohort model, distinguishing between intentional and unintentional DT was not feasible. Moreover, data for these subgroups was unavailable.

Similarly, another simplification concerns the transition from LVAD as BTT to HTx. Specifically, the model does not account for the necessary recovery period following LVAD implantation before patients can safely undergo a heart transplant. In the current model, patients are able to transition directly to HTx after the cycle in which they receive their LVAD, which does not accurately reflect clinical practice. In reality, transplanting patients too soon, within one month after LVAD implantation, can lead to poor outcomes due to insufficient recovery [62]. While the optimal timing for transplantation varies depending on the individual patient's health, recovery, and other factors, it is generally recommended that the window for heart transplant occurs between 3 and 12 months after LVAD implantation [62]. By not considering this recovery period, the model assumes that patients transition to the HTx state too early, which likely results in an overestimation of the number of patients transitioning to HTx.

Overall, these data limitations and simplifications have a small effect on the model's accuracy and its reflection of real-world scenarios. However, it is inevitable to make assumptions when using these kind of models. These assumptions have probably not have such a great impact that the order of the strategies in terms of cost-effectiveness changes. The assumptions are something to keep in mind, but do not make the results invalid.

### *5.5 Future research*

Based on the outcomes of this study, recommendations for future research can be made. Future studies could explore patient-level models instead of a cohort model to better capture individual variations in disease progression and treatment response. In patient-level models, each patient is treated as an individual, while in cohort models aggregate data is used which oversimplifies the outcome. Ultimately, a patient-level model could provide a more detailed and personalized assessment of cost-effectiveness of each of the strategies.

Another possible direction is to broaden the comparison made in the research question. Currently, this CEA focuses on comparing DT as an alternative to BTT and HTx, but it would be valuable to include DT as part of the overall treatment strategy. So, the comparison would be LVAD as DT in combination with usual care, compared against usual care right now (Combined strategy). This would require a restructured model that incorporates new health states, such as splitting the PM state into two states: PM on the waiting list and PM not on the waiting list. The restructured model could also incorporate a BTC state, as previously mentioned. This state represents patients with an LVAD who are not on the heart transplant waiting list due to not meeting the selection criteria, but who may improve their health status over time and eventually become eligible for a transplant.

This expanded model would require data not just for patients on the HTx waiting list, but also for those who are not on the HTx waiting list and receive DT, potentially broadening the patient population. While this would provide a more real-world representation, it would introduce challenges such as the need for additional data on survival and quality of life for patients that are not on the HTx waiting list and BTC patients. Increased complexity from the additional health states and transitions should

also be considered. However, expanding the model in this way could improve the understanding of the cost-effectiveness of LVAD as DT within the current usual care and offer valuable insights into treatment strategies for a broader patient population.

# 6 Conclusion

In conclusion, this CEA demonstrated that LVAD as DT, when compared to usual care, is not yet cost-effective for ESHF patients in the Netherlands. While the costs associated with LVAD as DT are relatively low, the QALYs remain similarly low. This is likely due to the fact that survival for LVAD as DT is lower than that for LVAD as BTT and HTx, and because fewer ESHF patients are eligible for LVAD as DT. OWSA highlighted that the most influential parameters on cost-effectiveness are related to the LVAD as BTT and HTx health states, suggesting that to effectively alter the cost-effectiveness of the LVAD as DT strategy, adjustments to the BTT or HTx parameters would be more impactful than changing those specific to LVAD as DT. Scenario analyses revealed that limiting access to heart transplants due to donor organ scarcity does not improve the cost-effectiveness of LVAD as DT. However, lowering the costs of the LVAD device could make LVAD as DT more cost-effective in comparison to HTx. Ultimately, for LVAD as DT to become truly cost-effective, improvements in both survival and quality of life are essential, particularly in comparison to the other strategies.

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# Appendix A: AI statement

"During the preparation of this work I used ChatGPT in order to help during the programming in R and for language checks. After using this tool, I reviewed and edited the content as needed and take full responsibility for the content of the work."

# Appendix B: Medication

## *B.1 Medication ESHF patients in PM health state*

Patients with ESHF are prescribed medications. In the 'Farmaceutisch Kompas' and NHG guidelines chronic heart failure is given an overview of the steps to take to medicate these patients [42, 40]. In table 6, these steps are shown, with the associated costs. For each step, an assumption has been made about which medication has been used. Total costs should reflect an estimate of the average cost per patient.

| **Steps** | **Type of medication** | **Costs (€, per patient, per month)** |
|---|---|---|
| 1: Non-pharmaceutical management | NA | NA |
| 2a: Lisdiureticum | Bumetadine | 2.40 |
| 2b: ACE inhibitors | Cibacen | 19.20 |
| 3: -blocker | Bisoprolol | 25.50 |
| 4: Aldosterone receptor antagonists | Spironolacton | 7.20 |
| 5: Secondary care | Digoxine | 16.80 |
| **Total** | | 71.10 |

Table 8: Medication ESHF patients

## *B.2 Medication HTx patients*

Heart transplant patients need to take immunosuppressive medication. In table 7, the type of drugs that patients need to take are shown, with their costs per month. The type of drugs are retrieved from the article by Söderlund et al., and the costs are from 'Farmaceutisch Kompas' [48, 42]. To get an estimation of the average cost, the total costs has been divided by two because of every drug type, patients only get one of the two drugs. So the total amount that has been used in this CEA is €600.

| **Drug type** | **Drug** | **Costs (€, per patient, per month)** |
|---|---|---|
| Calcineurin inhibitors | Tacrolimus | 251.10 |
| | Cyclosporine | 177 |
| Antimetabolites | Mycophenolate mofetil | 129.30 |
| | Azathioprine | 25.80 |
| Mammalian target of rapamycin inhibitors | Everolimus | 328.20 |
| | Sirolimus | 321.90 |
| **Total** | | 1233.30 |

Table 9: Medication HTx patients

# Appendix C: Cost input

Table 8 shows the separate elements of the cost input for in the model per health state.

| | **PM (all months)** | **LVAD DT (month 1)** | **LVAD DT (month 2+)** | **LVAD BTT (month 1)** | **LVAD BTT (month 2+)** | **HTx (month 1)** | **HTx (month 2+)** |
|---|---|---|---|---|---|---|---|
| **Drugs** | 75 | - | - | - | - | - | 600 |
| **Diagnostics** | - | 1994.59 | - | 1994.59 | - | 25949.77 | - |
| **Device** | - | 93955.78 | - | 93955.78 | - | - | - |
| **Surgery** | - | 7946.40 | - | 7946.40 | - | 52280.43 | - |
| **Hospitalization, intensive care** | - | 5921.70 | - | 5921.70 | - | 2842.22 | - |
| **Hospitalization, nursing ward** | - | 27269.58 | - | 27269.58 | - | - | - |
| **Support during HTx trajectory** | - | - | - | - | - | 39490.23 | - |
| **Hospitalization, complications/readmission** | 699.22 | - | 150.96 | - | 150.96 | - | - |
| **Check up hospital** | - | - | 43.43 | - | 65.15 | - | - |
| **Thrombosis service** | - | - | 68.76 | - | 68.76 | - | - |
| **Total** | 774.22 | 137088.05 | 263.15 | 137088.05 | 284.87 | 120562.65 | 600 |

Table 10: Cost input, per patient, per month, in €

# Appendix D: Survival curves

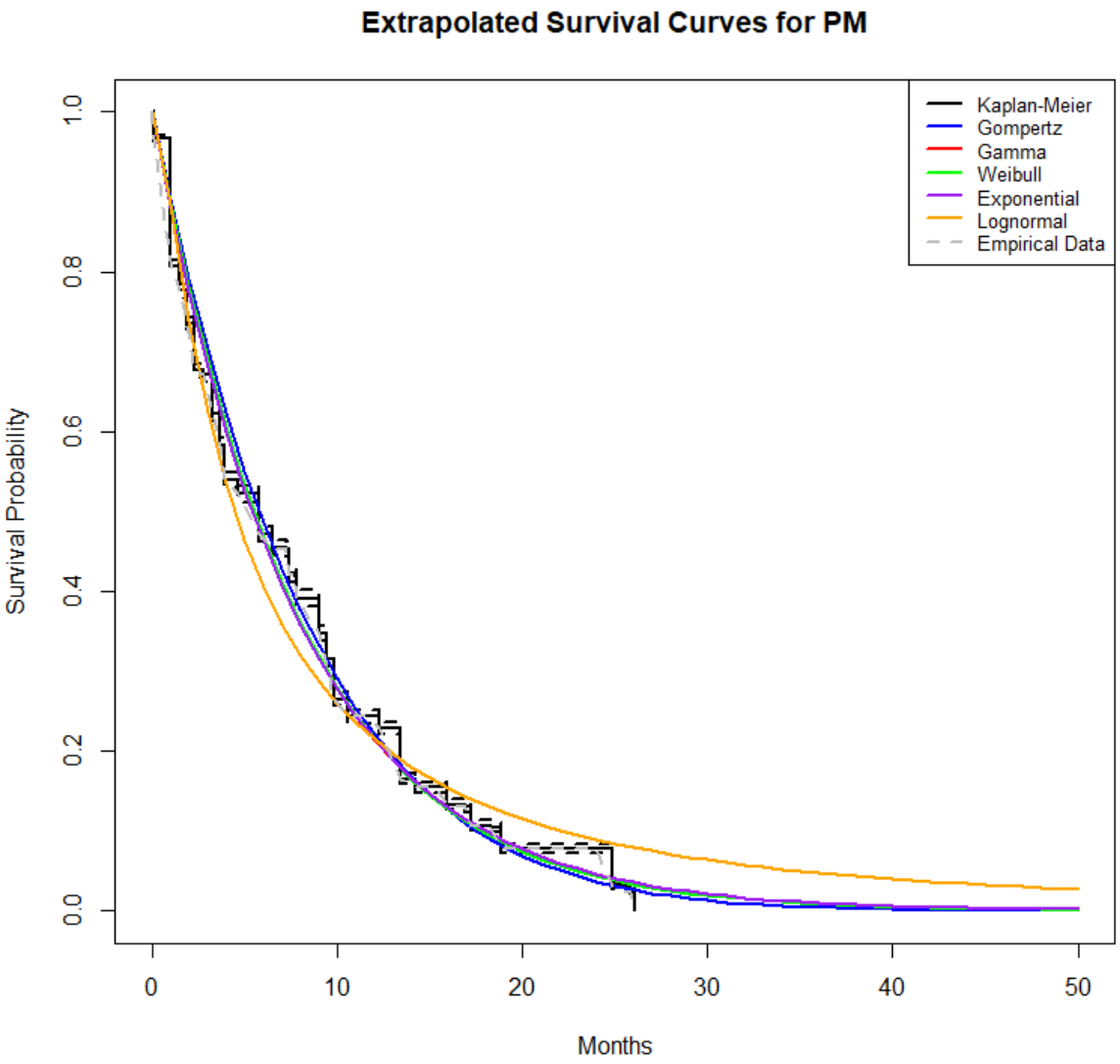


Figure 15: Extrapolated survival curves - PM

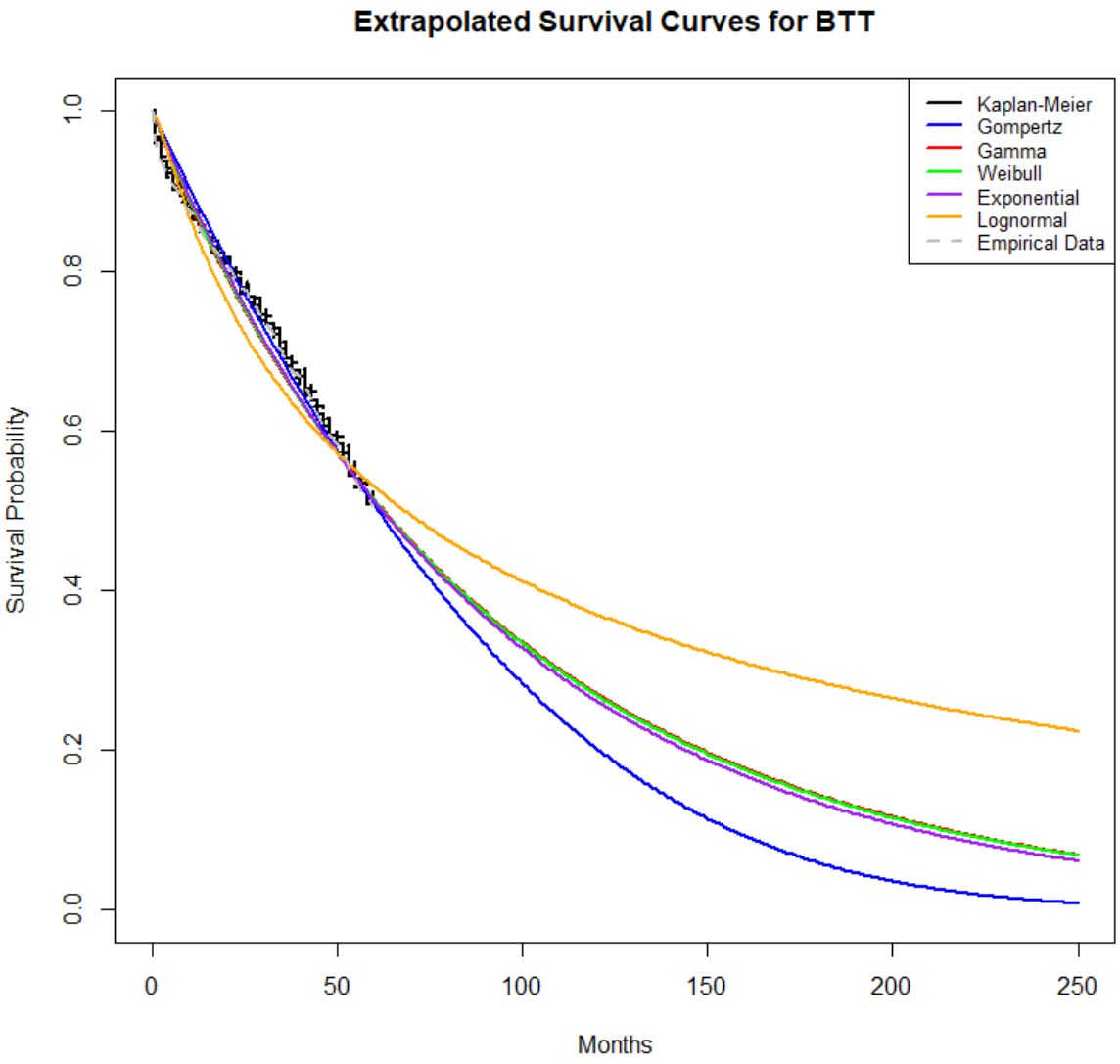


Figure 16: Extrapolated survival curves - LVAD as DT

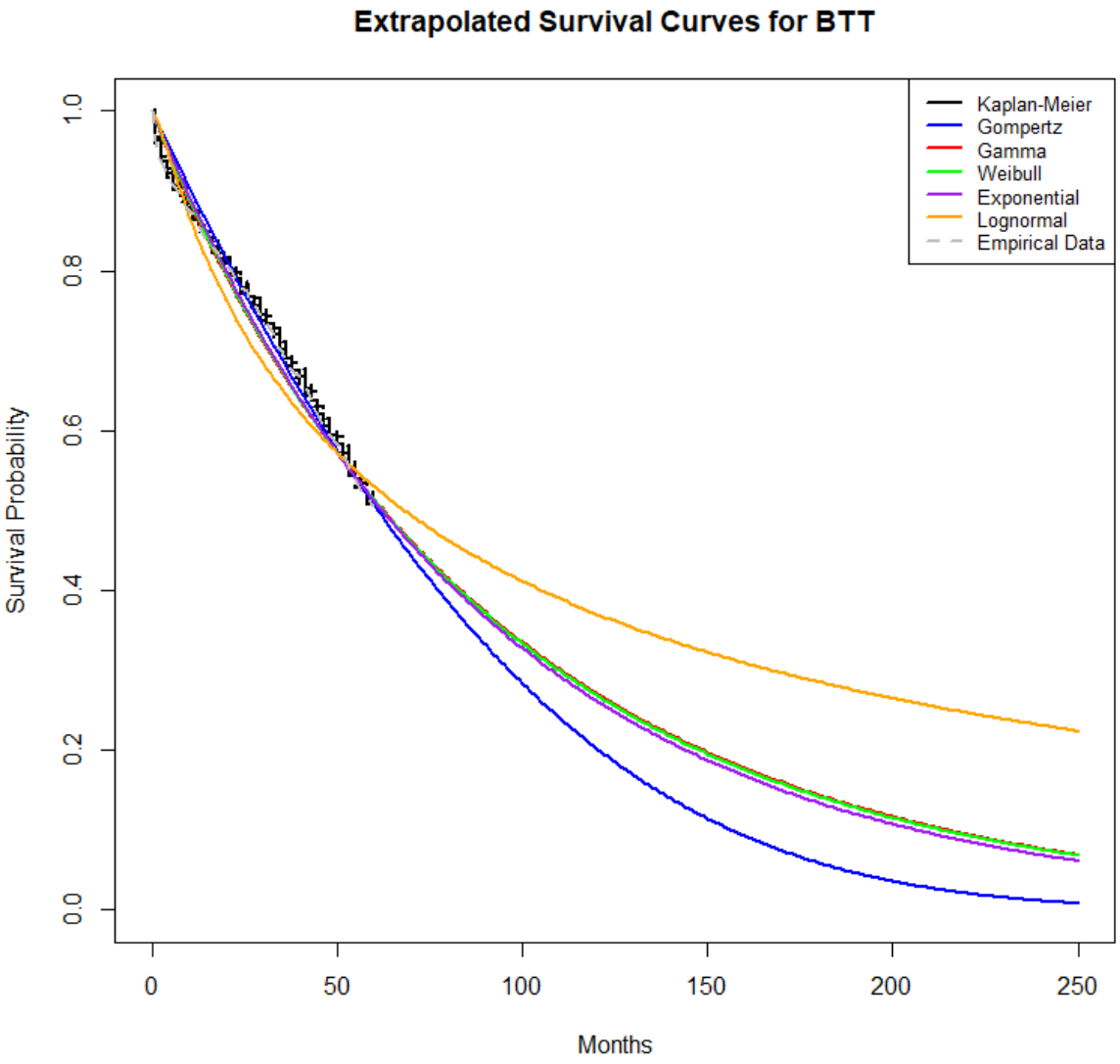


Figure 17: Extrapolated survival curves - LVAD as BTT

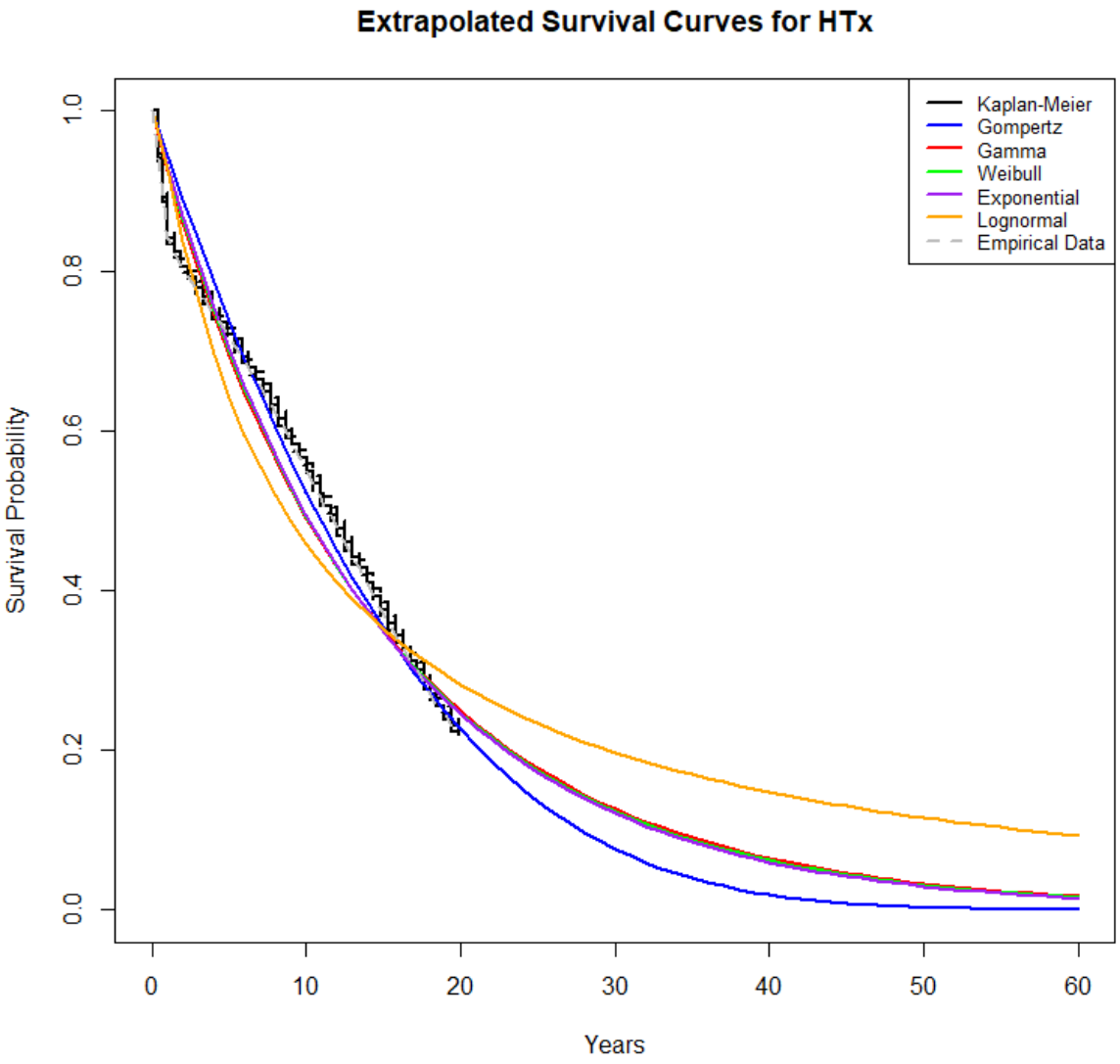


Figure 18: Extrapolated survival curves - HTx