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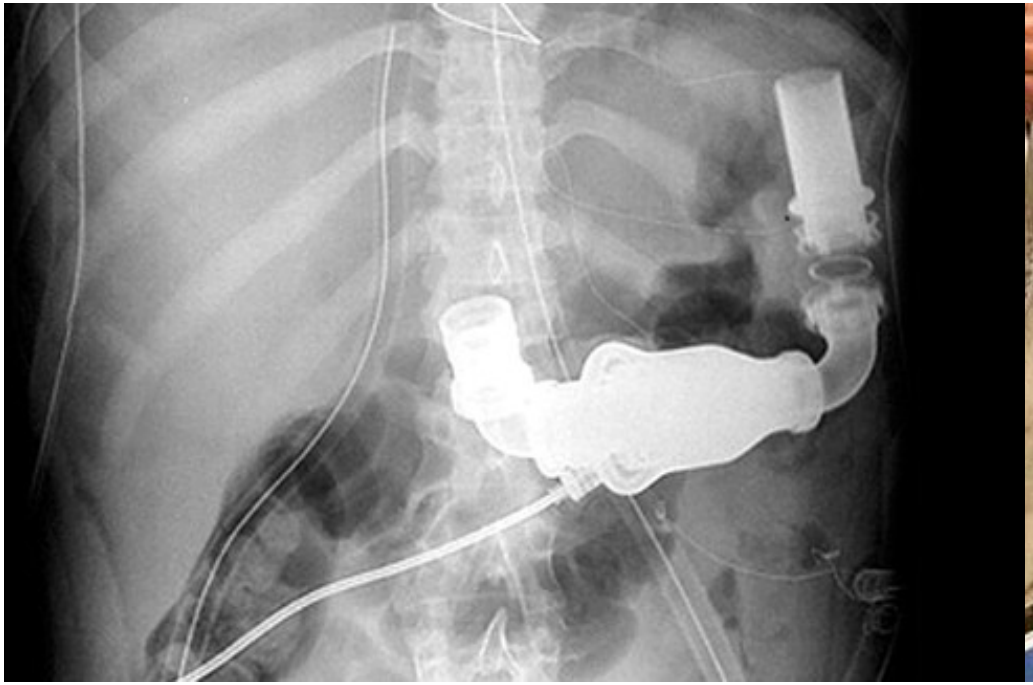
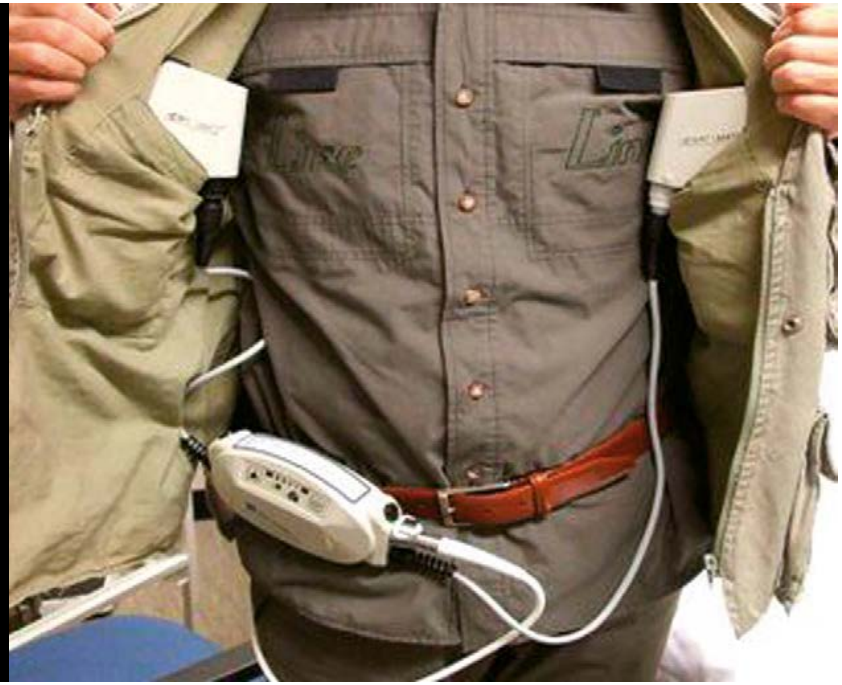
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

LEFT VENTRICULAR ASSIST DEVICES IN THE TREATMENT OF END-STAGE HEART FAILURE





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HEALTH TECHNOLOGY ASSESSMENT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AG&AI	Actuarieel Genootschap & Actuarieel Instituut
BACTS	Belgian Association for Cardio-Thoracic Surgery
BTC	bridge to candidacy
BTD	bridge to decision
BTT	bridge to transplantation
CCP	cardiac care program
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CF LVAD	continuous-flow LVAD
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
CRD	Centre for Reviews and Dissemination
CUA	cost-utility analysis
DT	destination therapy
EPS	permanent sample (Échantillon permanent – Permanente steekproef)
EQ-5D	EuroQol-5 Dimensions
EUROMACS	European Registry for Patients with Mechanical Circulatory Support
FDA	Food and Drug Administration
HF	heart failure
HM-II	HeartMate II
HRQoL	health-related quality of life
HTX	heart transplantation
IABP	intra-aortic balloon pump

IC	incremental costs
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDMT	inotrope-dependent medical therapy
IE	incremental effects
IMA-AIM	Intermutualistisch Agentschap – Agence Intermutualiste
INAHTA	International Network of Agencies for Health Technology Assessment
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
LVAD	left ventricular assist devices
LVEF	left ventricular ejection fraction
LYG	life years gained
MCS	mechanical circulatory support
MID	minimally important difference
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MSOF	multisystem organ failure
NHLBI	National Heart, Lung and Blood Institute
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance (RIZIV — INAMI)
NYHA	New York Heart Association classification
OHT	orthotopic heart transplantation

OMT	optimal medical therapy
PBU	Power base unit
PF LVAD	Pulsatile-flow LVAD
PM	Pacemaker
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QoL	quality of life
RCTs	randomized controlled trials
RHM – MZH	résumé hospitalier minimum – minimale ziekenhuisgegevens
RIZIV – INAMI	Institut national d'assurance maladie-invalidité – Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (NIHDI)
RVAD	right ventricular assist device
SHA – AZV	séjours hospitaliers anonymes – anonieme ziekenhuisverblijven
TCT	Technische Cel – Cellule Technique
UMC	University Medical Center
VAS	visual analogue scale
WTP	Willingness to pay

1 BACKGROUND

1.1 Heart failure

Heart failure (HF) is a complex syndrome that can result from any cardiac disorder that impairs the ability of the heart to function as a pump. The most common underlying conditions are coronary artery disease, arterial hypertension, malfunctions of heart valves and primary cardiac muscle diseases. HF is clinically characterised by breathlessness and fatigue and signs such as fluid retention. Symptoms vary considerably and are traditionally expressed on a scale of I to IV in the New York Heart Association classification (NYHA). A NYHA class I patient is not affected during normal daily activities. Class II patients find that ordinary daily activities cause them problems. Class III patients are affected by the least effort and class IV patients are even affected when at rest.[1]

HF is a common disease, especially in the elderly. The yearly incidence of HF in the Belgian adult population was estimated to be 194 patients per 100 000 inhabitants (95% confidence interval (CI): 172-218). At diagnosis, the median age of patients with HF was 79 years: 82 years for women and 76 years for men.[2] HF is the most frequent cause of hospitalisation among people older than 65 years of age. The prognosis of HF is worse than that of most cancers. Half of patients in whom the underlying disease cannot be corrected will die within 4 years; in patients with severe HF more than 50% will die within a year.[3]

HF can present itself both acutely and chronically. Acute HF can occur de novo in a patient without previously known cardiac dysfunction or as an acute decompensation of chronic HF.[1] Acute HF in its typical presentation is manifested as pulmonary oedema. The most severe cases present as cardiogenic shock representing a harbinger of imminent death.

The management of HF is aimed at a reduction of symptoms and an improvement of survival. Next to dietary measures, standard treatment includes drug therapy: diuretics, an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, a beta-blocker and an aldosterone antagonist.[4] In selected patients with HF who remain symptomatic despite optimal medical treatment, device therapy with a cardiac resynchronisation pacemaker can be indicated.[1] Selected patients with end stage HF can be considered for cardiac transplantation or a mechanical assist device.

1.2 Heart transplantation

1.2.1 Clinical practice

Patients with end stage HF and persistent signs and symptoms despite optimal medical management, and who have no major co-morbidities can be considered for heart transplantation. Age is not a formal contraindication to transplantation, but increasing age is often associated with other conditions rendering transplantation less effective. Most transplants are performed on patients below the age of 65 years. Transplantation commits the patient to a lifelong programme of monitoring and critical immunosuppression drug treatment.[5]

Although controlled trials comparing heart transplantation with other treatment options for HF have never been conducted, there is consensus that transplantation significantly increases survival, exercise capacity, and quality of life. Data on over 78 000 transplants show that half of the patients survive for more than 10 years.[5]

The scarcity of suitable donor hearts makes it necessary to carefully select potential heart transplant candidates. Selection is based both on the patients' clinical need and on their capacity to benefit. Allocation of donor hearts is based on donor-recipient matching, clinical priority, the need to limit operative cardiac ischaemia time and fairness.[5]

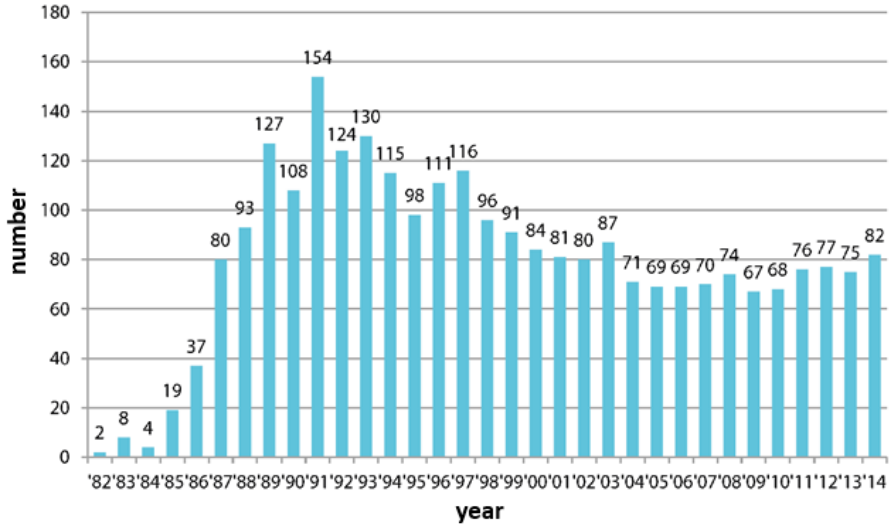
An urgent transplant list has been established, giving priority to patients in need for continuous intravenous inotropic drugs, intra-aortic balloon pump, mechanical temporary support with a short-term device, or patients with a long-term device with device-related complications. Patients on the non-urgent waiting list are allocated hearts when there are no suitably matched patients on the urgent list. Unfortunately, not all patients listed for transplantation will receive a heart.[5]

1.2.2 Regulatory and organisational issues in Belgium

In 1999, so-called "care programs" ("zorgprogramma's", "programmes de soins") have been installed by the Belgian federal government. They are related to a variety of hospital services such as geriatrics, paediatrics, oncology, reproductive health and cardiology. Further in this text, the latter will be referred to as "cardiac care program (CCP)". Several distinct CCPs have been defined: A, B, P, E, T, and C. Virtually all acute hospitals can have a CCP "A" certification allowing for clinical cardiology without

limitations as far as non-invasive diagnosis or non-invasive treatment is concerned. To obtain a higher level of CCP a hospital needs to adhere to a number of qualitative and quantitative criteria. Hospitals with a CCP "P" (P=pacemaker) are accredited to provide PM therapy, CCP "T", refers to heart- and lung transplantation, and CCP "C" to congenital heart disease. CCPs "B" and "E" are related to invasive coronary interventions and electrophysiology respectively.[6] At present, there are 7 heart transplant centres in Belgium, located in Antwerp, Brussels (2), Leuven, Gent, Aalst, and Liège. Worldwide there has been a marked decline in the number of transplantations performed over the last 20 years, from a peak in the early 1990s. This has been attributed to a decreasing number of patients dying from brain stem death coupled with increasing age and comorbidity within the remaining potential organ donors.[5] In Belgium, during the last years around 80 heart transplantations have been performed each year (Figure 1).

Figure 1 – Heart transplantations in Belgium



Source: Eurotransplant (https://www.eurotransplant.org/cms/)

1.2.3 Historical perspective

The shortage of donor hearts has encouraged the development of artificial mechanical devices that can assist or replace the function of the failing heart. These so-called mechanical circulatory support (MCS) devices were used in-hospital as a short-term (days up to weeks) support for patients with acute heart failure caused by temporary conditions such as following open heart surgery. With the development of smaller implantable pumps, patients could be ambulatory and supported on a device for longer periods of time. Durable MCS devices were first introduced as a bridge to transplant (BTT) in patients with rapidly deteriorating heart failure who were on the heart transplant waiting list. With heart transplants in limited supply and additional clinical experience gained, devices were subsequently also implanted as a permanent destination therapy.[7]

The present report focuses on the use of MCS devices used for long-term assist of the left ventricle and are further referred to as left ventricular assist devices (LVAD).

1.2.4 Technology description, patient involvement and self-care

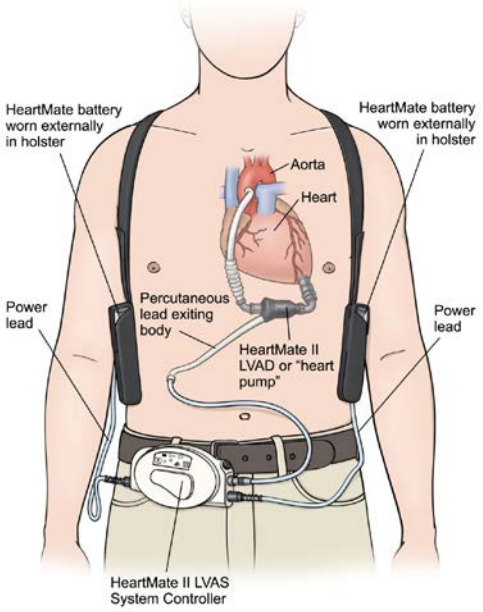
An LVAD is implanted with the patient under general anaesthesia and involves open heart surgery. An inflow pipe towards the pump is inserted into the left ventricle of the heart and an outflow pipe is inserted into the aorta (Figure 2). The LVAD draws blood from the failing left ventricle and pumps it in parallel into the systemic arterial system. A power cable attached to the pump is brought out of the abdominal wall to the outside of the body and attached to a control system and battery (Figure 2).

Patients need to carry this equipment with them at all times. A thorough understanding of the LVAD and system components by the patient and companion is necessary to ensure patient safety in the outpatient setting. The patient should be able to identify and respond appropriately to alarm symbols and audible tones. The device must have an adequate power supply at all times, and patients have to be trained estimating battery charge levels and switching between power sources.[8] Batteries have to be recharged every 8 hours. Replacement of the batteries is needed every 2 years.

Patients must avoid immersion in water. Immobilization of the driveline and aseptic maintenance of the exit site are critical self-care lessons that may

have a direct impact on the risk of infection around the power cable that penetrates the skin.[8] To prevent pump thrombosis, LVAD patients require systemic anticoagulation and/or anti-platelets, although the appropriate levels are subject of discussion.[8]

Figure 2 – Heartmate II continuous-flow pump configuration



Source: https://wikem.org/wiki/Left_Ventricular_Assist_Device_%28LVAD%29;
LVAD: left ventricular assist devices

The first LVADs used pulsatile pumps that mimicked the natural pulsing action of the heart. Newer devices use a rapidly spinning rotor to produce a continuous-flow of blood into the systemic arterial system.[10] Since 2010 continuous-flow pumps account for almost all patients receiving mechanical support implants.[11] Therefore, LVADs that make use of the older pulsatile technology will not be considered in the present report.

1.2.5 Clinical practice

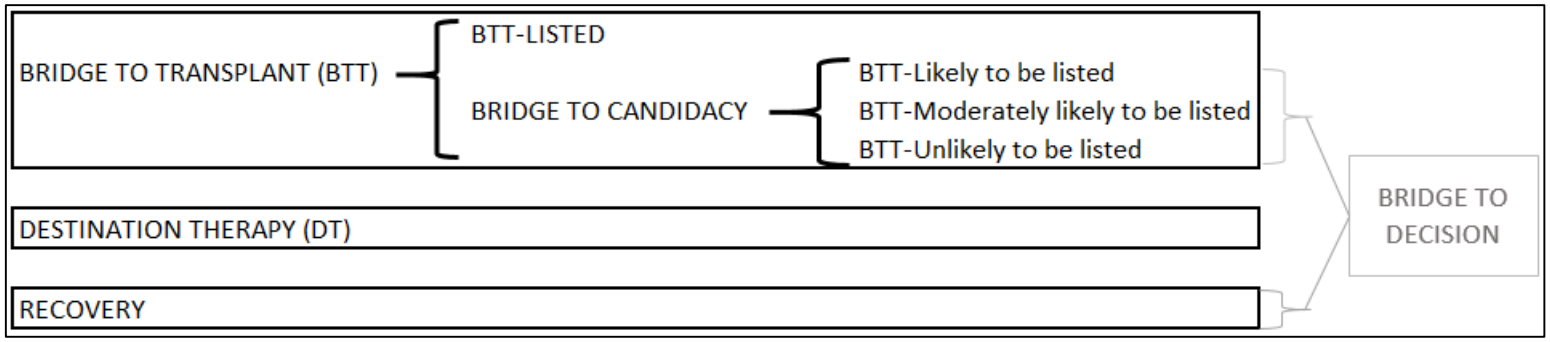
LVADs are used for 3 initial intents: as a bridge to transplantation (BTT), as a permanent destination therapy (DT) or as a bridge to recovery.

1.2.5.1 Bridge to transplant

BTT patients that are considered good candidates for transplantation are put on the waiting list for cardiac transplantation at the same time of the LVAD implantation procedure. Those patients are categorised as BTT-Listed.

In some cases, it is not yet clear at the time of LVAD implantation whether a patient is a good transplantation candidate. He might have been critically ill at the time of emergency device implantation and not been completely evaluated for transplantation, or he might have presented a major or relative contraindication to transplantation at the time of implantation.[12] These unlisted potential transplantation candidates are included in a bridge to candidacy (BTC) group (Table 1).[13] They are further sub-categorised depending on the likelihood that they will ever be listed for transplantation: BTT-likely to be listed, BTT-moderately likely to be listed, and BTT-unlikely to be listed.

Table 1 – Initial treatment intents for LVAD implantation according to the INTERMACS registry



"BTT-Listed" refers to patients that are listed on the waiting list for heart transplantation. The notation "bridge to decision" is not used in the INTERMACS registry.

1.2.5.2 Destination therapy

Heart failure patients ineligible for heart transplantation in whom an LVAD is implanted for permanent support, represent the destination therapy (DT) group.

1.2.5.3 Bridge to recovery

A third group of patients consists of those in whom an LVAD is implanted as a bridge to recovery. At the time of implant, it is hoped that their heart function might recover and they eventually might be weaned from the device. If not, they may become transplantation candidates or remain on the device as destination therapy. Patients labelled bridge to recovery as device strategy at implant represent less than 1% of the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) database patients.[14] It has been argued that bridge to recovery in essence is a retrospective diagnosis since it is hard to predict at the time of implantation which patients will experience myocardial recovery.[5]

Some authors merge BTC and bridge to recovery patients into one bridge to decision (BTD) group. This notation is also used in some Belgian regulatory documents on LVAD. The bridge to recovery concept however is most often used in the context of a non-implantable temporary mechanical assist device.[15, 16] Since almost all BTD patients are in fact BTC, it was decided, in agreement with the Belgian LVAD experts, to avoid using the BTD concept in the present report. This makes the terminology used here consistent with that proposed by the INTERMACS registry, i.e. the international reference.

1.2.5.4 Current practice

Over the years, the proportion of DT patients in the INTERMACS registry progressively increased from less than 10% in 2009 to 45% in 2014.[14] Cumulative proportions in 2012-2015 in this registry were 25.7% for BTT-Listed, 29.7% for BTC and 43.5% for DT (Table 2). According to an oral presentation of the Belgian Association for Cardio-Thoracic Surgery (BACTS) at a recent RIZIV – INAMI meeting (National Institute for Health and Disability Insurance (NIHDI), August 2015),[17] of 83 LVAD implants in 2014 and 2015, 70 (84%) were intended as BTT, 8 (10%) as BTC and 5 (6%) as DT. Data on Belgian practice will be discussed in detail further in this report.

Table 2 – Implants by initial treatment intent in the INTERMACS registry

	INTERMACS	2012 - June 2015		
		n	%	%
	BTT-Listed	2318	25,7	25,7
BTC	BTT-Likely	1640	18,2	29,7
BTC	BTT-Moderately likely	808	8,9	
BTC	BTT-Unlikely	236	2,6	
	DESTINATION THERAPY	3913	43,5	43,5
	RECOVERY	33	0,3	0,3

Source: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Quarterly Statistical Report 2015 Q2 p.16.[14] BTC comprises BTT-Likely, -Moderately likely and -Unlikely. "BTT-Listed" refers to patients who are listed on the waiting list for heart transplantation. Initial intents denoted in the INTERMACS registry as "Rescue Therapy" (n=39) and "Other" (n=6), are not represented in Table 2.

Patients considered for durable LVAD implantation are categorised in the INTERMACS registry into seven profiles by clinical severity of disease at the time of implantation (Table 3). Most of the patients enrolled in this registry (2012-2015) belong to the most severe HF profiles: critical cardiogenic shock (15.4%), progressive decline (34.8%), stable but inotrope dependent (31.5%) and resting symptoms (13.8%).[14]

Table 3 – INTERMACS patient profiles: definitions

1	Critical Cardiogenic Shock	A patient who is "crashing and burning", in which a patient has life-threatening hypotension
2	Progressive Decline	A patient who has been demonstrated "dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator.
3	Stable but Inotrope Dependent	A patient who is clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean
4	Resting Symptoms	A patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living
5	Exertion Intolerant	A patient who is comfortable at rest but unable to engage in any activity
6	Exertion Limited	A patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity.
7	Advanced NYHA Class III	A patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent

Source: Interagency Registry for Mechanically Assisted Circulatory Support. Quarterly Statistical Report 2015 Q2.[14]

On average, BTT-Listed patients are in a poorer hemodynamic condition at implantation than DT patients. In the INTERMACS registry, during the era 2012-2015, 16.7% of BTT patients were in INTERMACS profile 1 (critical cardiogenic shock), versus 12.7% of DT patients. The proportion of patients in profile 4 (resting symptoms) was 12.4% for BTT and 15.9% DT (Table 4).[14]

Table 4 – Patient profile by implant strategy in INTERMACS (2012-2015)

INTERMACS profile	BTT		DT	
	n	%	n	%
1	836	16,7	499	12,7
2	1855	37,1	1268	32,4
3	1494	29,9	1340	34,2
4	619	12,4	624	15,9
5	98	2,0	114	2,9
6	37	0,7	26	0,6
7	22	0,4	21	0,5

BTT (Bridge to transplant) refers to BTT-Listed and BTC (Bridge to candidacy) patients. INTERMACS profiles as shown in Table 3. Source: INTERMACS register, 2015 2nd Quarterly Statistical Report, p.16.[14] Patient profile is lacking in 64 cases (0.7%).

In recent years, a growing interest in treating less sick patients (INTERMACS profiles 4-6) with an LVAD has emerged. In 2012, a US pivotal randomized trial for the evaluation of HeartMate II LVAD as DT intervention in patients in the lower INTERMACS risk profiles was initiated: the "Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) Pilot Trial".[18] However, the data and safety monitoring board recommended the study to be closed due to lack of clinical equipoise (sic).[19] A changing trend in LVAD patients' profile is also exemplified by the recently presented results from the observational HeartMate-3 CE Mark Clinical Investigation Plan (ClinicalTrials.gov Identifier: NCT02170363). The HeartMate-3 device was granted a CE mark in October 2015 based on this study. Six-month survival on LVAD support was 92%. The investigators compare this figure with a corresponding 88% 6-month survival from INTERMACS. However, such comparison may not be appropriate because of the small sample size of the study (50 patients: 27 BTT and 23 DT) and the fact that the study patients were in a much better hemodynamic condition at the time of implant: none of them had an INTERMACS profile 1, whereas 40% had profile 4.[20]

1.2.6 Regulatory and organisational issues in Belgium

In Belgium LVADs are reimbursed by the RIZIV – INAMI under strict conditions. In 1999, with the development of implantable devices, distinct reimbursement rules were created (Art 35, category 5). A maximum of 20 patients per year were accepted for reimbursement and implantation had to take place in a cardiac centre performing heart transplantations (cardiac care program T). Patients had to be listed on the Eurotransplant waiting list for heart transplantation.

The yearly number of reimbursed devices was increased to 30 devices (including replacements) in 2007, to 40 in 2011, and 50 in 2014. On July 1, 2014, the agreement was adapted. Implantation as bridge to decision (cf. higher: BTC) was accepted for a limited number of patients for whom it is not clear at the moment of implantation whether they will become "transplantable". Inscription on the Eurotransplant waiting list for those patients was not necessary at the time of implantation. So far, there is no approval for destination therapy in Belgium. The limitative list of currently accepted devices is available from the RIZIV – INAMI's website: http://www.riziv.fgov.be/SiteCollectionDocuments/implants/Kunsthart.pdf)

The corresponding RIZIV – INAMI pseudo-nomenclature codes are:

- 684714-684725: "Materiaal voor ventrikelondersteuning gebruikt ingeval van "bridge-to-transplant": ventrikelondersteuning (bridge-to-transplant)"
- 701035: "Alle toebehoren nodig om het materiaal voor ventrikelondersteuning in geval van "bridge-to-transplant" correct te laten werken voor een ambulante patiënt gedurende het eerste jaar van de ondersteuning …"
- 701050: "Alle toebehoren nodig om het materiaal voor ventrikelondersteuning in geval van "bridge-to-transplant" correct te laten werken voor een ambulante patiënt na het eerste jaar van de ondersteuning …"

In Belgium, HeartMate II and Heartware are predominantly used for single left ventricular support. Of 224 LVADs implanted in Belgium between 2011 and medio 2015, 109 (49%) were Heartmate II and 93 (42%) were HeartWare Ventricular Assist Pump (HVAD) (source: BACTS[17]).

For a comprehensive discussion of current Belgian practice the reader is referred to chapter 7.

2 SCOPE AND RESEARCH QUESTIONS

2.1 Scope

The present report studies the clinical and cost-effectiveness of long-term support of a failing heart by means of a mechanical assist device. The primary focus will be on the use of those devices in patients ineligible for heart transplantation, in whom the device is intended for permanent support (destination therapy). Furthermore, the devices' effectiveness will be assessed in patients in whom it is not yet clear at the time of implantation whether they are appropriate candidates for heart transplantation (bridge to candidacy).

This report will consider only modern continuous-flow devices that are implanted for assisting the left ventricle of the heart. Conditions requiring a right- or a bi-ventricular assist device are out of scope.

2.2 Research questions

What is the safety, clinical effectiveness and cost-effectiveness of left ventricular assist devices (LVADs) as destination therapy (DT) or as a bridge to candidacy (BTC) for the treatment of heart failure?

Key points

- **A left ventricular assist devices (LVAD) is an implantable pump that assists the function of the failing heart.**
- **The power supply to the pump occurs via a cable that goes through the abdominal wall. It is attached to a control system and an external battery. Patients need to carry this equipment at all times. A thorough understanding of the LVAD and system components by the patient and companion is essential to ensure safety.**
- **LVADs represent a treatment modality in selected patients with end-stage heart failure. The present report focuses on the use of LVADs in patients ineligible for heart transplantation in whom the device is intended for permanent support (destination therapy - DT) or in whom it is not yet clear at the time of implantation whether they are appropriate candidates for heart transplantation (bridge to candidacy - BTC). The use of LVAD as a bridge to transplantation (BTT) is beyond the scope of this report.**
- **In Belgium, the NIHDI provides reimbursement for a yearly number of 50 LVADs for patients listed for transplantation (BTT) or in whom transplantation may be anticipated (BTC). There is presently no reimbursement for LVADs as destination therapy (DT). The present report is initiated with the aim to assess the clinical and cost-effectiveness of LVADs as DT or as BTC.**

3 SYSTEMATIC LITERATURE REVIEW

3.1 Methods

Two systematic searches for relevant publications were carried out in the electronic reference databases Medline and PreMedline (through OVID), EMBASE, and the Cochrane Library:

- Publications on LVAD as destination therapy published between July 2010 (i.e. search strategy of the ME-TA HTA report21 co-authored by one of the authors of the present report) up to August 2015.
- For publications on LVAD as bridge to decision/bridge to candidacy we chose an earlier inclusion date since the abovementioned ME-TA HTA report did not consider this indication. We searched papers published between 2005 (i.e. the start of the pivotal HeartMate II trial on continuous-flow LVAD) and August 2015.

No filters on study design were used. An overview of the inclusion and exclusion criteria is presented in Table 5. Further details on the search strategy are provided in Appendix 1.

Table 5 – PICO table and selection criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with end stage heart failure, NYHA class III/IV or cardiogenic shock	
Intervention	LVAD as DT or BTD/BTC (for the study of adverse events, LVAD as bridge to transplant (BTT) was also allowed)	RVAD, BiVentricualr AD, pulsatile LVAD (e.g. HeartMate XVE), extracorporeal heart support (e.g. Levitronix CentriMag), percutaneous extracorporeal heart support (e.g. Impella), paracorporeal left ventricular assist device (e.g. Nipro-LVAD), extracorporeal membrane oxygenation (ECMO) and total artificial heart
Comparator	Pulsatile LVAD (REMATCH study) or standard heart failure care	
Outcomes	Clinical effectiveness (in terms of survival and quality of life), adverse events	Cost-effectiveness studies
Study design	Systematic review, review, randomized controlled trial, comparative studies, case series ($n \geq 200$)	Case reports, case series ($n < 200$), simulation studies, animal studies, in-vitro studies, letters, editorials, notes, congress abstracts
Language	English, Dutch, French, German	All other languages

BTD: bridge-to-decision; BTC: bridge to candidacy; BTT: bridge-to-transplant; DT: destination therapy; LVAD: left ventricular assist device; NYHA: New York Heart Association; RVAD: right ventricular assist device.

The references from both searches (each performed in the three electronic databases) were first merged into a unique EndNote file so that duplicates could be removed. The references were then transferred into two separate excel files: one for the search on DT and the second for the search on BTD. In the latter all references that were also included in the DT excel file, were marked so that double shifting could be avoided (see further in Figure 3).

In a first round, each file was screened for eligible articles based on title, abstract and key words by one reviewer (HV or RL). The selected hits were screened by the other reviewer and discrepancies were solved by consensus. In a second round, the remaining papers were retrieved and read in full for a final selection of studies to be included in the review.

3.2 Quality appraisal

The methodology of systematic reviews was critically appraised by means of the AMSTAR checklist (http://amstar.ca/Amstar_Checklist.php) as documented in Appendix 2.2. We did not execute a formal appraisal of observational studies since by definition they provide low-quality evidence on effectiveness. They are however considered useful for the assessment of adverse events.

A critical appraisal of the RCTs that are referred to further in the text has been discussed previously[21]; the major findings are summarized in Appendix 2.3.

3.3 Results

3.3.1 Peer-reviewed studies

The flow chart of the literature selection process is presented in Figure 3. After removal of doubles, the DT file contained 800 references and the BTD/BTC file 819, of which 258 were already included in the DT file. After screening titles and abstracts, 31 records from the DT search and 14 records from the BTD/BTC search were retained (see Figure 3). Based on full-text evaluation, 6 of those studies were included. An overview of the 39 excluded studies and the rationale for exclusion is presented in Table 56 in Appendix 2.1. The list of included studies is provided in Table 6.

3.3.2 The INTERMACS registry and other registries

The literature search also resulted in the identification of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, from which several papers have been published. It is established in 2005 for patients who are receiving mechanical circulatory support device therapy as a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), clinicians, scientists and industry representatives. Data submission on all durable mechanical circulatory devices is mandatory for devices which are FDA-approved for clinical use. Devices implanted in the context of clinical trials are not included.[22]

To date, there are two implantable LVADs approved by the FDA: the HeartMate II Left Ventricular Assist System manufactured by Thoratec Corporation, approved for BTT in 2008 and DT in 2010 and the HeartWare Ventricular Assist System HVAD manufactured by HeartWare, Inc., approved for BTT in 2012 (www.fda.gov).

At each time interval beginning with the 3-month follow-up, re-assessment is documented regarding current intent, survival, quality of life, adverse events.[12] Completeness of follow-up of patients is monitored by the Data Coordinating Center. Form completion rates of <90% trigger a phone call to the local site investigators to improve follow-up. Lack of remediation can lead to expulsion of the site from INTERMACS.[23] We could not identify precise numbers on the completeness of the database. It is contended that "completeness of data far exceeds that of a typical registry"[12] but also that monitoring of case report forms and source documents is "less rigorous by INTERMACS compared with monitoring of data for a prospective randomized clinical trial".[23]

Data from the registry are published on-line every trimester, thus updating data published in peer reviewed journals.[13] The most recent quarterly report provides data up to the second quarter of the year 2015.[14] It contains implant and events from 14 746 adult patients registered between June 2006 and June 2015.

Given the size of this mandatory registry, we will often refer to it in the present report.

EuroMACS is a European database for mechanical support devices that has been designed in such a way that patient and device outcomes are comparable with that of the INTERMACS database. In contrast to INTERMACS, participation in the European database is not mandatory. A first peer-reviewed report representing data from EuroMACS was published

in 2015.[24] Between 1 January 2011 and 31 December 2013, 741 patients (mean age: 53.3, median: 56, range: 0–83 years) were registered. The study was excluded as the registry is not mandatory and as a consequence the results are prone to selection bias (see Table 56 in Appendix 2.1).

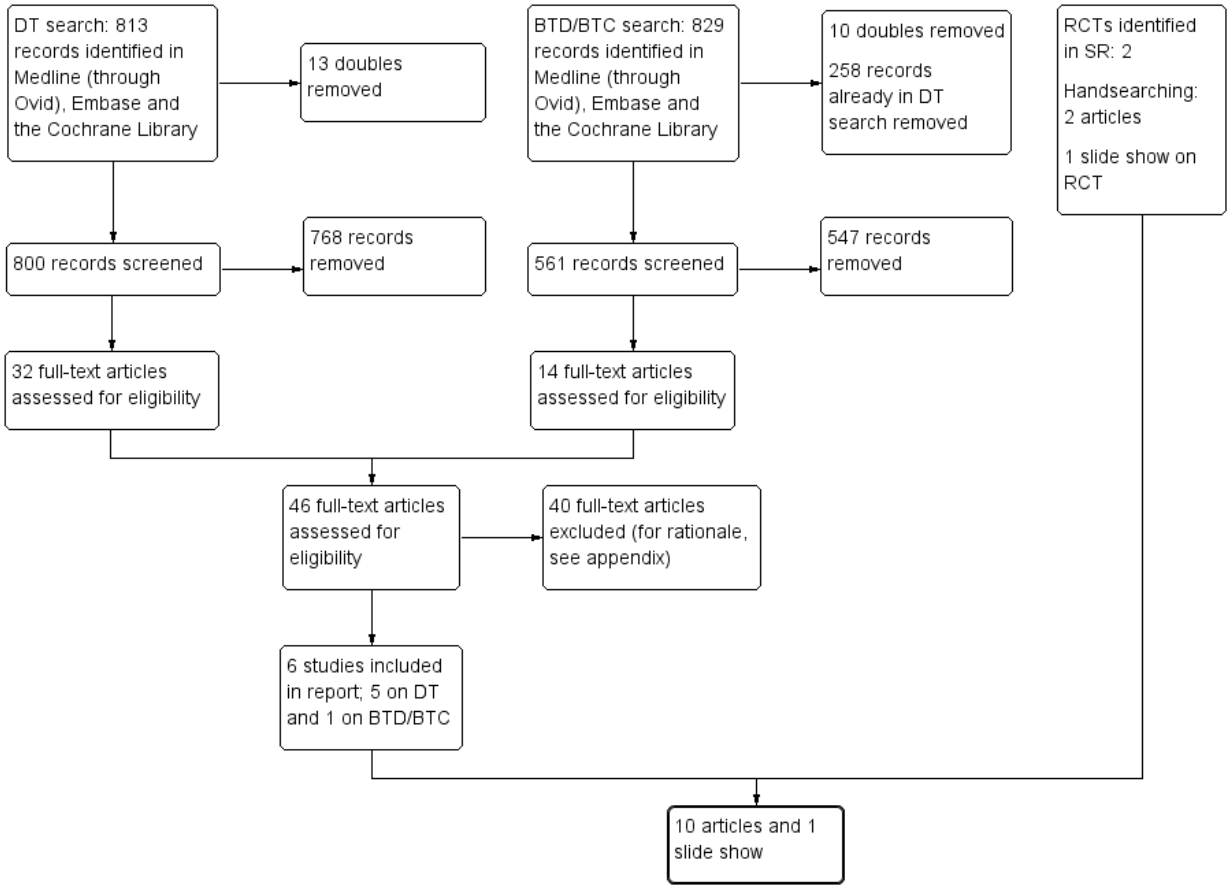
BeNeMACS is the name of a small LVAD study (n=10) (ClinicalTrials.gov Identifier: NCT00983190) of non-transplant patients implanted with the HeartMate II LVAD as destination therapy. Originally, centres from both Belgium and the Netherlands participated; however, no patients from the Netherlands have been enrolled. Data on six patients, including cost calculations, have been published in a peer-reviewed journal.[25]

3.3.3 Randomized controlled trials

In the present report, references are made to two RCTs on LVAD in DT that were identified in a previous HTA report[21] on this topic. The REMATCH trial was published in 2001 and compared a pulsatile LVAD with an optimal medical management.[26] The second RCT was published in 2009 and compared the effectiveness and safety of a continuous-flow LVAD with a pulsatile-flow LVAD.[7] Of note, there has been no RCT comparing a continuous-flow device with optimal medical management, being the real-life alternative intervention if an LVAD is not reimbursed. The inclusion of the REMATCH trial in our discussion allows to make an indirect comparison of a continuous-flow LVAD with optimal medical therapy.

A third ongoing RCT, the ENDURANCE trial, was identified via hand searching.[27] It compares the effectiveness of two continuous-flow LVADs. Some data from this RCT have been presented at scientific meetings. The authors were contacted in order to get a full text of the study, but they replied they were still working on the manuscript.

Figure 3 – Study selection flow diagram



BTC: bridge-to-candidacy; BTT: bridge-to-transplant; DT: destination therapy; RCT: randomized controlled trial; SR: systematic review.

Table 6 – Included studies

Reference	Study design	Evidence source for which part
Draper KV, et al. GI bleeding in patients with continuous-flow left ventricular assist devices: a systematic review and meta-analysis. Gastrointest Endosc 2014;80(3):435-446.e128	Systematic review	Adverse events
McIlvennan CK, et al. Clinical outcomes after continuous-flow left ventricular assist device: a systematic review. Circ Heart fail 2014;7(6):1003-1329	Systematic review	Clinical effectiveness, adverse events
Park SJ, et al. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circ Heart fail 2012;5(2):241-830	Observational study	Clinical effectiveness
Rogers JG, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55(17):1826-3431	Observational study	Clinical effectiveness
Teuteberg JJ, et al. Implant strategies change over time and impact outcomes: insights from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). JACC Heart Fail 2013;1(5):369-7832	Observational study	BTD/BTC
Xie A, et al. Durability of continuous-flow left ventricular assist devices: a systematic review. Ann cardiothorac Surg 2014;3(6):547-5633	Systematic review	Adverse events
References identified in previous SR and based on hand searching		
ENDURANCE trial27 (Pagani et al., 2015, currently limited to slideshow - authors were contacted for full text, but it was not publicly available yet)	RCT	Clinical effectiveness, adverse events
Grady KL et al. 2015 - Change in health-related quality of life from before to after destination therapy mechanical circulatory support is similar for older and younger patients: analyses from INTERMACS. J Heart Lung Transplant. 2015 Feb;34(2):213-21.34	Observational study	Clinical effectiveness
Kirklin JK et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2014 Jan;33(1):12-22.13	Observational study	Clinical effectiveness, adverse events
Rose EA, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435-43.26	RCT	Clinical effectiveness, adverse events
Slaughter MS, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241-51.7	RCT	Clinical effectiveness, adverse events

Key points

Our assessment of the clinical effectiveness of LVADs in terms of benefit is essentially based on data from randomized controlled trials (RCTs). For adverse events observational studies are considered as well.

Data sources were:

- **Two RCTs published in 2001[26] and 2009[7], and one RCT that was presented at international meetings (2015)[27] but that has not yet been published in a peer-reviewed journal.**
- **A large US database (INTERMACS) that has been initiated in 2005. It is mandatory for US centres to provide patient data on all implanted FDA-approved devices. It publishes quarterly updates on-line and presently includes follow-up data on almost 15 000 patients.[14]**
- **Four systematic reviews on adverse events.[13, 28, 29, 33] They summarise data from RCTs as well as from observational studies.**

4 THE CLINICAL EFFECTIVENESS OF LVAD AS DESTINATION THERAPY (DT)

4.1 Sources of information

4.1.1 Systematic reviews

From the literature search, we retained 1 systematic review on clinical effectiveness (McIlvennan et al. 2014[29]). No meta-analysis of results was performed; data were summarized in a tabular form and a narrative description was added. The quality appraisal of the included studies was limited. In the present report the review was used to supplement the data obtained from the abovementioned RCTs and the observational reports.

4.1.2 Randomized controlled trials

The assessment of the clinical effectiveness (e.g. in terms of survival) of a health technology requires high quality data from randomized controlled trials (RCTs). Only RCTs with a control arm in which patients receive "optimal medical management (without LVAD)" can reliably provide evidence on the clinical effectiveness of LVADs. Results from observational studies should be appreciated with caution, since selection bias cannot be ruled out in these types of studies.

So far, only two RCTs on the use of an LVAD as destination therapy have been published. In the first, conducted at 20 experienced cardiac transplantation centres, 129 patients (enrolled between 1998 and 2001) with end-stage heart failure (NYHA class IV) who were ineligible for cardiac transplantation were randomly assigned to receive a pulsatile HeartMate VE left ventricular assist device (n = 68) or optimal medical management (n = 61) (Rose et al., 2001[26]). For the optimal medical management, the medical committee developed guidelines with the goals of optimizing organ perfusion and minimizing symptoms of congestive heart failure. Specific guidance was given regarding the use of therapy with angiotensin-converting-enzyme inhibitors and the discontinuation of intravenous inotropic infusions was encouraged. In the second RCT the effectiveness and safety of a (newer generation) continuous-flow LVAD (n = 134) was compared with a (first generation) pulsatile-flow LVAD (n = 66) in patients with advance heart failure (NYHA class III-IV) ineligible for transplantation (Slaughter et al., 2009[7]).

In April 2015, a third RCT was presented on the annual meeting of the International Society for Heart and Lung Transplantation.[27] In this prospective and randomized trial the effectiveness and safety of the HeartWare HVAD system is compared to an FDA approved LVAD in patients with end-stage heart failure who are ineligible for heart transplantation. So far, the results have not been published in a peer-reviewed journal yet.

4.1.3 Observational studies

We identified a retrospective analysis of patients enrolled in the HeartMate II DT trial who were followed up for at least 2 years after LVAD implantation (Park et al. 2012[30]). The goal of the study was to compare outcomes in patients enrolled later under a so-called Continued Access Protocol (the Mid Trial group) with outcomes of the initial primary patient cohort (Early Trial group), driven by the hypothesis that patients implanted in the later part of the trial would have better clinical outcomes compared with those who were implanted earlier.[30]

Furthermore, we retained data on more than 10 000 patients (of which 5410 DT) treated from June 2006-June 2013 recorded in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) in the United States (Kirklin et al. 2014[11]). We also retained an article presenting data from 741 European patients (January 2011-December 2013) enrolled in the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) (de By et al. 2015[24]). Both registry-based studies comprise patients who received an LVAD as a BTT, as BTC or as DT. Quarterly reports of the INTERMACS registry are published on-line (https://www.uab.edu/medicine/intermacs/) and provide updates of the Kirklin et al. 2014 publication. The most recent quarterly report provides data up to the second quarter of 2015.[14] Whenever relevant data were available from this quarterly on-line report, we used them above those published by Kirklin et al. in 2014.[11]

Data on functional status and health-related quality of life (HRQoL) were retrieved from Rogers et al. 2010[31], Grady et al. 2014[35] and Grady et al. 2015[34]. Data in the first article originate from the HeartMate II BTT and DT clinical trials that were conducted between 2005 and 2009 at 38 centres in the US.[31] The article comprises 374 DT patients. The Grady et al. article is based on the INTERMACS registry and represents data from 1470 CF DT LVAD patients implanted between 2010 and 2012 in 108 institutions.[34] The 2014 publication from the same group was not further considered since only 118 out of 1559 patients (8%) received an LVAD as DT.[35]

Table 7 – Overview of relevant RCTs and observational studies

Randomized controlled trials
Rose et al., 2001[26] (REMATCH trial)
Funding: supported by a cooperative agreement among Columbia University, the NIH, and Thoratec Corporation; investigational-device exemption from the FDA
Patient enrolment: 5/1998 – 07/2001 in 20 heart transplant centres
Inclusion: adults with chronic end-stage heart failure (NYHA class IV) and contraindications for heart transplantation (HTX)
Intervention: HeartMate VE (n = 68, mean age: 66 ± 9.1 yrs., male: 78%)
Control: Optimal medical management (n = 61, mean age: 68 ± 8.2 yrs., male: 82%)
Notes:
Dembitsky et al. (2004) re-analysed the data of the REMATCH trial and provided an additional 375 patient months of LVAD experience over the initial publication in 2001.[36]

Park et al. (2005) analysed the extended survival and adverse events experience of patients adopted in the REMATCH trial, including an additional 125 patient-months of experience for the medical arm (total patient-months, 534) and 375 patient-months for the LVAD arm (total patient-months, 1009).[37]

Slaughter et al., 2009[7]

Funding: Thoratec Corporation

Patient enrolment: 3/2005 – 5/2007 in 38 centres in the US

Inclusion: adults with advanced heart failure (NYHA class III or IV), contraindications for HTX and refractory to optimal medical management

Intervention: CF LVAD: HeartMate II (n = 134, mean age: 62 ± 12 yrs., male: 81%)

Control: PF LVAD: HeartMate XVE (n = 66, mean age: 63 ± 12 yrs., male: 92%)

Pagani et al., 2015[27] (ENDURANCE trial; slideshow[a])

Funding: HeartWare

Patient enrolment: 8/2010 – 5/2012

Inclusion: adults with advanced heart failure and contraindications for HTX

Intervention: CF centrifugal HVAD pump (pericardial placement) HeartWare II (n = 297, mean (?) age: 63.9 yrs., male: 76%)

Control: CF axial pump LVAD (sub-diaphragmatic placement) (n = 148, mean (?) age: 66.2 yrs., male: 82%)

Observational studies

INTERMACS, quarterly report 2015 Q2[14]

Registry (US)

Funding: the INTERMACS device database is funded by a contract grant from the National Heart Lung and Blood Institute (HHSN2682011000250)

Patient enrolment: 6/2006 – 6/2015

Devices: since 2008, dominance of CF technology, including HeartMate II axial-flow pump (BTT and DT) and HeartWare HVAD centrifugal-flow pump (BTT); since 2010, CF pumps account for 100% of patients receiving DT

n = 5410 pts (only DT considered), no age data provided

Patient profile at time of implant:

Critical Cardio Shock: 679 (12.5 %)

Progressive Decline: 1821 (33.6 %)

Stable but Inotrope dependent: 1798 (33.2 %)

Resting Symptoms: 853 (15.7 %)

[a] The authors were contacted to obtain the full text, but it was not publicly available yet.

Exertion intolerant: 156 (2.8 %)

Exertion limited: 50 (0.9 %)

Advanced NYHA Class: 32 (0.5 %)

de By et al., 2015[24] - EUROMACS

Registry (Europe)

Funding: Initial funds provided by the Friede-Springer-Herz-Stiftung; supported by various manufacturers (CircuLite, Inc., HeartWare, Inc., Micro-Med, Syncardia Systems, Inc., Thoratec Corporation).

Patient enrolment: 1/2011 – 12/2013

Devices: long-term CF and PF LVADs and short-term devices

n = 741 pts (mean age: 53.3 yrs. (range: 0-83 yrs.), 82% male)

Patient profile at time of implant: no data provided

Park et al., 2012[30]

Case series (compared to historic control)

Funding: Thoratec Corporation (2 authors received research and training grants from Thoratec Corporation; 1 author is consultant for Thoratec Corporation; 1 author conducted training and occasional speaking for Thoratec Corporation; 1 author received a consulting fee from Thoratec Corporation; 2 authors are employees of Thoratec Corporation; and 1 author received research support from Thoratec Corporation.)

Patient enrolment: 5/2007 – 3/2009; multicentre; retrospective analysis

Inclusion: adults with advanced heart failure, contraindications for HTX and refractory to optimal medical management; at least 2 year FU after HeartMate II is implanted for DT

Intervention: HeartMate II (n = 281, mean age: 63.3 ± 12.6 yrs., male: 79%)

Control: historic control (i.e. CF intervention arm of the Slaughter et al. RCT)

Rogers et al., 2010[31]

Case series

Funding: Supported by Thoratec Corporation (1 author reports receiving consulting and grant support from Thoratec; 1 author has received a research grant from Thoratec, HeartWare, and Terumo, and is an unpaid consultant for Thoratec; 1 author receives consulting support from Thoratec; 1 author is a consultant for and has received research support from Thoratec; 1 author receives research and training grants from Thoratec, Abiomed, and St. Jude, and research grants from Edwards Life Sciences and Sorin; 1 author receives training and consulting support from Thoratec; 1 author received a research grant from Thoratec; 1 author is an investigator on the HM2 trial; 1 author is an employee of Thoratec with equity ownership in the company; 1 author receives grant support from Thoratec and Heartware.)

Patient enrolment: 2005 – 2009 in 38 centres in the US; retrospective analysis of the HeartMate II BTT and DT clinical trials
Inclusion:
BTT trial: NYHA class IV heart failure symptoms and listed as high priority for HTX
DT trial: NYHA class IIIB and IV heart failure, ineligible for HTX and refractory to optimal medical management
Intervention: Heartmate II
BTT trial: n = 281, mean age: 50 ± 13 yrs., male: 76%
DT trial: n = 374, mean age: 63 ± 12 yrs., male: 73%
Control: NA
Grady et al., 2015
Case Series
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Patient enrolment: 1/2010 – 3/2012 in 108 centres in the US; retrospective analysis of INTERMACS data
Inclusion: FDA approved CF LVAD as a primary implant for DT
Intervention: FDA approved CF LVAD, n = 1470, mean age at implant: 63.4 ± 11.8 yrs., male: 82%

BTT: bridge to transplantation; CF LVAD: continuous-flow LVAD; DT: destination therapy; FDA: Food and Drug Administration; HTX: heart transplantation; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVAD: left ventricular assist device; NYHA: New York Heart Association; PF LVAD: Pulsatile-flow LVAD; RCT: randomized controlled trials

4.2 Survival

4.2.1 Actuarial survival

4.2.1.1 Introduction

Since extending life is one of the primary goals of an LVAD, survival is one of the outcomes of dominant interest for the majority of patients. Although survival is an objective measure, characterizing long-term survival after LVAD implantation is complicated by several factors, including finite study time periods, patient loss to follow-up, and censoring of patients at the time of transplantation.[29] Even in the DT subgroup, some patients receive a heart transplant (based on the INTERMACS quarterly report of 2015 Q2: 433/ 5410 (8%)). Therefore, estimated actuarial survival data are most often reported.

4.2.1.2 Results from RCTs

The oldest RCT, comparing pulsatile-flow LVADs with optimal medical care, revealed a 48% reduction in the risk of death from any cause in the group that received an LVAD, as compared with the medical-therapy group (relative risk: 0.52, 95% CI: 0.34 - 0.78).[26] The 1- and 2-year Kaplan–Meier survival estimates were 52% and 23% in the pulsatile-flow LVAD group and 25% and 8% in the medical-therapy group; the difference being statistically significant at 1 year (not at 2 year evaluation) (see Figure 4). The most common causes of death in the device group were sepsis (41% of deaths) and device failure (17%) whereas in the medical-therapy group, terminal heart failure caused the majority (93%) of deaths.[26] Re-analysis of the same data (and inclusion of an extra 375 patient months of LVAD experience) yielded 1- and 2-year survival estimates of 52% (95% CI: 40 - 63%) and 29% (95% CI: 19 - 40%) for LVAD patients versus 28% (95% CL; 17%-39%) and 13% (95% CI: 5 - 22%) for patients on medical treatment.[36]

The Slaughter et al. RCT, which compared a pulsatile-flow LVAD with a continuous-flow LVAD, revealed significantly better actuarial survival with continuous-flow LVAD (1- and 2-year survival estimates of 68% (95% CI: 60 - 76%) and 58% (95% CI: 49 - 67%) respectively) compared to pulsatile-flow LVAD (55% (95%CI: 42 – 69%) and 24% (95%CI: 1 -46%) respectively)[7] (see Figure 4). In addition, 18 of the pulsatile-flow LVADs were replaced with a continuous-flow LVAD during the follow-up period, leaving only two patients with a pulsatile-flow device (which had been replaced) at 2 years. The leading causes of death among the patients with a continuous-flow LVAD were haemorrhagic stroke (in 9% who had device implantation), right heart failure (in 5%), sepsis (in 4%), external power interruption (in 4%), respiratory failure (in 3%), cardiac arrest (in 3%), and bleeding (in 3%). Among pulsatile-flow LVAD patients, the leading causes of death were haemorrhagic stroke (in 10% who had device implantation), right heart failure (in 8%), multisystem organ failure (in 7%), and ischaemic stroke (in 5%).[7]

4.2.1.3 Results from observational studies

The longest follow-up (up to four years) and largest database (n = 5410 pts) of DT patients are provided in the INTERMACS registry. The 2015 Q2 report presents 1- , 2-, 3- and 4-year survival data of 76%, 63%, 52% and 42% respectively for the DT population (see Figure 4).[14] Not unexpectedly, these values are well below those for the BTT population (85%, 77%, 66% and 54%) and BTC population (82%, 72%, 62% and 51%). Unfortunately, the EUROMACS report[24] provided no separate survival data for the DT subpopulation.

The patients adopted in the Park et al. study were not included in the INTERMACS database as there was no FDA approval yet for LVADs as DT at the time of enrolment (personal communication). Yet the results are in the same order of magnitude with 1- and 2-year survival data of 73% and 63%.[30]

Figure 4 – Actuarial survival – a. Pulsatile-flow LVADs vs. optimal medical care (RCT[37]); b. INTERMACS registry[14]

a.

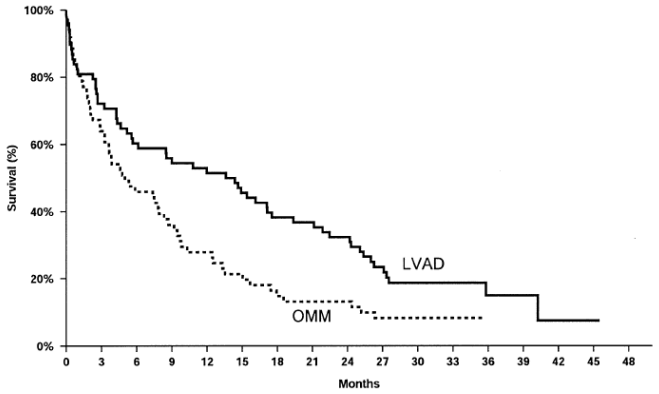


Figure 1. Kaplan-Meier survival curve ($P = .0077$).

b.

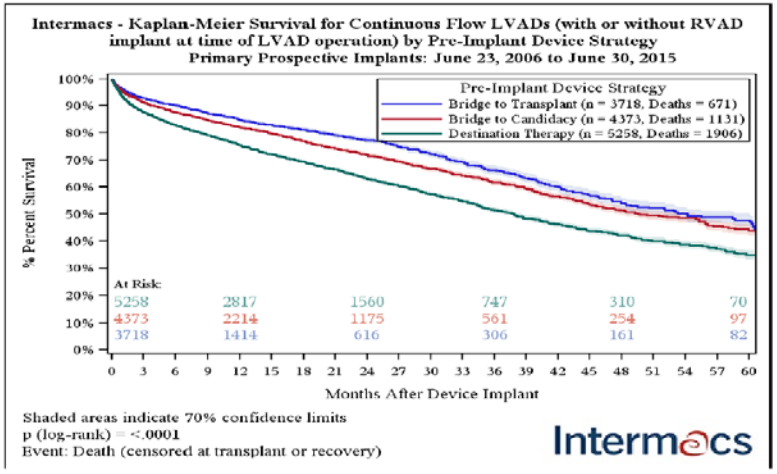


Table 8 – Actuarial survival after continuous-flow LVAD as Destination Therapy

Evidence base	1 year	2 year	3 year	4 year
RCTs				
Rose et al., 2001[26]				
Medical therapy	25% (no CI provided)	8% (no CI provided)		
PF LVAD	52% (no CI provided)	23% (no CI provided)		
Dembitsky et al., 2004[36]				
Medical therapy	28% (95% CL; 17%-39%)	13% (95% CI: 5 - 22%)		
PF LVAD	52% (95% CI: 40 - 63%)	29% (95% CI: 19 - 40%)		
Slaughter et al., 2009[7]				
PF LVAD	55% (95%CI: 42 – 69%)	24% (95% CI: 1 -46%)		
CF LVAD	68% (95% CI 60 - 76%)	58% (95% CI 49 - 67%)		
Observational studies				
Park et al., 2012[30]	73 ± 3%	63 ± 3%		
INTERMACS Report 2015 Q2[14]	76% (no CI provided)	63% (no CI provided)	52% (no CI provided)	42% (no CI provided)

Results presented in grey not from CF LVAD, but given as background info.

4.2.2 Survival free from major events

In the Slaughter et al. RCT[7], the primary end point was survival free from disabling stroke and reoperation to repair or replace the device at two years, which was achieved in 62 (46%) patients who had received a continuous-flow LVAD as DT, compared to only 11% in the pulsatile-flow LVAD (Table 9). The first events that prevented a patient from reaching the primary end point were death within 2 year after implantation (33% (95% CI 25 - 41%)), disabling stroke (11% (95% CI 6 - 17%)) and reoperation to repair or replace the pump (10% (95% CI 5 - 15%)). In Park et al., 166 out of 281 patients (59%) reached the composite end point at two years.[30] This outcome was formulated in a slightly different way in the ENDURANCE trial, more precisely as "survival at two years free from disabling stroke (Modified Ranking Score[b] ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery".[27] The result obtained with HeartWare HVAD (55%) was not inferior to that obtained with the FDA approved continuous-flow LVAD.

[b] The modified Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale runs from 0-6, running from perfect health without symptoms to death.

Table 9 – Survival free from major events

Evidence base	2 year
RCTs	
Slaughter et al., 2009[7]	
PF LVAD	11% (95%CI: 3 – 18%)
CF LVAD	46% (95%CI: 38 – 55%)
Observational studies	
Park et al., 2012[30]	59% (no CI provided)
Pagani et al., 2015[27]	
HeartWare HVAD	55% (no CI provided)
FDA approved CF LVAD	57% (no CI provided)

The composite outcome "survival free from major events" was somewhat different among studies. In Slaughter et al. and Park et al. "major events" were "disabling stroke and reoperation to repair or replace the device" whereas in Pagani et al. the composite outcome was formulated as "survival free from disabling stroke (Modified Ranking Score ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery".

4.2.3 Peri-operative mortality

None of the retrieved studies or registry documents reported any data on peri-operative or 30-day mortality. The ME-TA HTA reported a 30-day mortality of 10.1% (7/69) observed at the University Medical Centre of Utrecht, which was comparable to the 30-day mortality of 10.3% (6/58) reported by Coyle et al.[21, 38] The latter was not included in the present report since the study was limited to patients with a body mass index greater than 30. These data are very well in line with what can be deduced from the survival plots reported by e.g. Slaughter et al.: for continuous-flow the 30-day mortality is about 9% and for pulsatile-flow it is around 11%.[7]

Key points

In patients with end-stage heart failure and contraindications for heart transplantation,

- **implantation of a pulsatile-flow LVAD was associated with a 48% reduction in the risk of death from any cause compared to optimal medical therapy.[26] The difference in survival estimates was significant at 1 year, but not at 2 year evaluation.**
- **significantly better 1- and 2-year actuarial survival rates were observed with continuous-flow LVAD (68%, 95% CI: 60 - 76% and 58%, 95% CI: 49 - 67%, respectively) compared to pulsatile-flow LVAD (55%, 95%CI: 42 – 69% and 24%, 95%CI: 1 - 46%, respectively).[7] The INTERMACS registry reported 1- , 2-, 3- and 4-year survival data of 76%, 63%, 52% and 42% respectively for the DT population.[14]**
- **survival free from disabling stroke and reoperation to repair or replace the device at two years was achieved in 46% of patients who had received a continuous-flow LVAD compared to 11% of patients with a pulsatile-flow LVAD.[7] In Park et al., 59% of patients reached this end point at two years.[30]**
- **None of the retrieved studies or registry documents reported any data on peri-operative or 30-day mortality. The ME-TA HTA report and the 2004 publication by Coyle et al. reported a 30-day mortality of about 10%, which corresponds well with the survival plots of the retrieved studies.[21, 38]**

4.3 Functional status and health-related quality of life (HRQoL)

4.3.1 Introduction

When reading the results presented below, it should be born in mind that functional status data and HRQoL have typically censored patients at the time of death, which can progressively enrich for a healthier population.[29] In addition, missing data for functional status data and HRQoL measures are more common than for an outcome like survival. The failure to complete health status assessments is in itself also informative, with, in general, worse outcomes commonly seen in these patients.[29] Rogers et al. formulate it as follows: "*The variable number of patients studied at each time interval due to factors as death, transplantation, staff availability, or scheduling, may introduce ascertainment bias due to exclusion of sick patients, but this may be partially offset by simultaneous exclusion of healthy patients who underwent transplantation.*"[31] Of course, the latter group is of less relevance in a DT LVAD population.

4.3.2 Functional status

Next to improving survival, a key objective of LVAD implantation is the improvement of the functional capacity and HRQoL. Improvements in New York Heart Association (NYHA) functional class after LVAD implantation have been reported.[29] However, the usefulness of the NYHA classification is limited by its varying interpretation by different cardiologists and its poor reproducibility.[39] Nevertheless, this classification still has an important role in both scientific and regulatory documents.[19]

4.3.2.1 Results from RCTs

In the REMATCH trial, nearly all patients (97%) were in NYHA class IV at baseline. At 1 year, only 17% of surviving medically managed patients improved to class I/II, whereas 71% of surviving patients receiving LVADs improved to this level (p<.0017).[37] (Table 3).

Slaughter et al. [7] reported that 80% of patients with continuous-flow LVAD implanted as DT had NYHA class I or II symptoms at 24 months, but it should not be neglected that the number of patients tested decreased from 126 at baseline, to 72 at 12 months down to 50 at 24 months (see.

Table 10), while the number of patients alive in the trial was higher, respectively 133, 82, and 62. In the same study the mean distance walked during 6 minutes increased from 182 m ± 140 (n=50) to 372 m ± 191 (n=36).[7] A comparison with the control group is difficult: of the 59 patients who underwent pulsatile-flow LVAD implantation, 20 required 21 pump replacements (3 replaced with another pulsatile-flow device and 18 with a continuous-flow device) and one additional patient required urgent transplantation and 3 additional patients required device explantation, owing to bearing wear, valve malfunction, or infection. At 24 months only one patient was left in this group for evaluation.

4.3.2.2 Results from observational studies

Significant improvements in functional status over time were observed by Park et al.: about 80% of patients improved from NYHA class IIIB/IV to NYHA class I/II by 6 months and this was sustained through 24 months. [30] (cf.Table 11) The six-minute walk distance for patients who could walk at baseline improved from 225 m ± 142 (n=36) to >340 m by 6 months and was sustained through 24 months. As the data are only presented in a graph and not in a table or more detailed in the text, they are not presented in Table 11.

Comparable results were reported by Rogers et al.[31]: in the DT group, approximately 30% (value derived from Figure 2 in the original article) had NYHA class III and 70% class IV at baseline. After 1 month of support, 47% of DT patients improved to NYHA class I or II, increasing further after 6 months of support to 80% (DT). Approximately 80% of DT patients remained in NYHA functional class I or II from 6 through 24 months.[31] Again, these results should be interpreted with caution since it is not clear what proportion of available patients (i.e. alive at the moment of evaluation) were actually evaluated. The same prudence holds for the 6-min walk test; only 129 of 374 DT patients (34%) were able to perform the test at baseline (mean distance: 204 m (SD: 150 m)), at 6 months 199 patients were tested (mean distance: 350m (SD: 198 m)), and at 24 months 75 patients (mean distance: 360 m (SD: 210 m)), but the total number of patients available was not mentioned.

No relevant data with regard to functional status were identified in the INTERMACS or EUROMACS publications.

Table 10 – Functional status after LVAD as Destination Therapy – NYHA class (change)

Evidence base	Baseline	3 months	6 months	1 year	2 years
RCTs					
Park et al., 2005[37]					
Medical therapy	NYHA class IV: 100% (61/61[$])			NYHA class I or II: 17%	
PF LVAD	NYHA class IV: 100% (68/68[$])			NYHA class I or II: 71%	
Slaughter et al., 2009[7]					
PF LVAD	NYHA class III or IV: 100% (66/59[$])	NYHA class I or II: 68% (n=38/?[$])		NYHA class I or II: 61% (n=18/19[$])	NYHA class I or II: 100% (n=1/2[$])
CF LVAD	NYHA class III or IV: 100% (134/133[$])	NYHA class I or II: 75% (n=91/?[$])		NYHA class I or II: 76% (n=72/82[$])	NYHA class I or II: 80% (n=50/62[$])
Observational studies					
Rogers et al., 2010[31]	NYHA class III or IV: 100% (374/374[$])	NYHA class I or II: 74%* (n=265/?[$])	NYHA class I or II: 80%* (n=245/?[$])	NYHA class I or II: 75%* (n=200/?[$])	NYHA class I or II: 79%* (n=99/?[$])
Park et al., 2012[30]	NYHA class IIIB or IV: 100% (281/281[$])		NYHA class I or II: 82% (n=191/215[$])	NYHA class I or II: 77% (n=161/187[$])	NYHA class I or II: 81% (n=103/146[$])

*[$]: the first number refers to the number of patients tested, while the second number refers to the number of patients alive; *: result derived from figure and not from a table or text.*

Table 11 – Functional status after LVAD as DT – 6-minute walk distance (mean ± SD)

Evidence base	Baseline	3 months	6 months	1 year	2 years
RCTs					
Slaughter et al., 20097					
PF LVAD	172 ± 108 (n=19/59$)	291 ± 134 (n=29/?$)		306 ± 145 (n=12/19$)	277* (n=1/2$)
CF LVAD	182 m ± 140 (n=50/133$)	319 m ± 191 (n=77/?$)		318 m ± 164 (n=61/82$)	372 m ± 191 (n=36/62$)
Observational studies					
Rogers et al., 201031	204 m ± 150 (n=129/374$)		350 m ± 198 (n=199/?$)		360 m ± 210 (n=75/?$)

$: the first number refers to the number of patients tested, while the second number refers to the number of patients alive.

4.3.3 Health related quality of life (HRQoL)

4.3.3.1 Introduction

Instruments frequently used to assess HRQoL in patients with heart failure include disease-specific measures, such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ)[c], the Kansas City Cardiomyopathy Questionnaire (KCCQ)[d], and generic measures such as the EuroQol-5 Dimensions (EQ-5D)[e]. These are often prospectively collected in LVAD studies.[29] With regard to disease-specific measures, it has been argued that the HRQoL measures developed in patients with chronic heart failure may not perform as intended when applied to the LVAD population, given that many heart failure–related symptoms are traded for other unique symptoms and burdens.[29]

4.3.3.2 Results from RCTs

The Minnesota Living with Heart Failure (MLHF) Questionnaire improved (i.e. values decreased) from baseline to 1 year later in both treatment groups in the REMATCH RCT (see Table 12 and Table 13).[26] At 1 year, the score was better in the device group compared to the medical treatment group, but the difference was not statistically significant. Re-evaluation of the data revealed that the MLHF score was significantly better for the patients receiving LVADs over the course of the study ($p<0.007$).[37]

Likewise, Slaughter et al. reported improvements in Minnesota Living with Heart Failure Questionnaire and Kansas City Cardiomyopathy Questionnaire scores from before surgery to all time points assessed after device implantation (see Table 12 and Table 13).[7]

Table 12 – Health related quality of life (HRQoL) assessed with Minnesota Living with Heart Failure questionnaire

Evidence base	Baseline	3 months	6 months	1 year	2 years
RCTs - mean ± sd					
Rose et al., 2001[26]					
Medical therapy	75 ± 17 (n=?/61[$])			58 ± 21 (n=6/11[$])	
PF LVAD	75 ± 18 (n=?/68[$])			41 ± 22 (n=23/24[$])	
Observational studies - median					
Rogers et al., 2010[31]	75*[#] (n=323/374[$])	34*[#] (n=258/?[$])		32*[#] (n=197/?[$])	34*[#] (n=90/?[$])

*[$]: the first number refers to the number of patients tested, while the second number refers to the number of patients alive; *: No sd reported (n=1); # Exact data derived from McIlvennan et al. since data presented in the form of a figure in original article.*

[c] Scores on the 21-question Minnesota Living with Heart Failure questionnaire range from 0 to 105, with higher scores indicating a worse quality of life.

[d] Scores on the Kansas City Cardiomyopathy questionnaire range from 0 to 100, with higher scores indicating a better quality of life.

[e] The EuroQol five-dimensions questionnaire(EQ-5D-3L) is a generic instrument which consists of five questions that assess the HRQOL dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression and for which a three-level response format (no problems, some or moderate problems, extreme problems) is provided. The EQ-5D-3L also includes an overall health status rating, using a vertical visual analogue scale (VAS) with 0 representing the worst possible health state and 100 representing the best. The results of the 5 dimensions can be translated into utility values by applying country-specific value sets with 0 representing death and 1 perfect health.

Table 13 – Health related quality of life (HRQoL) assessed with Kansas City Cardiomyopathy questionnaire – Overall summary score

Evidence base	Baseline	3 months	6 months	1 year	2 years
RCTs - mean ± sd					
Slaughter et al., 2009[7]					
PF LVAD	26.5 ± 17.4 (n=47/59[$])	56.7 ± 21.1 (n=36/?[$])		59.1 ± 20.3 (n=18/19[$])	33.3* (n=1/2[$])
CF LVAD	27.4 ± 16.3 (n=115/59[$])	63.4 ± 18.5 (n=89/?[$])		65.9 ± 20.0 (n=76/82[$])	69.9 ± 18.7 (n=47/62[$])
Observational studies - median					
Rogers et al., 2010[31]	24*# (n=318/374[$])	68*# (n=262/?[$])		70*# (n=203/?[$])	74*# (n=97/?[$])

[$]: the first number refers to the number of patients tested, while the second number refers to the number of patients alive; *: No sd reported (n=1); # Exact data derived from McIlvennan et al. since data presented in the form of a figure in original article.

4.3.3.3 Results from observational studies

Rogers et al.[31] also reported improvements in Minnesota Living with Heart Failure Questionnaire and Kansas City Cardiomyopathy Questionnaire scores from before surgery to all time points assessed after device implantation (see Table 12 and Table 13). They further commented that both MLWHF and KCCQ represent heart-failure related quality of life measures, whereas a wider range of domains of quality of life would provide a more complete assessment.

Grady et al. reported on 1470 CF DT LVAD patients at 108 centres participating in INTERMACS between 2010 and 2012.[34] The 1470 patients were divided into 3 age cohorts (<60 y.o. (n = 457); 60 to 69 y.o. (n = 520) and ≥70 y.o. (n = 493)) as the main objective of the study was to determine if the change in HRQoL from before to after continuous-flow DT LVAD was comparable in different age groups. Change in VAS score of >10 units was considered clinically relevant, a decision that was based on the cancer literature (which estimates a change of 8 to 12 in VAS scores as a "minimally important difference" (MID) for self-rated health status among cancer patients) as no MIDs for VAS scores in other disease were identified by the authors.[34] In case patients were too sick to respond, a response level of "extreme problems" was assigned (post hoc) for the dimensions mobility, self-care and usual activities (but not for pain/discomfort or anxiety/depression), which might avoid potential overestimation of QoL due to missing data. In all age groups mean VAS scores improved from pre-implant to 1-year follow-up (see Table 14 and Table 15), yet it is important to mention that for only 435 out of 1470 included patients (i.e. 30%) paired data were available, which may have probably overestimated the results. The authors mention that before implant 70%, 73% and 76% of data for the 3 age cohorts were available, but these proportions included patients who were too sick to respond and for whom the VAS score was assigned a value of 0, again trying to avoid potential overestimation of QoL due to missing data At 12 months after implant, EQ-5D completion rates for the three age groups ranged from 52% to 64%. After implant, very few patients were too sick to respond and the reasons for post-implant lack of survey completion were according to the authors "primarily administrative" (no consent, no contact with the patient during the window of time that a survey was due) and patients' refusal to participate. For all dimensions, patients reported fewer problems from pre-implant to 1 year post-implant (see Table 16). Multivariable analyses revealed that fewer rehospitalisations after implant were associated with improvement in HRQoL. Unfortunately, the EQ-5D scores were not translated into utility values.

Table 14 – Health related quality of life (HRQoL) assessed with European Quality of Life-5 Dimensions (EQ-5D) - Change in mean VAS scores

Evidence base	Baseline	1 year
Observational studies		
Grady et al. 2015[34] (paired data only)	35.8	70.7
<60 y.o. (n=124)	37.7	72.7
60 - 69 y.o. (n=144)	44.4	77.0
≥70 y.o. (n=167)		

Table 15 – Health related quality of life (HRQoL) assessed with European Quality of Life-5 Dimensions (EQ-5D) - Change in mean VAS scores Pre-implant versus 1-year follow-up

Evidence base	n	Proportion (%)
Observational studies		
Grady et al. 2015 (paired data only, n=435)	26	6
>10 units worse: 26	22	5
>1-10 units worse	19	4
No change	45	10
1-10 units better	151	35
11-40 units better	172	40
41+ units better		

Table 16 – Health related quality of life (HRQoL) assessed with European Quality of Life-5 Dimensions (EQ-5D) - Change in dimensions

Evidence base Observational studies	Baseline	1 year
Grady et al. 2015 (paired data only)	n=1068	n=588
Mobility	49%	39%
Some problems	28%	3%
Extreme problems	n=1068	n=588
Usual activities	39%	38%
Some problems	45%	6%
Extreme problems	n=1068	n=588
Self-care	28%	22%
Some problems	26%	3%
Extreme problems	n=865	n=578
Pain/discomfort	44%	34%
Some problems	8%	5%
Extreme problems	n=860	n=578
Anxiety/depression	47%	30%
Some problems	7%	2%
Extreme problems		

This information is based on the data published in the study of Grady et al.[34] In the original results, a distinction was made according to age (<60, 60-69, 70+). The above numbers are weighted averages combining the results of the three age categories. We remark that a lot of information is lacking (see further discussion in part 9.3).

Key points

In patients with end-stage heart failure and contraindications for heart transplantation

- **implantation of a pulsatile-flow LVAD resulted in a statistically significant improvement of NYHA class compared to optimal medical therapy at one year.[37]**
- **implantation of a continuous-flow LVAD resulted in a statistically significant improvement of NYHA class and 6-Minute walk test, which was not statistically significantly different from the improvement seen after 1 year of pulsatile-flow LVAD implantation.[7]**
- **implantation of a pulsatile-flow LVAD resulted in a statistically significant improvement in quality of life (as assessed with the Minnesota Living with Heart Failure Questionnaire) that lasted for up to two years.[37]**
- **implantation of a continuous-flow LVAD resulted in a statistically significant improvement of quality of life (as assessed with the Minnesota Living with Heart Failure Questionnaire), which was up to two years statistically significantly better than the improvement seen with pulsatile-flow LVAD implantation.[7] The Kansas City Cardiomyopathy questionnaire improved statistically significantly over the course of the first year after implantation in both groups, but the differences between groups were not statistically significant.**

5 THE CLINICAL EFFECTIVENESS OF LVAD AS A BRIDGE TO CANDIDACY (BTC)

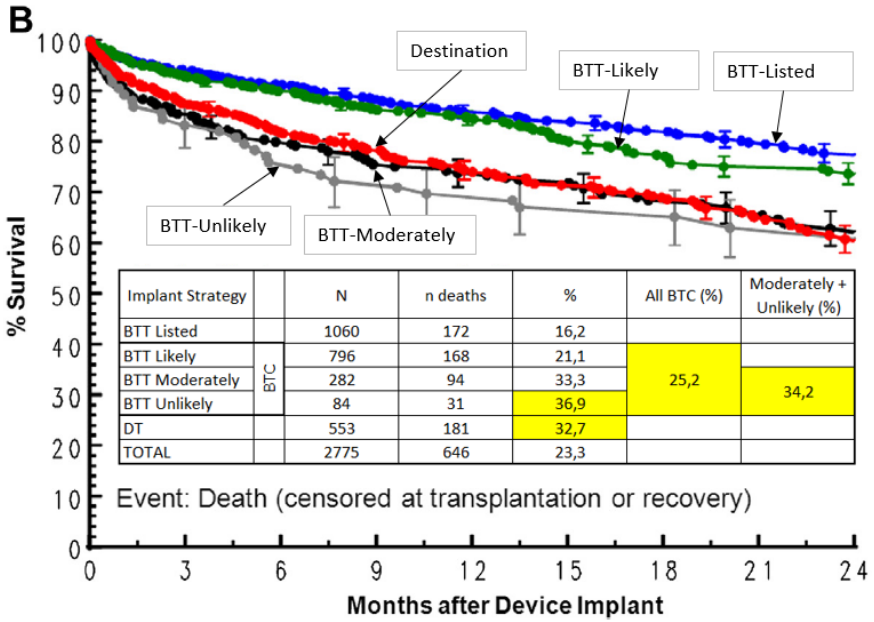
5.1 Sources of information

We performed an extensive literature search for studies related to LVAD implants with the initial strategy of bridge to decision and bridge to candidacy (BTC). We did not identify randomized trials that compared BTC patients with other initial intent modalities. An additional search on the clinicaltrials.gov website did not identify ongoing clinical trials specifically addressing the subject of BTC. Accordingly, evidence on the effectiveness of LVAD as a BTC is derived from observational data only.

5.2 Survival

The 2015 Q2 report of the INTERMACS registry presents 1- , 2-, 3- and 4-year survival data for the overall BTC population of 82%, 72%, 62% and 51% respectively.[14] One single paper provides outcome data of BTC patient subgroups separately, extracted from the INTERMACS registry and related to 2816 primary continuous-flow LVAD devices, implanted between March 2006 and March 2011.[32] Implant strategy was 1060 (38%) BTT, 1,162 (42%) BTC (BTC-Likely 796, BTC-Moderately likely 282, BTC-Unlikely 84), and 553 (20%) DT (abbreviations: cf. Table 1). At baseline, BTC patients were more critically ill (i.e. hemodynamically poorer condition) at the time of implant than BTT-Listed or DT recipients. 18% were in INTERMACS profile 1, versus 13% of BTT-Listed and 6% of DT recipients. They were on average of the same age as BTT-Listed patients (53 yrs.) but 11 years younger than DT patients (64 yrs.). Diabetes and chronic obstructive lung disease were more prevalent than in BTT-Listed patients, but less than in DT patients. Two-year survival (alive on support, transplant, or recovered) after primary LVAD implant was 77.7% for BTT-Listed, 70.1% for the BTC-overall category, and 60.7% for DT. The 2-year survival for the BTC patients were 73.7% for BTC-Likely, 62.8% for BTC-Moderate, and 62.9%% for BTC-Unlikely. Kaplan-Meier estimates of survival by implant strategy is depicted in Figure 5. The higher mortality of the overall BTC group (25.2%) than the BTT-Listed can at least partly be explained by their poorer hemodynamic condition at the time of implant. Initial INTERMACS profile has been shown to be a determinant for survival up to 2 years.[32]

Figure 5 – Survival by implant strategy



Implant Strategy		N	n deaths	%	All BTC (%)	Moderately + Unlikely (%)
BTT Listed		1060	172	16,2		
BTT Likely	BTC	796	168	21,1	25,2	
BTT Moderately	BTC	282	94	33,3	25,2	34,2
BTT Unlikely	BTC	84	31	36,9	25,2	34,2
DT		553	181	32,7		
TOTAL		2775	646	23,3		

Adapted from Teuteberg et al.[32]

The combined mortality at 2 years of BTT-Unlikely and BTT-Moderately patients in this study is of the same magnitude as the DT patients' mortality (Figure 5): 34.2% vs. 32.7% in Teuteberg's report.[32] These figures were 33.3% vs. 35.9% respectively in the INTERMACS 2015Q2 report.[14]

In the absence of randomized trial data, the available observational data do not allow to draw firm conclusions on the clinical effectiveness (in terms of survival) of BTC as initial implant strategy vs. other treatment strategies. In the INTERMACS registry, determination of initial intent is made at the discretion of the implanting centre rather than upon standardised criteria. It cannot be excluded that BTC patients do not fare better than DT patients, which clearly depends on the qualifications (Likely/Moderately/Unlikely)

attributed to BTC patients in an individual implant centre (Figure 5). In INTERMACS, during 2012-2015, 25.7% of implants was for BTT-Listed, 29.7% for BTC and 43.5% for DT.[14]

Key points

- **Patients in whom an LVAD is implanted as a bridge to candidacy (BTC) are those in whom it is not yet clear at the time of implantation whether they are good candidates for transplantation. If later on it appears that they are no transplantation candidates, they remain on the device as destination therapy (DT).**
- **The concept op BTC has not been standardised. The decision to label a given LVAD implantation as BTC (instead of BTT or DT) may vary across implanting physicians and may depend on several circumstances, such as the hemodynamic and general condition of the patient, or donor availability.**
- **Observational data indicate that overall, long-term survival of BTC patients is in-between that of BTT and DT patients. Subsets of BTC patients have a survival similar to that of DT patients.**
- **We did not identify any randomized trial comparing LVADs as BTC with other treatment modalities.**

6 ADVERSE EVENTS ASSOCIATED WITH LVAD THERAPY

6.1 Sources of information and data extraction

As explained earlier, a comprehensive literature search was performed in order to document adverse events associated with LVAD therapy. Whereas the assessment of clinical effectiveness in terms of survival requires data from high quality randomized controlled trials (RCT), observational data may be crucial when the aim is to identify adverse events.[40] Observational data often consider larger populations than RCTs, the latter lacking power to reliably detect differences in the occurrence of rare events between the intervention and control groups. Furthermore, observational studies may provide data over longer time periods. They also include less strictly selected patients, often with more co-morbid conditions than those enrolled in RCTs. Observational studies may reflect more recently induced changes in practice or updated device versions.

The INTERMACS registry in the present report represents a huge database, with data on almost 15 000 patients (cf. chapter 3.3.2). It represents the main source of information of adverse events related to LVADs in the present report. Data from this registry are extracted from peer reviewed journals, updated with the most recent quarterly report which was published on-line on September 28, 2015.[14]

In addition to data from INTERMACS, we extracted data from high quality systematic reviews: McIlvennan (general systematic review, 2014)[29], Draper (gastro-intestinal bleeding, 2014)[28], and Xie (device durability, 2014)[33]. Although Kirklin's report on device thrombosis was not a formal systematic review, we also included it in our assessment because of its relevance.[13]

Published data on adverse events in patients receiving a continuous-flow device, both as BTT or DT, were taken into consideration for assessing adverse events.

It may not always be possible to correctly attribute a given adverse event to the device, to the underlying condition (heart failure) or to a patient's baseline characteristics. On one hand, BTT-Listed patients are in a more critical hemodynamic condition at baseline than DT recipients. Data from the INTERMACS registry on continuous LVADs implanted in 2012-2015 show

that among BTT-Listed patients 13.5% are in INTERMACS profile 1 and 39.3% in profile 2 (sum: 52.8%). In DT these numbers are 12.7% and 32.4% (sum: 45.1%) respectively.[14] On the other hand, DT patients are on average 11 years older than BTT-Listed patients: 64 versus 53 years.[32]

6.2 Adverse events reported in RCTs

The occurrence of adverse events from RCTs on continuous-flow devices is shown in Table 17. Data from the control group in Rose's RCT were included in the table (shaded area) as a comparator since they provide outcome data from heart failure patients receiving optimal medical treatment.[26] The reported high prevalence of sepsis in the medical control group is unexpected and to some extent in contrast with the observation that sepsis was the cause of death in 17 out of 68 patients treated with a (pulsatile) LVAD versus in only 1 out of 61 patients treated medically.[26] Device-related infections (relating to the percutaneous lead, pump, or pump pocket) obviously do not occur in patients that are treated medically. Bleeding and stroke are clearly more prevalent in patients in whom an LVAD is implanted. Differences in the occurrence of bleeding across RCTs may be induced by changing approaches in anticoagulation management over time.

Table 17 – Adverse events reported in RCTs on continuous-flow LVADs

Adverse event	Rose - DT	Slaughter - DT	Pagani - DT (2 years follow-up)	
Device	Medical therapy	HeartMate	Heartware	HeartMate
Non-neurologic bleeding	0,06	1,89	0,98	0,96
Stroke - any	0,09	0.17 "other neurologic events"	0,27	0,09
haemorrhagic	NA	0,07	0,11	0,03
ischaemic	NA	0,06	0,16	0,06
Device-related infections	0	0.48	0,18	0,12
Sepsis	0,30	0,39	NA	NA
Right heart failure	NA	0,16	0,31	0,22
Arrhythmias	0,59	0,69	0,43	0,40
Renal failure	0,18	0,10	0,13	0,22
Hepatic failure	0,00	0,01	NA	NA
Hospitalisation	16% of days alive spent in hospital	2,64 rehospitalisations per patient-year	NA	NA

In Rose and Slaughter, incidence is expressed as rate per patient-year. Data from Pagani are after 2 years of follow-up. DT; destination therapy. NA: not available. Sources: Slaughter et al.[7] and Pagani[27]. Shaded column represents adverse events in patients that were treated medically as observed by Rose et al.[26]

In a safety communication on August 5, 2015, the FDA reported serious adverse events reported in the Endurance trial where stroke occurred significantly more often in patients who received the HeartWare Ventricular Assist System compared with those who received the control device (i.e. Heartmate) (http://1.usa.gov/1OQwgwX).[27] This can also be inferred from Table 17: the incidence rate of stroke over 2 years was 0.27 in the HeartWare, versus 0.09 in the HeartMate LVADs.

6.3 Adverse events reported in observational studies

The most commonly studied and reported major adverse events after continuous-flow LVAD implantation are bleeding, neurological events, and infection. Additional complications that can be equally devastating or have an effect on quality of life include rehospitalisation, recurrent heart failure, renal dysfunction, and device malfunction.[29] Adverse event rates with continuous-flow pumps are significantly lower than with previous pulsatile technology.[11]

6.3.1 Bleeding

Bleeding is the most commonly reported adverse event of continuous-flow LVADs. Most patients experience some type of bleeding.[29] Bleeding events are reported as early (<30 days) or late (>30 days) to differentiate postoperative bleeding from non-surgical bleeding. The greatest risk of bleeding is within the first weeks postoperatively and is reported in up to 100% of patients (Table 18).[29] Late bleeding occurs in 12 to 23% of patients and is predominantly from gastro-intestinal origin.[29] One meta-analysis calculated a pooled incidence rate of gastro-intestinal bleeding occurring later than 15 days after implantation of 23% (95%CI 20-26%).[28] Recurrent gastro-intestinal bleeding occurred in 9.3% of patients (95%CI 7.1-12.0%).

In the INTERMACS registry, the early (three months) event rate for bleeding was 18.25 per 100 patients-months, indicating that on average 55% of patients has a bleeding event during the first three months.[14] The late (after the third month) event rate was 3.30 per 100 patients-months, indicating that on average 41% of patients has a bleeding event per year after the first 3 months.

In the early postoperative phase, up to 1% of patients die because of bleeding. Bleeding is the primary cause of death in 2.9% of INTERMACS patients.[14]

Table 18 – Adverse events associated with LVAD

		Systematic reviews (incidence in % of patients)		INTERMACS Registry (event rate per 100 patient-months)	
Bleeding	Early	% per patient	8 - 100	first 3 months	18.25
	Late	% anytime	12 - 23	per year long-term	3.30
Stroke	Ischemic	% per patient-2-years	8	first 3 months any stroke	4.12
	Haemorrhagic		11	per year long-term any stroke	1.23
Sepsis		Anytime	20 - 36	first 3 months any infection	15.41
				per year any infection	3.98
Right heart failure		Anytime	5 - 25		NA
					NA
Renal dysfunction		Anytime	7 - 14	first 3 months	3.86
				per year long-term	0.46
Device malfunction		Major - first 500 days	1 - 11	first 3 months any dysfunction	2.70
				per year long-term any dysfunction	1.46
Rehospitalisation		First year	>100	first 3 months	21.07
				per year long-term	15.90

Data extracted from systematic reviews and INTERMACS registry (see text for details).

6.3.2 Stroke

The overall annual risk of stroke in LVAD patients seems to be substantial but the reported rates are variable and likely reflect differences in study follow-up time and the patient population studied.[29] Ischaemic and haemorrhagic stroke occur in 8% and 11% respectively in the first 2 years after LVAD placement (Table 18).[7, 29]

In the INTERMACS registry, stroke is counted within a broader category of adverse events, described as "neurological dysfunction", including ischaemic stroke, intracranial haemorrhage and transient ischaemic attack. The early (three months) event rate for stroke was 4.12 per 100 patients-months. The late (after the third month) event rate was 1.23 per 100 patients-months. The actuarial freedom from (any) stroke at 1 and 2 years was 89% and 83% respectively.[41]

Haemorrhagic stroke is the leading cause of death among the patients with a continuous-flow left ventricular assist device.[7] Stroke is the primary cause of death in 18.1% of INTERMACS patients.[14]

6.3.3 Infection

Bacterial infections after LVAD implantation may occur locally, at the driveline, the pump pocket, or systemically. Developing any type of infection is associated with decreased survival. Local infections are reported in 20 to 49% of patients, driveline infections in 12 to 22%, pocket infections in 0 to 5%, and sepsis in 20 to 36% of patients (Table 18).[29] Sepsis is defined as an infection manifested by positive blood cultures. In McIlvennan's SR, the highest risk for sepsis was from Slaughter's RCT on destination therapy.[7] In this study, sepsis was observed in 36% of patients (0.39 events per patient-year) in the continuous-flow arm of the study, versus 44% (1.11 events per patient-year) in the pulsatile-flow arm. The smaller pump and percutaneous lead in the continuous-flow devices require less surgical dissection for implantation, which might explain the lower risk for infection as compared with the pulsatile-flow device.[7]

In the INTERMACS registry, the early (three months) event rate for infection was 15.41 per 100 patients-months, indicating that on average 47% of patients has a (major) infection during the first three months. The late (after the third month) event rate was 3.98 per 100 patients-months, indicating that on average half of patients has an infection per year.

In the INTERMACS registry, major infection is the primary cause of death in 8.9% of patients with a decreasing trend over time (15.2% before 2010, 10.5% in 2010-2011 and 5.6% in 2012-2015). However, the overall survival of patients did not significantly change by implant era.[14]

6.3.4 Right Heart Failure

Right heart failure is a clinical diagnosis characterised by oedema, weight gain and ascites. Patients with left heart failure often develop right heart failure as well. After implanting an LVAD, right heart failure may continue to pose clinical problems, contributing to increased postoperative morbidity and mortality. Its reported incidence after LVAD varies across studies, due to the lack of a uniform definition and the fact that a range of co-morbid conditions such as arrhythmias may play a role in its development.

In the SR of McIlvennan, right heart failure requiring inotropic support is reported in 5 to 25% of patients (Table 18).[29] In the largest series included in this SR, 98 (20%) of 484 patients had some form of right heart failure, defined as either the need for an RVAD [in 30 (6%) patients] in addition to the LVAD, or continuous inotropic support for at least 14 days after implantation.[42] 35 (7%) patients required at least 14 days of continuous inotropic support early after implantation, and 33 (7%) patients required late inotropic support starting after the 14th day. Early right heart failure had a substantial impact on survival. In this BTT series of patients, 1-year survival was 78% in those without right heart failure, as opposed to 75% and 59% in those with late and early right heart failure respectively. In a recently published series 33 of 293 patients required re-admission related to right heart failure.[43]

The INTERMACS registry's quarterly reports do not report the incidence of right heart failure.[14]

6.3.5 Renal dysfunction

Postoperative renal failure has been reported to range from 7% to 56%.[29] The large variation in incidence is ascribed to different time periods during which the study was performed, the baseline severity of heart failure, and the incidence and severity of pre-existing renal disease. In recent studies using continuous-flow devices the incidence of acute renal failure after LVAD implantation ranged from 7% to 14% (Table 18).[44] Improvement in renal function has been reported in 74% of patients with baseline renal

dysfunction. The likelihood of improvement is less with more severe pre-implant dysfunction.

In the INTERMACS registry, the early (three months) event rate for renal dysfunction was 3.86 per 100 patients-months. The late (after the third month) event rate was 0.46 per 100 patients-months.

Renal dysfunction is the primary cause of death in 1.1% of patients.[14]

6.3.6 Device malfunction

There are several causes of LVAD malfunction, including thrombus formation, mechanical failure, and driveline lead fractures. Pump thrombosis is the most dreaded incident that may require emergency surgery. One SR on continuous-flow LVAD identified 12 observational studies with a total of 5,471 patients.[33] Device failure was defined as device malfunction necessitating exchange or explantation, or causing death. The overall incidence of device failure was 3.9% (range 1-11.3%) with a mean duration of LVAD support of 504.7 (range 303-568) days (Table 18). Device failure rates at 2-, 6-, 12-, 18- and 24-months post-implantation were 0.5%, 1.8%, 2.9%, 4.5% and 6.5%, respectively. Pump thrombosis was the most common cause of device failure (50.5%), followed by lead or cable damage (21.7%), mechanical pump failure (11.6%), device related infection (11.1%), and surgical complications from implantation (2.5%).

Of note, a recent study from 837 patients, not included in the abovementioned SR, showed an increase in the rate of pump thrombosis at 3 months after implant from 2.2% before March 2011 to 8.4% by January 2013.[29, 45] This finding was confirmed by data from the INTERMACS registry on 6,910 adult patients from 132 institutions who received a continuous-flow LVAD.[13] In this study there was a six fold increase in the need for device exchange or death due to thrombosis from 1% at 6 months in 2009 to 6% in 2012. When considering any reason pointing towards long term device malfunction (6910 pumps implanted from April 2008 through December 2012, with follow-up through June 2013), 9.5% of devices were exchanged or potentially involved in death (Table 19). Mortality associated with pump exchange is 6.5% among 77 replacement procedures.[13] In a safety communication issued on August 5, 2015, the FDA reported on this higher incidence of pump thrombosis compared to that observed during the clinical trials conducted in 2008 and 2010 to gain approval (http://1.usa.gov/1OQwgwX).

Table 19 – Left ventricular device failure (Heartmate II)

	n	% of total devices (N=6910)
Thrombus	337	4,9
Infection	76	1,1
Unclear	148	2,1
Exchange due to a problem	561	8,1
Death with a device that did not function normally	98	1,4
Device exchange or death with a device that did not function normally	659	9,5

Adapted from Kirklin et al.[13] Data on 6910 HeartMate LVADs implanted April 2008 - December 2012, with follow-up through June 2013.

In the most recent quarterly report of the INTERMACS registry, the early (three months) event rate for device malfunction was 2.70 per 100 patients-months, indicating that on average 8% of patients have a device malfunction during the first three months. The late (after the third month) device malfunction rate was 1.46 per 100 patients-months, indicating that on average patients 18% have such an event.[14] In this registry, device malfunction included both major and minor problems.

Device malfunction is the primary cause of death in 2.6% of (2012-2015) INTERMACS patients.[14]

6.3.7 Other serious adverse events

In the INTERMACS registry, "other serious event" is briefly described as "An event that causes clinically relevant changes in the patient's health" (https://www.uab.edu/medicine/intermacs/images/protocol_4.0/protocol_4.0_MoP/INTERMACS_MOP_Protocol_4_0_V1_0__06-3-2014.pdf). Nevertheless, its early (three months) event rate is 12.97 per 100 patients-months, indicating that on average 32% of patients have such an event during the first three months. The late (after the third month) rehospitalisation rate was 1.87 per 100 patients-months, indicating that on average one quarter of patients have such an event per year.[14]

6.3.8 Rehospitalisation

Recurrent hospital admission is a common occurrence in patients with LVAD.[29] Most discharged LVAD patients have 1 and often multiple readmissions within the first year (Table 18).[46] In McIlvennan's SR, one trial including 133 DT patients reported a readmission rate of 94% over a 24-month period. In another trial reporting on 111 DT patients, 2.8 admissions per patient-year were observed. The 30-day readmission rate was 26.1% (36 of 138) in a recent observational study that was not part of McIlvennan's SR.[47] Approximately 70% of post-operative readmissions occurred within 10 days of the patient's initial hospital discharge. Recurrent heart failure and gastrointestinal bleeding were the most common causes for 30-day readmission.

In the INTERMACS registry, the early (three months) event rate for rehospitalisation was 21.07 per 100 patients-months, indicating that on average 60% of patients have a rehospitalisation during the first three months. The late (after the third month) rehospitalisation rate was 15.90 per 100 patients-months, indicating that on average patients are readmitted twice per year.[14]

Neither McIlvennan's SR, nor the INTERMACS registry, differentiate between planned and unplanned rehospitalisation. In one series with a minority of DT patients (20 out of 118), of 92 patients discharged after initial implantation, 72 (78%) were readmitted a total of 211 times as of end of follow-up (mean follow-up was 1.3±0.47 years).[46] Of these, 177 were unplanned in 48 patients. Most (74%) of the 34 planned readmissions were for cardiac transplantation (n=25) or other elective procedures. Forty-eight patients (52%) had unplanned hospital readmissions.

6.4 Mortality due to adverse events

Most patients in whom an LVAD is implanted eventually die either due to complications related to the device, either due to residual (right) heart failure. In a series of 414 patients who received a HeartMate II LVAD, 150 (36%) died at 2 years follow-up.[30] The primary cause of death in those patients is shown in Table 20.

Table 20 – Primary cause of death of 150 HeartMate II patients

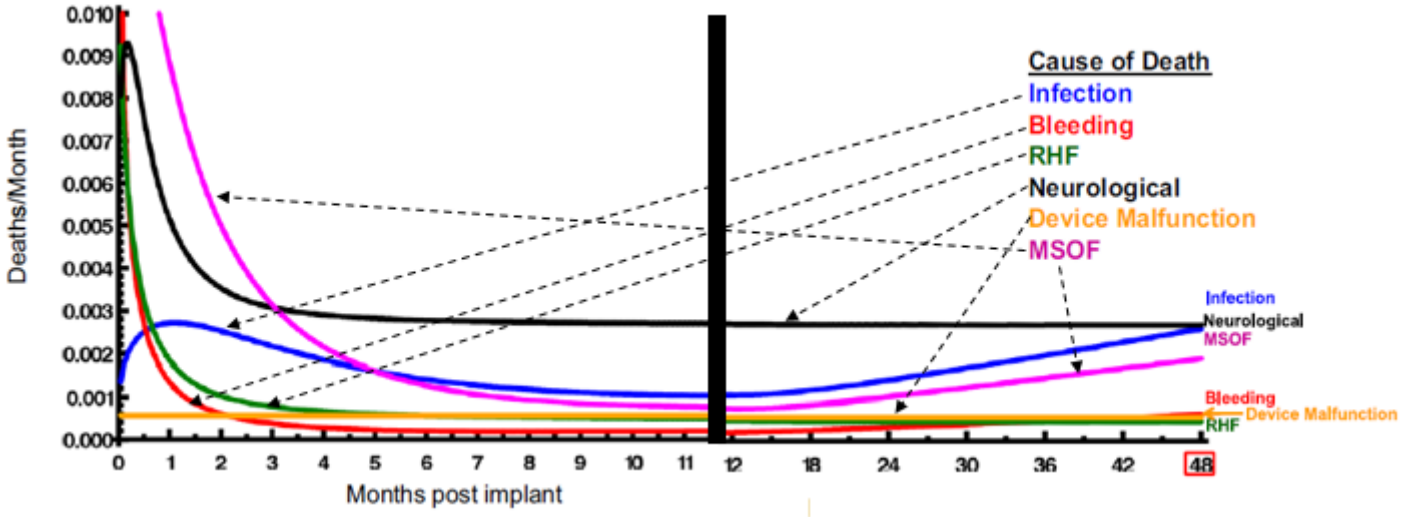
	n	%
Hemorrhagic stroke	16	10,7
Right heart failure	17	11,3
Bleeding	14	9,3
Sepsis	13	8,7
Multisystem organ failure	7	4,7
Ischemic stroke	10	6,7
External components, loss of power	9	6,0
Internal components, thrombosis, cable	10	6,7
Other	54	36,0
Sum	150	100,0

Adapted from Park et al.[30] Other causes of death include air embolism, anoxic brain injury, traumatic brain injury, cardiac arrest, cardiac failure, heart failure, respiratory failure, pneumonia, amyloidosis, cancer, liver failure, pancreatitis, withdrawal of support, respiratory failure, ruptured bladder, subdural hematoma, and unknown.

The most prominent primary causes of death in the INTERMACS registry (2033 deaths registered in 2012-2015) are multisystem organ failure (20.7%), neurological dysfunction (17.8%), major infection (5.6%), respiratory failure (5.4%), device malfunction (2.6%), and bleeding (2.4%).[14] Multisystem organ failure (MSOF) does not appear as such in the list of adverse events in Table 18. In fact this syndrome represents a final common pathway of several life-threatening conditions and represents the most common cause of death for patients admitted to a contemporary intensive care unit (http://www.ncbi.nlm.nih.gov/books/NBK6868/). Accordingly, death due to sepsis, bleeding, respiratory failure, or renal failure in one database, may as well be labelled as multisystem organ failure in another. This also explains the apparently contradictory incidence of MSOF reported in Table 20 versus Figure 6.

The time dependency of mortality due to these adverse events from INTERMACS is illustrated in Figure 6.

Figure 6 – Hazard function for death after primary continuous-flow LVAD implant (2008-2013)

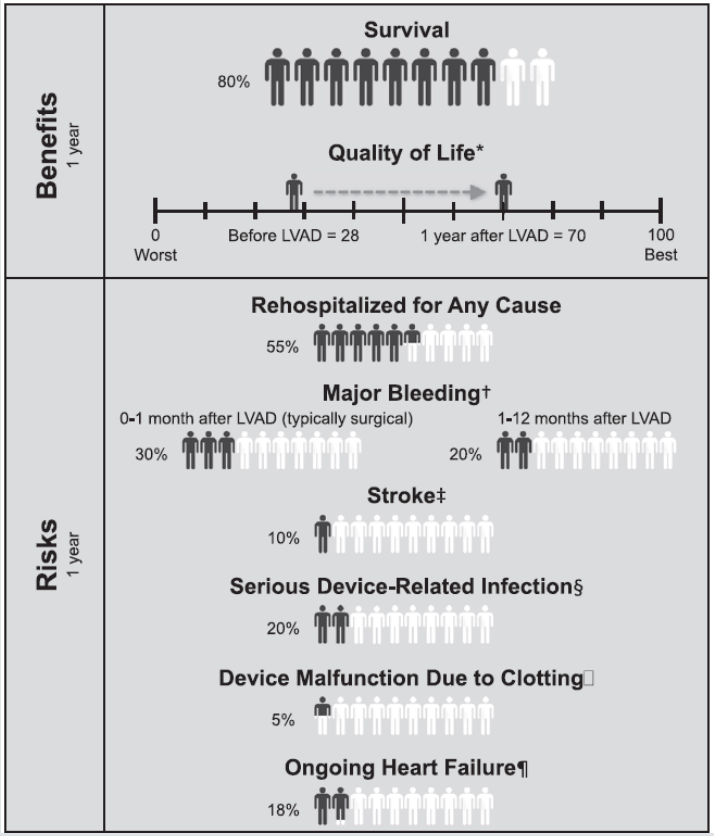


Adapted from Kirklin et al.[11] Graphs show the instantaneous risk for death for specific causes. E.g.: a patient who is alive at month-6 has a 0.3% absolute risk of dying from a neurologic event within the following month. RHF: right heart failure. MSOF: multisystem organ failure. Data also include patients treated with biventricular devices (BiVAD), representing 154 out of 9372 subjects. Note: time axis scale changes at 12 months, indicated by the black vertical line.

Key points

- **Bleeding is the most commonly reported adverse event of continuous-flow LVADs. Most patients experience some type of bleeding. The greatest risk of bleeding is within the first weeks postoperatively and is reported in 8 to 100% of patients. Late bleeding occurs in 12 to 23% of patients and is predominantly from gastro-intestinal origin.**
- **Ischaemic and haemorrhagic stroke occur in 8% and 11% of patients respectively in the first 2 years after LVAD placement.**
- **Infections after LVAD implantation may occur locally, at the driveline, or systemically. Local infections are reported in 20 to 49% of patients, driveline infections in 12 to 22%, and sepsis in 20 to 36% of patients.**
- **Right heart failure requiring inotropic support is reported in 5 to 25% of patients.**
- **Device failure rates at 12 and 24-months post-implantation are 2.9% and 6.5% respectively. Pump thrombosis accounts for half of the causes of device failure. In one series of 6 910 patients who received a continuous-flow LVAD and who were followed for up to 7 years, 9.5% of devices were eventually exchanged or potentially involved in death.**
- **McIlvennan et al. developped a pictograph (copied in Figure 7 below), intended for patients and their families, summarising an estimate of the full range of LVAD outcomes at 1-year based on weighted averages of all trial, registry, and single-center data identified through their systematic review.29**

Figure 7 – One-year outcomes of LVAD patients



*Source: McIlvennan et al.[29] Shaded: affected. *Kansas City Cardiomyopathy Questionnaire score. Major bleeding: requiring transfusion or urgent medical attention. Stroke: combined ischaemic (5±5%) and haemorrhagic (5±4%). Infection: 18±2% driveline and 2±2% pocket. Device malfunction: requiring replacement. Ongoing heart failure: requiring inotropes. Rehospitalisation: 55±2%.*

7 BELGIAN PRACTICE

7.1 Introduction

Implantable cardiac assist devices have been reimbursed since 1 July 1999 in Belgium for the indication bridge to transplant (nomenclature codes 684714-684725).

7.2 Data sources and methodology

IMA — AIM(Intermutualistisch Agentschap-Agence Intermutualiste) data have been analysed in this section, corroborated by TCT (Technische Cel-Cellule Technique) data. We also used data from the BACTS[17] (Belgische Vereniging voor Cardio-thoracale Heelkunde, Société Belge de Chirurgie Cardio-thoracique) registry[f] to count the number of interventions per year in order to compare different data sources (Table 21). BACTS registry data show a greater number of implanted LVADs per year; this can be partly explained by implanted LVADs included in studies and not eligible for reimbursement by RIZIV — INAMI.

Table 21 – Number of implanted left ventricular assist devices per year in Belgium

Year	IMA-AIM	BACTS
2006	10	20
2007	21	40
2008	28	41
2009	32	45
2010	30	N/A§
2011	38	50
2012	47	51
2013	45	55
2014	17*	63

** Data not available for the whole year. § No data received for this year.*

7.2.1 IMA — AIMdata

Data were extracted from the Intermutualistisch Agentschap-Agence Intermutualiste (IMA-AIM). Most of the Belgian residents are affiliated to one of seven sickness funds (verzekeringsinstellingen/organismes assureurs) to cover the majority of their health expenditures with the compulsory insurance. The sickness funds collect administrative and billing data so that affiliates can have health services reimbursed. The AIM-IMA centralises the data from all sickness funds for study purposes. There are three administrative databases containing data at the individual level:

- the population database containing population characteristics
- the health services database containing billing data for all reimbursed health care services
- the reimbursed drugs database (Pharmanet) containing reimbursed pharmaceuticals from public pharmacies

The health services database contains reimbursement codes of medical procedures, health care services, hospital admissions, drug use in hospital, etc. It also includes dates, providers, institutions and costs. The database of the permanent sample (EPS, Échantillon permanent – Permanente steekproef), which is a subset of the IMA — AIM data accessible to a limited number of Belgian government agencies (including the KCE), has also been used.

The records selected from the complete IMA — AIM database were all the health care and pharmaceuticals records from patients who underwent a left ventricular assist device implant (nomenclature codes 684714-684725) between 1 January 2006 and 31 December 2013, along with the population data to describe these patients. IMA — AIM data have limitations: since these are administrative data only, no diagnosis or other medical data are provided. The month and year of decease are also recorded in the population database.

[f] http://www.healthstat.be/web/register.xhtml?registerId=60

7.2.2 TCT data

Data from the Technische Cel-Cellule Technique (TCT, https://tct.fgov.be/) were also available, from 2008 to 2012[g]. This dataset is a coupling of RHM-MZH (résumé hospitalier minimum – minimale ziekenhuisgegevens) data (with diagnostic and procedures ICD-9-CM codes) and SHA-AZV (séjours hospitaliers anonymes – anonieme ziekenhuisverblijven) data (including costs). Since TCT data cover only hospital stays, the decease of a patient outside the hospital is not registered, which prevents patient follow-up. We therefore have used the TCT data mainly to corroborate the IMA — AIM data.

7.2.3 Population description

The mean (median) age of the selected IMA — AIM population (i.e. 179 male (75%) and 59 female (25%) Belgian residents who received an LVAD as BTT between 1 January 2006 and 31 December 2013) is 48 (51) years. The subgroup of patients with a continuous-flow LVAD (CF LVAD, i.e. HeartMate II, HeartWare) also has a mean (median) age of 48 (51) years and a comparable gender distribution.

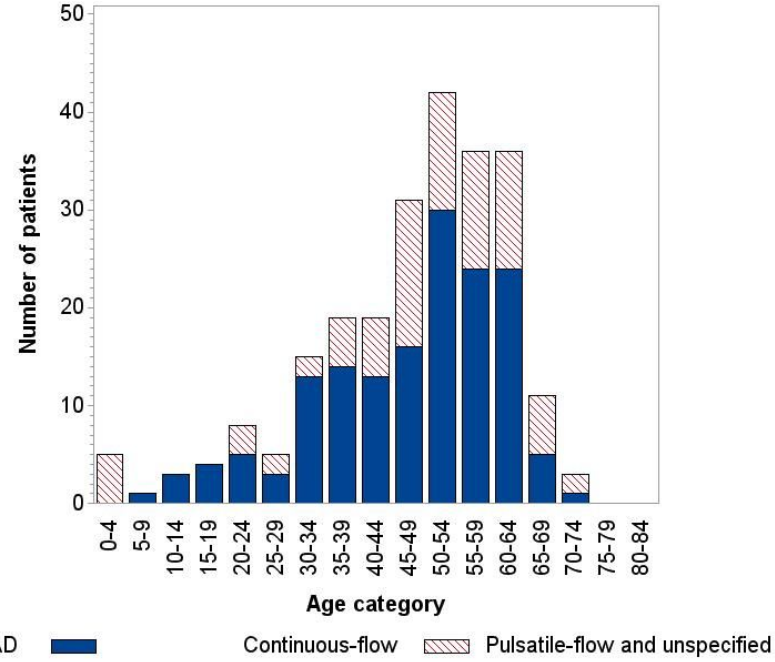
Figure 8 shows the age distribution for the whole LVAD population (n=238), which was subdivided in 2 groups: patients with a continuous-flow LVAD (n=156) and patients with other or unspecified devices (n=82).

7.3 Results

7.3.1 IMA — AIMdata

Patients included in the study have been followed since their first LVAD implantation. The yearly number of patients receiving a first LVAD is shown in Table 22. The number of patients in whom the device was a CF LVAD is shown separately. Over the years, an increase in proportion of CF LVADs is manifest.

Figure 8 – Age distribution of the study population (n=238)



Source: IMA — AIM(2006-2013).

[g] Longitudinality is broken at the end of 2011: the unique identifier assigned to each patient in the period from 2008 to 2011 is different from the one assigned from 2012 onwards.

Table 22 – Number of first LVADs

Year	All patients	Patients with continuous flow LVAD	% patients with CF LVAD
2006	10	0	0%
2007	21	2	10%
2008	23	12	52%
2009	32	19	59%
2010	30	23	77%
2011	36	23	64%
2012	43	40	93%
2013	43	37	86%
2006-2013	238	156	66%

Source: IMA — AIM(2006-2013).

Table 23 shows the 30-day mortality for these 238 patients: 7.1% of CF LVAD patients die within 30 days after LVAD implantation. For those patients who did not undergo a heart transplantation within the observation period, the respective proportion was 6.0%.

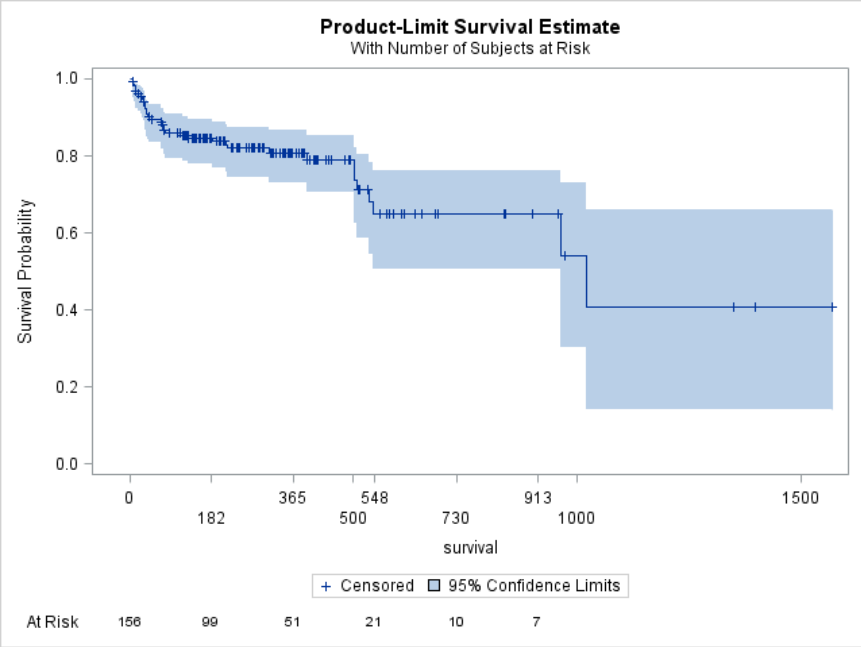
Table 23 – 30-day mortality after first LVAD implantation

Patients	All types of LVADs				Continuous-flow LVADs			
	Patients with any LVAD		Excluding patients undergoing a HTX within 30 days after LVAD implantation		Patients with CF LVAD		Excluding patients undergoing a HTX within 30 days after LVAD implantation	
	n	%	n	%	n	%	n	%
Alive after 30 days	205	87.2%	197	87.6%	143	92.9%	141	94.0%
Deceased within 30 days	30	12.8%	28	12.4%	11	7.1%	9	6.0%
Total	235*	100.0%	225	100.0%	154*	100.0%	150	100.0%

** The 3 patients undergoing a LVAD implantation in December 2013 have been excluded as follow-up would have been less than 30 days*
HTX: heart transplantation.
Source: IMA — AIM (2006-2013).

Actuarial survival analysis was performed by means of the Kaplan–Meier method. Time-to-event was calculated from the time of first LVAD implantation to either death (70 patients), heart transplantation (118 patients) or end of follow-up (50 patients). This analysis was performed both for all patients (n=238) and for those in whom a CF LVAD was implanted (n=156, Figure 9). The Kaplan–Meier estimates of survival for all patients is 71.3% at one year (number at risk: 60) and 55.5% after two years (number at risk: 12). For patients with a CF LVAD, the survival proportion is 80.8% after one year (number at risk: 51) and 64.9% after two years (number at risk: 10). The censoring is mainly due to patients receiving a heart transplantation (only three patients alive without HTX were not followed-up until the last month of the studied period).

Figure 9 – Kaplan-Meier survival curve for patients with a continuous-flow LVAD



Source: IMA — AIM(2007-2013).

The mean follow-up time for patients receiving a CF LVAD was 10.3 months (8.6 months for all patients). The mean number of hospitalisations (including the initial hospitalisation) was 2.96 for CF LVAD patients and 2.88 for all patients. After the initial stay, CF LVAD patients spent 5.53% of the time in hospital (7.45% for all patients).

Healthcare payer, patient costs and supplements (also paid by the patient) for Belgian patients along with length of stay (starting the day of the LVAD implantation) are summarised in Table 24 for the initial hospitalisation. Patients undergoing a heart transplantation or a second LVAD implantation during the initial hospitalisation have been excluded, as well as patients for whom there are no follow-up data after they have left the hospital alive. Patients with a CF LVAD have a more expensive device and higher costs in hospital, but a shorter initial hospitalisation (41.86 days on average) and consequently a lower cost for the initial stay (€45 788). The standard deviation of the supplements for the device cost is very high compared to the mean: most of the patients did not have to pay a supplement while one patient had a supplement above €80 000 (which probably includes the price of an LVAD).

Table 24 – Initial hospitalisation: healthcare payer, patient costs and length of stay (all patients and patients with a CF LVAD)

Category	Variable	All patients			Patients with a CF LVAD		
		N	Mean	Std Dev	N	Mean	Std Dev
Initial stay (days)	Length of stay*	211	46.70	41.35	148	41.86	29.64
Device cost (EUR)	RIZIV – INAMI (1)	211	66 915.56	18 604.80	148	73 710.33	12 331.05
	Patient (2)	211	3.52	22.68	148	0.00	0.00
	Total (1) + (2)	211	66 919.09	18 601.78	148	73 710.33	12 331.05
	Supplements	211	400.47	5 666.93	148	556.07	6 764.86
Costs initial stay (device excluded) (EUR)	RIZIV – INAMI (1)	210†	47 368.70	34 059.29	148	45 139.20	29 990.44
	Patient (2)	210†	688.36	362.63	148	648.53	278.58
	Total (1) + (2)	210†	48 057.07	34 317.36	148	45 787.73	30 176.50
	Supplements	210†	2 120.58	2 579.80	148	2 130.61	2 716.66

** Counting started from the day of the LVAD implantation.Source: IMA — AIM (2006-2013).*
† One patient was excluded because the RIZIV – INAMI costs were negative.

Table 25 shows the hospital stays characteristics for all patients and for the subgroup who received a CF LVAD. There are fewer patients (n=167) with days after the initial stay due to patients not leaving the hospital before the end of the period studied, patients deceased during the initial hospitalisation and patients receiving a heart transplantation during the initial stay.

Table 25 – Follow-up, hospitalisations and number of days in and out of hospital (all patients and patients with a CF LVAD)

Variable	All patients				Patients with CF LVAD			
	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median
Follow-up (days)	238	261.38	263.39	196.00	156	314.21	274.56	273.50
Number of (nb) hospitalisations	238	2.88	3.25	2.00	156	2.96	2.81	2.00
Nb days in hospital, initial stay included†	238	65.01	63.41	47.00	156	56.60	50.01	46.00
Nb days in hospital after initial stay	167	21.02	46.77	6.00	132	15.95	31.11	5.00
Nb days out of hospital after initial stay	167	286.44	251.38	239.00	132	307.91	256.72	253.00
% of days in hospital after initial stay	167	7.45	14.42	2.32	132	5.53‡	9.76	1.59

† Counting from the day of the LVAD implantation on.
‡ This is the mean per patient; in the chapter with the context-specific economic evaluation, the percentage for all patients is used: total number of days in hospital / total number of days = 2105 / (2105 + 40644) = 4.92% (2105 = 132 x 15.95; 40644 = 132 x 307.91)
Source: IMA — AIM(2006-2013).

Monthly costs in and out of the hospital after the initial hospitalisation are presented in Table 26. The monthly in-hospital costs are somewhat higher for patients with a CF LVAD (€26 431) compared to all patients' costs (€23 563), whereas the out-of-hospital costs are comparable (ca. €1300). Due to the nature of the data (administrative database), it was not possible to analyse the type of complications for the rehospitalisations.

Table 26 – Monthly costs in and out of the hospital after the initial hospitalisation (all patients and patients with a CF LVAD)

Category	Variable	All patients		Patients with a CF LVAD	
		N	Cost/month	N	Cost/month
Monthly in-hospital costs after initial stay (EUR/month)	**RIZIV-INAMI (1)**	211	23 328.14	156	26 160.29
	Patient (2)	211	234.63	156	270.67
	Total (1) + (2)	211	23 562.77	156	**26 430.96**
	Supplements	211	552.95	156	483.07
Monthly costs out-of-hospital after initial stay (EUR/month)	**RIZIV-INAMI (1)**	211	1 221.99	156	1 234.50
	Patient (2)	211	76.44	156	70.43
	Total (1) + (2)	211	1 298.42	156	**1 304.94**
	Supplements	211	26.85	156	28.48

Source: IMA — AIM(2006-2013).

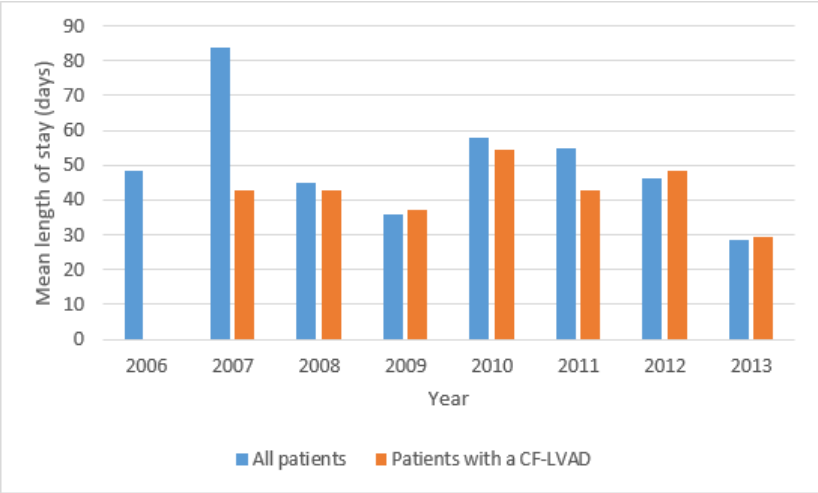
Table 27 presents the length of initial stay (from the day of the LVAD implantation), the costs for the device and the stay (from the day of the LVAD implantation, not counting the device) classified by year of LVAD implantation for all patients and patients with a CF LVAD separately. For all patients, the cost of the implant rises as the yearly proportion of implanted CF LVADs increases. The evolution of the length of the initial stay has been represented in Figure 10. Apart from the early years (2006 and 2007), the length of stay is similar for patients with a CF LVAD and all patients. There is a large variation in hospital stay during each year. In 2013, the length of stay was much lower than in previous years. More complete data from one hospital show that hospital stay was indeed lower during 2013-2015 in comparison with 2009-2012, with the shortest length of stay also in 2013 (see Appendix 3).

Table 27 – Stays characteristics per year (all patients and patients with a CF LVAD)

	All patients							Patients with a CF LVAD						
		LoS (days)		Costs: INAMI-RIZIV + patient (EUR)					LoS (days)		Costs: INAMI-RIZIV + patient (EUR)			
Year	N			Device		Initial stay (without device)		N			Device		Initial stay (without device)	
		Mean	Std Dev	Mean	Std Dev	Mean	Std Dev		Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
2006	6	48.50	58.76	64 680	38 885	41 157	29 546	0						
2007	13	83.92	92.26	57 735	13 286	65 659	51 093	2	43.00	29.70	69 239	0	34 589	19 530
2008	22	45.14	28.62	60 823	31 746	46 331	20 666	12	42.67	20.12	80 779	26 951	47 581	19 230
2009	28	35.96	20.43	59 185	16 749	38 573	14 936	18	37.00	19.62	69 239	0	39 140	15 113
2010	28	58.04	37.42	60 830	16 897	57 042	41 529	21	54.48	37.67	66 137	14 214	57 049	45 307
2011	35	54.86	43.92	66 627	18 166	56 694	44 459	23	43.00	26.05	74 521	14 824	46 405	25 815
2012	38	46.39	39.77	75 672	7 808	50 510	37 159	36	48.28	39.94	76 257	6 399	52 177	37 440
2013	41	28.37	14.32	75 007	8 383	34 938	17 649	36	29.47	14.42	75 191	6 595	35 784	18 457
2006-2013	211	46.70	41.35	66 919	18 602	48 057	34 317	148	41.86	29.64	73 710	12 331	45 788	30 177

Source: IMA — AIM(2006-2013).

Figure 10 – Mean length of stay per year for all patients and for patients with a CF LVAD



Source: IMA — AIM(2006-2013).

7.3.2 TCT data

Table 28 shows the number of stays since the LVAD implant, number of days at hospital, patient age and the length of the first hospital stay (placing of the LVAD): TCT data were used as a second source of Belgian data to confirm the results from the IMA – AIM data analysis. Data are congruent with the IMA – AIM data (comparing with all patients). Some patients are not included in the TCT because the coupling between clinical data (RHM – MZG data) and billing data (SHA – AZV data) could not be achieved; this explains why there are differences between the two datasets.

- Number of stays: the mean is a bit higher (3.44 vs 2.88 for IMA – AIM data), the median is the same (2);
- Number of days at hospital (including the initial stay): TCT data values are a bit higher (mean: 68.93 days vs 65.01 days for IMA – AIM data) while the median for TCT data is clearly higher (61 days vs 47 for IMA – AIM data)
- Length of stay for the initial stay: again the mean is higher (50.11 days vs 46.70 days for IMA – AIM data), the median is quite similar;
- Age is almost the same, patients are 47 years old on average (48 for IMA – AIM data) and the median is the same (51) in both datasets.

Table 28 – Patients characteristics

Variable	n	Minimum	Maximum	Mean	Std Dev	p25	Median	p75
Number of stays	133	1	17	3.44	2.84	1	2	5
Days at hospital	133	1	245	68.93	50.69	33	61	84
Length of stay (first stay, days)	133	2	240	50.11	39	26	42	62
Age when first LVAD implanted	133	1	70	47.28	15.21	38	51	59

Source: TCT data, 2008-2012.

Key points

- **Between 2006 and 2013, LVAD techniques have evolved in the Belgian practice: CF LVAD implants started in 2007 and comprise the vast majority in 2013.**
- **The survival for patients with a CF LVAD is 81% after one year follow-up and 65% after two years follow-up; 30-day mortality is 7%.**
- **Over 60% of LVAD patients are between 45 and 64 years when they are implanted; less than 5% are 65 years or older.**
- **Costs (heathcare payer + patient costs, not counting the supplements): the mean cost for a CF LVAD is €73 710, the mean cost for the initial hospital stay is €45 788 for a mean length of initial stay of 42 days.**

8 COST-EFFECTIVENESS OF LVAD: LITERATURE REVIEW

8.1 Literature search

8.1.1 Search strategy

A systematic search for economic literature about the cost-effectiveness of LVADs was performed by consulting various databases. First of all, reviews on this topic were searched by consulting the CRD (Centre for Reviews and Dissemination) HTA database and websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website. Websites of ex- or non-member HTA institutes such as NICE (National Institute for Health and Care Excellence) were also consulted. We also consulted the EUnetHTA's (European Network for Health Technology Assessment) POP database (Planned and Ongoing Projects).

The NHS EED (CRD's Economic Evaluation Database), Medline (OVID), and EMBASE databases were searched to retrieve both full economic evaluations and reviews of full economic evaluations of LVADs. No language restrictions were imposed.

The search strategy was performed in August 2015 and was an update of a search strategy performed by one of the authors of the current report which also co-authored a previous HTA report for the Dutch government[21] on the same topic. The results of this previous systematic review were published.[21,48] An overview of this (updated) search strategy and results is provided in Appendix 3.

8.1.2 Selection criteria

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 29). For the population, intervention and comparator, we refer to the medical in- and exclusion criteria (see part 3.1). The design is restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Cost-minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses were eligible.

The selection of relevant articles was performed in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. The primary full economic evaluations were summarized in an in-house data extraction sheet (see Table 66 in appendix). This in-house document is used as a reporting checklist to gather all relevant information. The data extraction sheets of all identified studies are working documents that provide the basis for summary tables and a critical assessment of identified economic evaluations.

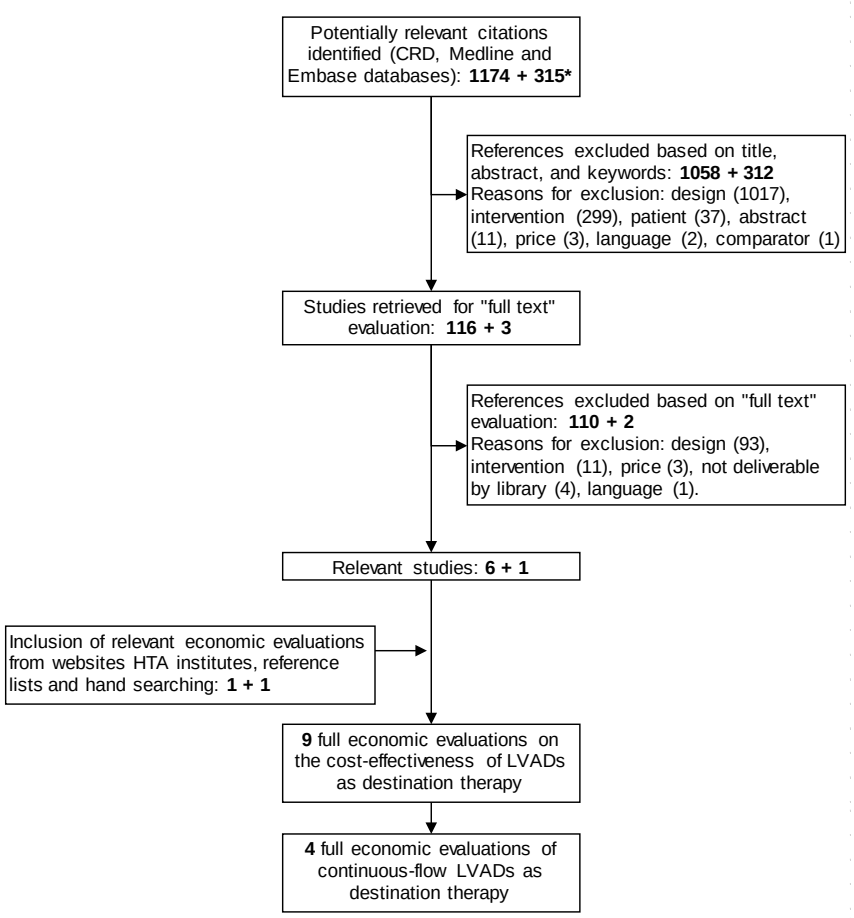
Table 29 – Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population, Intervention and Comparator	See Table 5	
Design	Full economic evaluations	Other designs such as cost calculations

8.2 Results of the economic search strategy

Figure 11 provides the flow chart of this process. In the end, in comparison with the previously published systematic review, one extra economic evaluation[49] was selected and the full HTA report for the Netherlands[21] was also included in the list of selected economic evaluations (Table 30).

Figure 11 – Selection of relevant articles



** The first number refers to the references identified in the previous search performed in December 2013.[48] The second number refers to the update of this search strategy performed in August – October 2015.*
CRD: Centre for Reviews and Dissemination; EED: Economic Evaluation Database; HTA: Health Technology Assessment; LVAD: left ventricular assist device.

Table 30 – List of selected economic evaluations

References
Pulsatile-flow LVADs
Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, et al. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. Health Technol Assess. 2005;9(45):1-132.[50]
Clegg AJ, Scott DA, Loveman E, Colquitt J, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for people with end-stage heart failure: a systematic review and economic evaluation. Int J Technol Assess Health Care. 2007;23(2):261-8.[51]
Adang E, Groenewoud H, van Hees F, Krabbe P, van der Wilt G. Invoering van kunst-en steunhart als bestemmingstherapie voor patiënten met eindstadium hartfalen- Gevolgen voor ziektelast en kosten van behandeling. Nijmegen: Universitair Medisch Centrum St Radboud; 2006.[52]
Girling AJ, Freeman G, Gordon JP, Poole-Wilson P, Scott DA, Lilford RJ. Modeling payback from research into the efficacy of left-ventricular assist devices as destination therapy. Int J Technol Assess Health Care. 2007;23(2):269-77.[53]
Messori A, Trippoli S, Bonacchi M, Sani G. Left ventricular assist device as destination therapy: application of the payment-by-results approach for the device reimbursement. J Thorac Cardiovasc Surg. 2009;138(2):480-5. [54]
Continuous-flow LVADs
Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circ Heart Fail. 2012;5(1):10-6.[55]
Neyt M, Smit Y, Van den Bruel A, Vlayen J. Left ventricular assist device (LVAD) toegepast als bestemmingstherapie bij patiënten met eindstadium hartfalen. Rapport voor het college voor zorgverzekeringen. 2011.[21]
Neyt M, Van den Bruel A, Smit Y, De Jonge N, Erasmus M, Van Dijk D, et al. Cost-effectiveness of continuous-flow left ventricular assist devices. International Journal of Technology Assessment in Health Care. 2013;29(3):254-60.[56]
Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. Circulation: Heart Failure. 2014;7(3):470-8.[49]

The above-mentioned economic evaluations of pulsatile LVADs relied on the results of the REMATCH trial to compare a pulsatile-flow LVAD with optimal medical therapy (OMT). These evaluations were performed before the publication of the HeartMate II (HM-II) Destination Therapy Trial which compared a pulsatile-flow with a continuous-flow LVAD. In current practice, continuous-flow LVADs are used. Therefore, we do not include the economic evaluations on pulsatile-flow LVADs in this overview. For more details on these analyses, we refer to a systematic review of this literature in a previously published HTA report[21] (in Dutch) or published review article[48] (in English). In the present report, we focus on the published economic evaluations on continuous-flow LVADs as these are commonly used nowadays.

Two of the four identified economic evaluations will be discussed as one study since some analyses in the HTA report by Neyt et al.[21] were published in an international journal[56] without changes in the methodology and results.

One reference was not a full economic evaluation, but may provide interesting information on the costs of LVADs as destination therapy in the Belgian context.[25] This article will not be discussed in the overview of

economic evaluations, but will be used for validation purposes of the Belgian data used in the context-specific economic evaluation (see chapter 9).

The POP database indicated that our Italian HTA colleagues were also working on this topic. Due to a difference in timing, collaboration was difficult. In January 2016, we received a first draft of the Italian HTA report on LVADs.[57] As a validation of our search strategy, we checked if additional references were identified in the Italian report. In the Italian HTA report, six evaluations [49, 55, 56, 58-60] were included in the economic review. One study[58] was merely a cost analysis and thus excluded in this report. Three studies[58-60] assessed LVADs as BTT. Two studies[55, 56] analysed the implantation of LVAD as DT and one study[49] focused on both BTT and DT. In other words, we identified the same three studies[49, 55, 56] about LVADs as destination therapy as our Italian colleagues identified in their report.

8.3 Overview of economic evaluations

8.3.1 General information

The three included evaluations were carried out for the United States (US) (2) and the Netherlands (1) (Table 31). All studies use a Markov model to carry out a cost-utility analysis. A 5-year[55] or lifetime[21, 49] time horizon was applied. Discounting was performed for both costs and effects, with the exception of the study of Long et al.[49] not discounting life years.

The age of the population in one study[49] is somewhat different. All studies refer to the results of the REMATCH trial[26] and the HeartMate II Destination Therapy Trial[7] to model outcomes for optimal medical therapy and continuous-flow LVADs. The weighted average age in these trials is 64 years, with an 83% male/female proportion. In contrast, the age in the reference analysis of Long et al.[49] is 50 years. This is because their analysis does not only focus on a comparison of LVADs as destination therapy versus optimal medical therapy for transplant-ineligible patients, but also includes a comparison between inotrope-dependent medical therapy (IDMT, what we refer to as OMT), orthotopic heart transplantation (OHT), BTT-LVAD, and DT-LVAD for transplant-eligible patients. In their initial analysis, they assume an average age of 50 years for all these alternatives. In this overview, we will only present the results for the in scope analysis for transplant-ineligible patients.

8.3.2 Costs

Table 32 provides an overview of the most important cost items and their valuation. All economic evaluations included direct medical costs. To reflect a broader societal perspective, the Dutch analysis[21] also included travel costs. However, these costs were so small relative to the medical cost that they could be neglected. Long et al.[49] performed the analysis 'from a societal perspective'. However, non-healthcare related costs (such as impact on productivity or travel costs) were not included, which rather reflects a healthcare payer perspective.

The largest cost is for the initial LVAD implantation: $193 812[55]; €126 505[21]; $239 160[49]. All studies also include a monthly outpatient costs and costs for rehospitalisations. After an LVAD implantation, complications include stroke, gastrointestinal bleeding, driveline infection, or pump failure requiring device replacement. In two studies, a general cost for such complications is included. In Long et al.[49] a complication-specific cost is included. The two US studies also include an end-of-life cost ($44 200[55] and $49 800[49]).

Table 31 – General information on the identified economic evaluations

Reference (country) Conflict of interest	Time horizon Discount rate	Analytic technique Design	Population Intervention and comparator
Rogers et al., 2012 (US) Thoratec provided funding support. Authors have served as consultants for Thoratec, received a research grant, or are employee of Thoratec.	5 years 3% for both costs and effects	CUA Markov model	Patients with predominantly NYHA class IV symptoms and an LVEF of <=25%. These patients were ineligible for heart transplantation. Continuous-flow LVAD as destination therapy versus OMT.
Neyt et al., 2011/2013 (the Netherlands) No conflict of interest.	Lifetime Costs: 4% Effects: 1.5%	CUA Markov model	Adults (age 64 years, 83% male) with chronic end-stage heart failure, contraindications for a heart transplant, LVEF of 25 percent or less, and NYHA class IV for at least 90 days despite OMT. Continuous-flow LVAD as destination therapy versus OMT.
Long et al., 2014 (US) One of the authors received speaking fees and consulting fees from Thoratec Corporation.	Lifetime 3% for both costs and effects (QALYs) No discounting for life years.	CUA Markov model	Patients aged 50 years with inotrope-dependent stage D heart failure. Transplant-ineligible patients (amongst others). Continuous-flow LVAD as destination therapy versus OMT.

CUA: cost-utility analysis; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OMT: optimal medical therapy.

Table 32 – Cost information

Reference	Rogers et al., 2012	Neyt et al., 2011/2013	Long et al., 2014
Perspective	Healthcare payer perspective.	Societal perspective.	Healthcare payer perspective.
Currency & year	$, 2009	€, 2010	$, 2010
Cost information	- LVAD implantation hospital cost: $193 812 - LVAD implantation professional service cost: $8841 - LVAD replacement cost: $131 430 - Monthly LVAD replacement rate: 0.005 - Rehospitalization cost (per event): $6850 - Monthly rehospitalization rate for LVAD: 0.21 - Monthly rehospitalization rate for OMT: 0.1325 - Monthly outpatient costs (LVAD & OMT): $2331 - End-of-life cost (LVAD & OMT): $44 211 Total costs (discounted): - OMT: $62 856 - LVAD: $360 407 - Incremental cost: $297 551	Data from UMC Utrecht (69 patients with HM-II implantation as BTT). - LVAD implantation cost: €126 505 (incl. LVAD device of €70 000). - cost rehospitalization (excl. LVAD replacement): €8118 Number of repeat hospitalizations: - HM-II group: 2.64 per patient-year - OMT group: 3.15 per patient-year Monthly costs: - LVAD €1261 (incl. rent PBU and LVAD accessories) - OMT: €1047 Total costs (discounted): - OMT: €30 900 - LVAD: €330 000 - Incremental cost: €299 100 (95% CI, 190 500–521 000)	Direct costs for repeat hospitalizations and outpatient care were derived from 3674 patient-months (June 2011 to May 2013 at Yale-New Haven Hospital), which included 30 LVAD, 32 OHT, and 32 IDMT patients. Monthly cost of OMT (IDMT): - $9072 12 months before death, - $4404 12-24 months before death, and - $2039 more than 24 months before death. LVAD (DT): - index hospitalization: $239 160 - $10 984 first 12 months - $3121 after 12 months. Others: - End of life: one-time cost of $49 838. - Acute stroke: $20 155 - Monthly poststroke care: $3076 - Gastrointestinal bleed: $12 165 - Driveline infection: $41 504 - LVAD replacement surgery: similar cost to the original procedure. Total costs (discounted): - OMT: $112 600 - LVAD: $593 000 - Incremental cost: $480 400

BTT: bridge to transplantation; DT: destination therapy; HM-II: HeartMate II; IDMT: inotrope-dependent medical therapy; LVAD: left ventricular assist devices; OMT: optimal medical therapy; PBU: Power base unit; UMC: University Medical Center

8.3.3 Survival

The economic evaluations combined the results of the REMATCH trial[26] and the HeartMate II Destination Therapy Trial[7] or the INTERMACS registry[41] to make an indirect comparison of a continuous-flow LVAD with OMT. The difference in survival for the OMT group, all based on the REMATCH trial (Table 33), was based on the use of the original 2001 publication (2-year survival of 8%[26]) versus an updated publication published in 2004 (2-year survival of 13%[36]). The one and two-year survival in the LVAD group was also somewhat better in the study of Long et al.[49] which referred to the INTERMACS study. The authors mentioned they made an adjustment to obtain survival rates for transplantation-ineligible patients. Due to the limited follow-up period in the trials, extrapolation to a longer (lifetime) horizon was necessary to calculate the number of life-years and quality-adjusted life-years (QALYs) gained. In the reference case of the Dutch study, an age- and sex-adjusted increase in mortality was included in the extrapolation phase.

The estimated survival in the OMT group is similar between the three studies (on average 0.64 - 0.81 life years). In the LVAD group, the relatively low survival in the study of Rogers et al.[55] is in contrast with the two other studies. This is related to the extrapolation assumption in this study which is based on the mortality during the first two years, including the relatively high surgery-related mortality. The two other studies refer to the mortality during the second year for their extrapolation.

8.3.4 Quality of life

All economic evaluations performed a cost-utility analysis. Unfortunately, the published RCTs did not provide measures of quality of life (QoL) that result in utility weights which can be used in economic evaluations. As a result, all economic evaluations tried to include the impact on QoL in one or another way. Rogers et al.[55] mapped NYHA classes with utilities (Table 34).

Neyt et al.[21] applied the results from the study of Moskowitz.[61] At the moment of their analysis, only Moskowitz et al. (8) directly measured utility values applying the standard gamble technique in patients with a pulsatile-flow LVAD as bridging therapy. Due to a lack of better and more recent data, the utility measures from this study were applied in their model: 0.548 (±0.276, 95 percent CI, 0.39–0.71) before implantation and 0.809 (± 0.136, 95 percent CI, 0.75–0.87) during LVAD support. These utilities were kept constant in their extrapolations.[21] The use of these utility values and the extrapolation assumption was considered as a rather optimistic scenario by the authors.

Long et al.[49] referred to several other studies for utility weights attached to OMT,[55, 62] LVAD during the first month[62] and thereafter[41]. The latter is based on results from the INTERMACS study. Utilities related to complications were based on a previous literature review on stroke[63] or based on expert opinion for gastrointestinal bleeding and driveline infection. If an event occurred, the authors assumed a decrement in quality-of-life during the initial month (Table 34).

The QALYs gained were the largest in the Dutch analysis[21] (2.83 QALYs gained versus 2.38 QALYs in the study of Long et al.[49]), mainly due to the very optimistic QoL values applied in this model.

Table 33 – Survival in the identified economic evaluations

Reference	Survival
Rogers et al., 2012	OMT: KM survival curve from the REMATCH trial. Continuous-flow LVAD: KM survival curve from the HeartMate II Destination Therapy trial. Extrapolation past 24 months: based on exponential survival curve using the constant hazard rate observed within 24 months - OMT: 0.105 per month - Continuous-flow LVAD: 0.023 per month (base case analysis). LVAD vs. OMT: 2.42 versus 0.64 life years (discounted).
Neyt et al., 2011/2013	OMT: survival from the REMATCH trial. - 1 year: 28% - 2 year: 13% Continuous-flow LVAD: survival from the HeartMate II Destination Therapy trial. - 30 days: 89.9% - 1 year: 68% - 2 year: 58% Extrapolation past 24 months (base case scenario): - OMT group: 2-year survival of 13%; no survival after 3 years. - Continuous-flow LVAD: the monthly mortality during the second year is used to extrapolate results. In the reference case, age and gender-adjusted increase in monthly mortality risk is applied according to Dutch life table. LVAD vs. OMT: 4.04 versus 0.81 life years (discounted) Discounted incremental effect: 3.23 life-years gained (LYG) (95% CI, 2.18–4.49).
Long et al., 2014	OMT: Survival rates of 23% at 1 year and 8% at 2 years (based on the REMATCH trial). - 6 months: 51% - 1 year: 26% - 2 year: 8% LVAD: Survival as destination therapy for patients ineligible for heart transplantation: - 6 months: 85% - 1 year: 77% - 2 year: 62% Beyond 12 months, a constant monthly mortality hazard rate was assumed based on a similar observation in INTERMACS from 12 to 48 months. LVAD versus OMT: 4.42 versus 0.78 life years (undiscounted).

KM: Kaplan-Meier; LVAD: left ventricular assist devices; LYG: life years gained; OMT: optimal medical therapy

Table 34 – Quality of life in the identified economic evaluations

Reference	Quality of life
Rogers et al., 2012	Mean utility values of 0.855, 0.771, 0.673, and 0.532 for NYHA classes I, II, III, and IV. Probability of belonging to a specific NYHA class: Monthly estimates obtained from the REMATCH and HeartMate II Destination Therapy trials for the OMT and LVAD arms (probabilities of being in NYHA I-IV at 0, 1, 3, 6, 9, 12, 18 and 24 months in original text). LVAD vs. OMT: 1.87 versus 0.37 QALYs (discounted)
Neyt et al., 2011/2013	QoL (Moskowitz et al., 1997) - LVAD: 0.809 (95% CI 0.745 – 0.873) - OMT: 0.548 (95%CI 0.389 – 0.708) QALYs for LVAD and OMT group were not separately published. Discounted incremental effect: 2.83 QALYs gained (95% CI, 1.91–3.90)
Long et al., 2014	QoL: - OMT: 0.53 (Rogers et al., 2012; and Sharples et al., 2006) - LVAD month 1: 0.51 (Sharples et al., 2006) - LVAD after first month: 0.72 (Kirklin et al., 2013) - Stroke: 0.68 (Post et al., 2001) - Gastrointestinal bleed: 0.60 (expert opinion) - Driveline infection: 0.60 (expert opinion) LVAD vs. OMT: 2.79 versus 0.41 (discounted)

LVAD: left ventricular assist devices; NYHA: New York Heart Association; OMT: optimal medical therapy; QALY: quality-adjusted life year; QoL: quality of life

8.3.5 Uncertainty

Most input parameters are surrounded by uncertainty and can be described by a probability distribution, rather than a point estimate. For parameter uncertainty, most guidelines recommend probabilistic sensitivity analysis (PSA).[64] This technique is only applied in the Dutch study.[21] Beta distributions were applied to transition probabilities and utilities, gamma distributions for costs, lognormal distributions for hazard ratios and a wide uniform distribution for number of events per patient-year.

On the other hand, all studies performed one- or multi-way sensitivity analysis changing one or more variables at the same time. Rogers et al.[55] changed long-term survival extrapolation for patients with an LVAD, hospital costs for an LVAD implantation, rehospitalisation costs, monthly rehospitalisation rate for OMT patients, and utilities for the different NYHA classes. The Dutch study[21] performed scenario analyses changing the discount rate for both costs and effects, applying different extrapolation scenarios, changing the number of hospitalisations per patient-year, assuming a different service life of the device, decreasing QoL in both the LVAD and OMT group, and lowering the cost of the LVAD device. Long et al.[49] performed sensitivity analyses in the transplant-ineligible population changing age, medical therapy mortality, and complication rates.

The most determining variables are mentioned in the results section.

8.3.6 Results and authors' conclusions

Table 35 provides an overview of the results of the identified economic evaluations.

While the ICER for a continuous-flow LVAD as destination therapy is very high in the study of Rogers et al.[55], i.e. $198 184 per QALY and $167 208 per life year gained, the conclusions of the authors sound more optimistic. This is because they compare this ICER with the result for a pulsatile-flow device, being $802 700 per QALY. The authors anticipate that "*continued refinement of patient selection criteria, technological advances, and improvements in management strategies will converge and result in the demonstration of LVADs as an economically effective treatment option for patients with advanced heart failure.*"[55] Further evidence is needed to be able to support this forecast. The results were most sensitive to the cost of device implantation, long-term survival, cost per rehospitalisation, and utility associated with patients' functional status.[55]

The Dutch analysis provided ICERs of more than €100 000 per QALY gained, based on multiple analyses with several optimistic assumptions.[21] The authors acknowledge the improvement in survival and quality of life. However, based on the relatively high ICERs, the authors conclude that "*from an efficiency point of view, based on currently available evidence and costs, reimbursement of LVAD implantation as destination therapy is very questionable. These results remain up-to-date until new evidence with significantly better outcomes for mortality, QoL, side effects and/or costs are presented.*"[56] Results were most sensitive to changes in device and implantation costs, and QoL.

Finally, also the study of Long et al.[49] provides ICERs of about $200 000 per QALY gained. The conclusion is in line with those of the Dutch study: "*In patients ineligible for transplantation, DT-LVAD substantially improves survival compared with medical therapy, although advances in medical complication rates or implantation costs must improve to render it as cost effective as other medical technologies.*"[49] ICERs remained relatively high for different ages and further increased with improving outcome of the OMT group. If complications were eliminated completely, then LVAD as destination therapy would cost about $100 000 per QALY gained.[49]

Table 35 – Results and conclusions of the identified economic evaluations

Reference	Result
Rogers et al., 2012	- ICER: $198 184/QALY (1,5 QALYs gained and additional cost of $297 551) and $167 208/LYG (1,78 LYG and additional cost of $297 551). Authors' conclusions: "*The cost-effectiveness associated with continuous-flow LVADs for destination therapy has improved significantly relative to the pulsatile flow devices. This change is explained by significant improvements in survival and functional status and reduction in implantation costs.*"
Neyt et al., 2011/2013	- ICER: €107,600/QALY (95% CI, 66,700–181,100) (2.83 QALYs gained and additional cost of €299,100) and €94,100/LYG (95% CI, 59,100–160,100) (3.23 LYG and additional cost of €299,100) Authors' conclusions: "*Although LVAD destination therapy improves survival and quality of life, it remains a relatively expensive intervention which renders the reimbursement of this therapy questionable.*"
Long et al., 2014	- $201,600/QALY (2.38 QALYs and additional cost of $480,400) and $131,800/LYG* (3.64 (undiscounted) life years Authors' conclusions: "*Destination therapy-LVAD significantly improves life expectancy in OHT-ineligible patients. However, further reductions in adverse events or improved quality of life are needed for destination therapy-LVAD to be cost effective.*"

**: life years (gained) were not discounted.*
LYG: life-year gained; QALY: quality-adjusted life year.

Key points

- **Previous economic evaluations performed for the US and the Netherlands provide relatively high ICERs of on average about $200 000 per QALY gained (two US studies) or more than €100 000 per QALY gained (Dutch study).**
- **The cost-effectiveness of CF LVADs has improved much in comparison with PF LVADs. However, based on previously published economic evaluations, its cost-effectiveness remains unfavourable and further improvements (better survival, less adverse events, more pronounced QoL improvement, lower implantation costs, etc.) are needed to make this technique acceptable from a medical/economic point of view.**

9 COST-EFFECTIVENESS OF LVAD: CONTEXT-SPECIFIC ECONOMIC EVALUATION

In this report, we have Belgian observational data at our disposal, which we intend to use in a context-specific economic evaluation. Therefore, we performed an update of a previously published model.[21, 56] Different scenarios are applied. To provide full transparency, we provide information on both the input in the initial model that was performed for the Netherlands[21] and the adjustment carried out in this updated analysis for Belgium. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist was used to be sure that all of the relevant information is transparently reported (Appendix 5).[65]

9.1 Input

9.1.1 Perspective of the evaluation

Following the Dutch economic evaluation guidelines,[66] the initial analysis was performed from a societal perspective. Next to the direct healthcare related costs, this included travel costs (direct costs outside the health sector). No impact was assumed on productivity, given the average age of patients in this population (see 9.1.2). Travel expenses, however, were minimal (<€300 per year) compared to the total cost of the LVAD implantation (about €126 000), rehospitalisation- and other follow-up costs. In the current analysis we follow the Belgian guidelines[67] to perform economic evaluations and perform the analysis from the perspective of the healthcare payer. Differences in costs are transparently published further in this report (see 9.1.10).

9.1.2 Population

The target group consists of patients with end stage heart failure, receiving an LVAD as destination therapy. The results of the model are applicable to patients with the same selection criteria as in the most recent trial on which the model is based, being the HeartMate II Destination Therapy Trial of Slaughter et al.[7] This is the case in both the original and updated economic evaluation. In this trial, patients with the following characteristics were selected:

- Patients with advanced heart failure, left ventricular ejection fraction <25%, who do not qualify for heart transplantation,
- NYHA Class IIIB or IV for at least 45 of the 60 days before inclusion, or
- dependence of an intra-aortic balloon pump (IABP) for 7 days or inotropes for at least 14 days prior to inclusion,
- VO2 max less than 14ml/kg/min or less than 50% of the predicted value.

The treatment effect (see 9.1.7) is based on the REMATCH[26] and HeartMate II Destination Therapy Trial[7] studies. The age and the male/female ratio of the population in the model is a weighted average based on these studies, being 64 years and 82.7% men.

9.1.3 Intervention and comparator

The implantation of an LVAD as destination therapy in patients who are not eligible for heart transplant is compared with getting optimal medical therapy (OMT) (see 9.1.10.4). We do not consider pulsatile-flow LVADs, but only continuous-flow LVADs (HeartMate II and HeartWare).

9.1.4 Analytical technique

Since the improvement of quality of life is one of the important goals of LVAD implantation, a cost-utility analysis (CUA) is performed. Results of the cost-effectiveness analysis (CEA) in which the years of life are not adjusted for quality of life are also presented. Both incremental costs (IC), incremental effects (IE) in life years gained and QALYs gained, and incremental cost-effectiveness ratios (ICER) will be presented separately.

9.1.5 Time horizon and discount rate

The implantation of an LVAD has a significant impact on mortality. Adopting a lifetime time horizon is necessary in order to capture the impact on all relevant incremental costs and effects. Therefore, results are extrapolated after the trial follow-up period until all patients in the theoretical cohort are deceased.

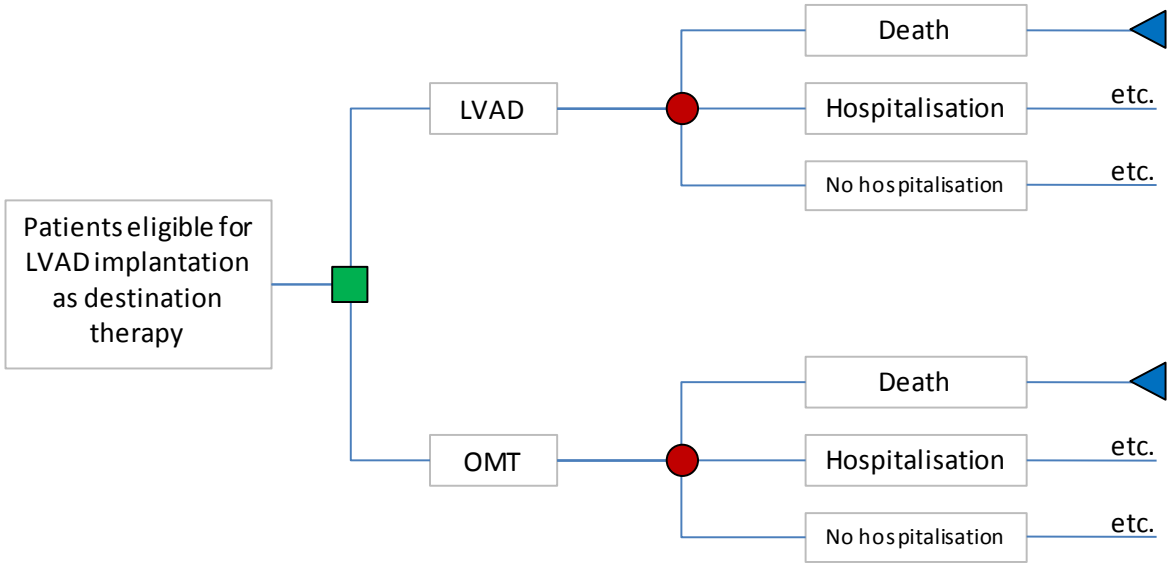
Costs and effects are discounted on a monthly basis in the Markov model with monthly cycles (see 9.1.6). The original model was set up for the Netherlands. According to the Dutch guidelines for economic evaluations,[66] the annual discount rate should be 4% and 1.5% for costs and effects,

respectively (or a monthly discount rate of 0.33% and 0.12%). The current model is set up for Belgium. According to the Belgian guidelines for economic evaluations,[67] a yearly discount rate of 3% and 1.5% for costs and effects, respectively, should be applied (or 0.25% and 0.12% monthly). Following the Belgian guidelines for economic evaluations,[67] this is changed in scenario analyses to 0%, 3% and 5% for both costs and effects.

9.1.6 Markov model

A hypothetical cohort of 1000 patients was modelled in Microsoft Excel 2010, using @Risk software (Palisade Corporation) to incorporate uncertainty around the input variables. This cohort reflects the population from the trials that demonstrate the evidence of efficacy of an LVAD. Figure 12 reflects the structure of the model. The green square (a choice node) indicates the choice between LVAD and OMT. In the LVAD arm, the costs for the LVAD implantation are allocated to all patients at the start of the model. The red circles (chance nodes) indicate a possibility that a patient dies in a given period (the blue triangle being an endpoint), is hospitalised, or not hospitalised. For those who survive, the same events can occur in the following monthly Markov cycles. Half cycle correction is applied to reflect that patients do not all die at the beginning or at the end of a monthly cycle, but on average halfway this cycle.

Figure 12 – Markov model for LVAD implantation as destination therapy



Source: Neyt et al.[21, 56]
LVAD: left ventricular assist device; OMT: optimal medical treatment

9.1.7 Treatment effect

9.1.7.1 Within trial follow-up period

This economic evaluation makes a comparison of a second-generation continuous-flow LVAD as destination therapy for patients with advanced heart failure who do not qualify for heart transplantation. The comparator is optimal medical treatment. However, there is no RCT making a direct comparison between these two alternatives. Nevertheless, an indirect comparison is possible by combining the results of the REMATCH study[26] and the HeartMate II Destination Therapy Trial study.[7]

The REMATCH study is a randomized trial that compares the optimal drug therapy with implantation of a first-generation pulsatile LVAD (HeartMate VE, Thoratec). The results for the primary endpoints are in favour of the LVAD:[26]

- One-year survival: 52% versus 25% (p = 0.002) (note: this was 52% versus 28% in an updated publication of this trial)[36]
- Two-year survival: 23% versus 8% (p = 0.09) (note: this was 29% versus 13% in an updated publication of this trial)[36]
- The relative mortality risk was 0.52 (95% CI 0:34 - 0.78, p = 0.001)

The HeartMate II Destination Therapy Trial study is a randomized trial comparing a first-generation pulsatile LVAD (HeartMate XVE, Thoratec) with a second-generation continuous-flow LVAD (HeartMate II, Thoratec). The results for the primary endpoints are in favour of the continuous-flow LVAD:[7]

- One-year survival: 68% (95% CI 60-76) versus 55% (95% CI 42-69)
- Two-year survival: 58% (95% CI 49-67) versus 24% (95% CI 1-46)
- The relative mortality risk was 0.54 (95% CI 0:34 - 0.86, p = 0.008)

In the original Dutch HTA report,[21] several approaches were used to model survival of the LVAD and OMT group. In a first approach, the relative risks were used to model survival. In a second approach, the yearly and two-yearly mortality rates from the trials were modelled. In both cases, several extrapolation scenarios were used to extend the 2-year time horizon of the trial to a lifetime horizon in the model. In the original publication the outcomes were somewhat more optimistic applying the second approach (on average €107 554 versus €116 272 per QALY gained).[21]

In the present HTA report, we only worked with this most optimistic approach, i.e. applying the observed mortality in both the OMT and LVAD arm from the original RCTs. No adjustments were made for this indirect comparison since the survival in the pulsatile-flow LVAD groups was similar in both trials (1-year survival: 52% versus 55%; 2-year survival: 23% versus 24%). In the reference case, the modelled mortality is thus as presented in Table 36.

We extend this reference case with several alternative scenarios, using the one- and two-year survival data in the LVAD group from other sources: the data used in the economic evaluation of Long et al.,[49] with a 1- and 2-year survival of 77% and 62%, respectively, and survival data for DT patients in INTERMACS with a 1- and 2-year survival of 76% and 63% (see part 4.2.1.3), respectively[14] (see Table 36).

The last scenario is based on survival data from the Belgian sample. This is mainly a BTT population and thus survival data can be considered as being optimistic for a DT or BTC population. Only continuous-flow LVADs were included. 30-day mortality was 6% and one-and two-year survival was 80.77% and 64.93% (see part 7.3.1).

Table 36 – Survival in the OMT and LVAD group (original and updated analyses)

Reference case	Mean	CI	Probability distribution	Source
OMT				
1-year survival	28%	17 - 39	Beta(17.6; 45.4)	Dembitsky et al., 2004[36] $
2-year survival	13%	5 - 22	Beta(7.7; 51.4)	
LVAD				
30-day mortality	10.1%	4 - 18*	Beta(7; 62)	UMC Utrecht[21] (en Coyle et al., 2010[38])
1-year survival	68%	60 - 76	Beta(88.1; 41.5)	Slaughter et al., 2009[7]
2-year survival	58%	49 - 67	Beta(66.4; 48.1)	
Changes in alternative scenarios				
LVAD surival based on Long et al.(2014)				
1-year survival	77%		Original distribution +9%	Long et al., 2014[49]
2-year survival	62%		Original distribution +4%	
LVAD survival based on INTERMACS DT population				
1-year survival	76%		Original distribution +8%	INTERMACS 2015 Q2 report: DT population[14]
2-year survival	63%		Original distribution +5%	
LVAD survival based the Belgian sample (mainly BTT)				
30-day mortality	6%		Beta(9; 141)	Belgian sample (mainly BTT, see part 7.3.1)
1-year survival	80.77%		Original distribution +12.8%	
2-year survival	64.93%		Original distribution +6.9%	

*$ We used the data from the publication of Dembitsky et al. (2004)[36] that re-analysed the data of the REMATCH trial and provided an additional 375 patient months of LVAD experience over the initial publication in 2001. * No confidence interval was published for the 30-day mortality. However, as the number of deaths and the size of the sample are known, the appropriate beta distribution can be modelled and the 2.5% and 97.5% values of this distribution can be established.*
BTT: bridge to transplantation; DT: destination therapy; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVAD: left ventricular assist devices; OMT: optimal medical therapy

9.1.7.2 Life-time extrapolation

The trials we rely on to model the treatment effect have a follow-up period of 2 years. To include all relevant incremental costs and effects, a lifetime time horizon is more appropriate. Therefore, the monthly mortality probabilities are extrapolated. In the LVAD group, the mortality risk in the second year (which is lower in comparison with the risk of dying during the first year) is used to extrapolate.

In the original model, three possible extrapolation scenarios were applied: 1) the monthly risk of death remains constant over time (exponential survival); 2) the monthly mortality risk increases with the absolute increase in the monthly mortality risk of the general Dutch population with the same age and male/female ratio; 3) the monthly mortality risk increases with the relative increase in the monthly mortality risk of the general Dutch population with the same age and male/female ratio. This was based on the Dutch 2003-2008 mortality tables as published by the Actuarieel Genootschap & Actuarieel Instituut (AG&AI) (www.ag-ai.nl/download/7693-AG-tafel+2003-2008DEF.pdf). In the base case scenario, the second extrapolation approach was applied (since the first approach is probably too optimistic and the third approach too pessimistic). The other two options were modelled in scenario analyses. For results of these extrapolation scenario analyses, we refer to the original Dutch report.[21]

In this report, we only model the second approach and we use the Belgian life tables, which are similar to the Dutch life tables (Appendix 6)

Based on results from the REMATCH trial, survival was only 13% after 2 years in the OMT group.[36] In the original model, based on expert opinion, it was assumed that all patients in the OMT group died after 3 years, with a linear monthly number of patients dying during the 3rd year. In this report, we apply the same approach.

9.1.8 Rehospitalisations

For this report, we have information at our disposal on the number of days patients are hospitalised in Belgium after an initial LVAD implantation. When hospitalisation for the initial continuous-flow LVAD implantation is not taken into account, patients were hospitalised for a total of 2105 days and out of hospital for a total of 40 644 days. In other words, after the 'initial' hospitalisation for LVAD implantation, patients were on average 4.92% of their time hospitalised. This probability is included in the model as a beta-distribution (Table 37). We use this information to model the time patients are hospitalised in the LVAD arm of our model.

For practical reasons, it was not possible to know the exact reason for these rehospitalisations. Given the severity of the disease, the intervention and potential complications, rehospitalisations are very likely linked to this disease and/or LVAD implantation. Therefore, we included all the real-life rehospitalisation costs in our calculations. It is possible that this might overestimate the direct health-care related costs. In our sensitivity analyses, we assume that the incremental cost difference between LVAD implantation and OMT decreases, to see how this impacts our results.

Table 37 – Percentage of time in and out of hospital after the initial LVAD implantation and in the OMT group

Ratio in/out of hospital	Mean	CI	Probability distribution	Source
After leaving the hospital for an LVAD implantation	4.92%	4.7% - 5.1%	Beta(2105; 40 644)	Belgian data (see part 7.3.1)
In the OMT group	20% higher in comparison to the LVAD group (changing this to 0% and 40%)			Indirect comparison based on Rose et al., 2001[26] and Slaughter et al., 2009[7] (+ Scenario analyses)
	16%	10.6% - 22.3%	Beta(24; 126)	Rose et al., 2001[26]

We don't have a sample of the OMT group at our disposal. The time these patients are hospitalised is thus modelled indirectly, by applying the same approach as in the original Dutch HTA report. In the that report, the number of hospitalisations in the continuous-flow LVAD group was based on the HeartMate II Destination Therapy Trial.[7] The rehospitalisation rate was 2.64 per patient year or 0.22 per patient month. For the OMT group, no such information was available and it was not clear whether there are more or fewer hospitalisations per patient year. The REMATCH trial indicates the median survival and number of days in the hospital (independent of the number of days to administer medication and LVAD implantation) for both the OMT and LVAD group. Based on this information, it was estimated that OMT patients were hospitalised for 16% of their time (24/150 days) compared with 21.6% with a pulsatile-flow LVAD (88/408 days) after hospital discharge for the initial LVAD implantation.[26] This corresponds to 25.8% less (16% versus 21.6%) hospitalisation time for patients in the OMT group compared to a pulsatile-flow LVAD. The HeartMate II Destination Therapy trial[7] indicates 4.25 rehospitalisations with a pulsatile-flow LVAD compared with a 2.64 with a continuous-flow LVAD per patient year. If we apply the same ratio between OMT and LVAD from the REMATCH trial this would result in 3.15 (= 4.25 x (1 – 25.8%)) rehospitalisations per patient year in the OMT group, or about 20% more than with a continuous-flow LVAD (3.15 compared to 2.64). Since this was a very uncertain estimate, scenario analyses was performed changing this percentage to 0% and 40%. We performed the same uncertainty analyses in the current analysis (see 9.1.11).

Several experts noticed that there might be an underestimation of the costs in the OMT group. Therefore, based on the REMATCH trial, we also assumed that OMT patients are hospitalised for 16% of their time (24/150 days).[26]

9.1.9 Quality of life

Quality of life is a very important outcome for patients with end stage HF. No generic utility instrument was used in the identified RCTs. Generic utility instruments are able to generate utility values reflecting preferences with a value of zero for 'death' and one for 'perfect health'. This allows the transfer of life years in so-called quality-adjusted life years (QALYs).

In the previous Dutch report,[21] one study was identified that tried to measure utilities in an LVAD population.[61] This study from Moskowitz and colleagues already dated from 1997 and used the standard gamble method to measure quality of life in patients with a pulsatile-flow LVAD as bridging therapy. This was done for three health conditions: before LVAD implantation, during LVAD support, and after heart transplantation. The study included 29 patients. Quality of life before implantation was only available for half of this group (n=14). Ten patients could not be interviewed because they were too weak and/or had a failed bypass surgery. The other five patients could not be questionned because the device was implanted in urgency. During LVAD support, 20 patients were questioned (five already died, two were to weak and another two refused the interview). Following transplantation (n=17) 11 patients were questioned. The utility values were 0.548 (± 0.276, 95% CI 0.389-0.708) before implantation, 0.809 (± 0.136, 95% CI 0.745-0.873) during LVAD support, and 0.964 (± 0.089, 95% CI, 0.902-1) after heart transplant.

In the original Dutch HTA report, due to a lack of better data, the utility values of this study were used to model the quality of life for the OMT and LVAD group in which each month is multiplied with the utility value of 0.548 and 0.809, respectively. The uncertainty surrounding these utilities were included as beta distributions. In this original analysis, this scenario was rather interpreted as an optimistic scenario since the missing information on quality of life is most probably not missing at random but related to the most sick patients. Furthermore, the authors of the study also refer to the so-called "honeymoon period" effect, [61] in which the patient is still aware of his situation before the surgery and very happy he survived the LVAD procedure but does not fully realize his new health status and the limitations and risks of living with an LVAD.

For this study, better information was identified, and the original data are used in a scenario analysis. In the reference case, quality of life values were included as applied in the study of Long et al.[49] (see part 8.3.4). This study refers to an analysis which was based on results from the INTERMACS study, providing QoL estimates of 0.51 the first month after an LVAD implantation and 0.72 thereafter. Unfortunately, in the original INTERMACS study,[41] information was missing for many patients. Before implantation, only half of patients (852 of 1694 patients) provided information for the EQ-5D-3L Visual Analogue Scale (VAS score). After one year, information was only

available for 281 patients. This might have biased outcomes (see part 9.3) In the OMT group QoL was 0.53. The latter value was obtained from a study that assigned this value to NYHA class IV.[68]

In two alternative scenarios, we used the results published by Grady et al..[34] This study also provided the outcomes for the five dimensions of the EQ-5D questionnaire: mobility, usual activities, self-care, pain/discomfort, and anxiety/depression. For each of these dimensions, the number of patients having extreme problems or some problems was transparently reported (see Table 16). Unfortunately, the dimensions were not linked to a value set, transforming these outcomes in a utility value. As a solution, a sample of 10 000 hypothetical patients was created with the same percentage of patients having problems or severe problems in those five dimensions. In a first alternative scenario, the 5-digit scores for these 10 000 patients were linked to the Belgian value set (based on a sample of 722 people from the general population and measured with the VAS-scale). The VAS scale might have problems with a ceiling effect. Therefore, in a second alternative scenario, the UK value set was used (i.e. the most robust valuation set based on a sample of 3395 patients and measured using the time-trade-off method) (http://www.euroqol.org/). The application of this approach did not take into account that correlations might exist in the outcomes of the five dimensions. Individual outcomes are needed to identify such correlations. Since we didn't have access to such data, no correlations were assumed. With the Belgian VAS value set, this results in QoL of 0.36 and 0.67 before and 12 months after the LVAD implantation, respectively. With the UK TTO value set, this becomes 0.32 and 0.71, respectively. The 'before' value is allocated to the OMT group. The 'after' value is used for all months after the first month of the LVAD implantation (see Table 38). Also in the study of Grady et al..[34] a lot of information was missing, possibly introducing a bias (see part 9.3).

The missing data might introduce a bias in favour of LVADs. For example, information is missing for more than 50% of the patients in the study on which the 0.72 utility value is based on (see discussion in part 9.3). To show the possible impact of this overestimation, a scenario analysis with an assumed 0.62 utility value in the LVAD arm was also performed.

Because no confidence intervals were published for the other data, the uncertainty around the original distribution (see Table 38) in the Dutch report is kept in all analyses. The utilities were also kept constant in the long-term extrapolations, which is a rather optimistic assumption.

Table 38 – Quality of life in the OMT and LVAD group (original and updated analyses)

	Mean	CI	Probability distribution	Source
Scenario analysis (QoL modelled as in the original Dutch analsyis)				
OMT	0.548	0.389 – 0.708	Beta(19.9; 16.5)	Moskowitz et al., 1997[61]
LVAD	0.809	0.745 – 0.873	Beta(116.4; 27.5)	
Changes in updated analysis: reference case				
OMT	0.53		Original distribution -0.018*	Long et al., 2014[49] referring to Rogers et al., 2012[55] and Sharples et al., 2006[62]
LVAD (first month)	0.51		fixed	Long et al., 2014[49] referring to Sharples et al., 2006[62]
LVAD (after first month)	0.72		Original distribution -0.089*	Long et al., 2014[49] referring to Kirklin et al., 2013[41]
Scenario analysis with Belgian value set				
OMT	0.36		Original distribution -0.188	Sampling based on data from Grady et al., 2015[34] in combination with Belgian value set.
LVAD (after first month)	0.67		Original distribution -0.139	
Scenario analysis with UK value set				
OMT	0.32		Original distribution -0.228	Sampling based on data from Grady et al., 2015[34] in combination with UK value set.
LVAD (after first month)	0.71		Original distribution -0.099	
Scenario analysis with lower QoL value				
OMT	0.53		See reference case	
LVAD (first month)	0.51		See reference case	
LVAD (after first month)	0.62		Reference case -0.1	Assumption

** The publications did not include confidence intervals. We preferred to keep the uncertainty around these numbers as published in the study of Moskowitz et al.[61] Therefore, we applied the original Beta-distributions (Beta (19.9; 16.5) and Beta (116.4; 27.5)) and shifted these distributions to obtain the new mean: e.g. 0.548 - 0.018 = 0.53 and 0.809 - 0.089 = 0.72.*

9.1.10 Costs

Costs were mainly based on the Belgian LVAD sample at our disposal (see chapter 7). Due to practical reasons, it was not possible to convert all costs in the administrative database to one common year. The year of costs for the calculation of the LVAD implantation costs, in-hospital and out-of-hospital costs after the initial LVAD implantation reflect the year in which the costs were made. This means that e.g. for the implantation costs, the year of costs ranges from 2007 to 2013, with about 50% of interventions being performed in 2012-2013 (77/156). The cost of the device and the drugs in the OMT group reflect the costs in the year 2015. All costs are expressed in euros.

9.1.10.1 Initial LVAD implantation costs

In the original analsyis, no cost data was available for LVAD implantation as destination therapy since, at the time of that study, the intervention was not included for this indication in the national care package in the Netherlands. LVAD as bridging therapy was considered the best available source for costs. Financial anonymized data of 69 patients with a continuous-flow LVAD (HeartMate-II) implanted at the UMC Utrecht were used. Costs for LVAD implantation were measured from the day of implantation up to the day of hospital discharge. The cost of an LVAD implant was approximately €126 000, of which the device itself represented the largest cost (€70 000), followed by the cost of inpatient days (including intensive care) being on average €42 400.[21, 56]

In the present analysis, Belgian data were used in the model. Also in Belgium, (most of) the patients received the LVAD as BTT. Costs were gathered for continuous-flow LVADs. Based on a sample of 148 patients, the average implantation cost (exclusive the cost of the device and exclusive supplements) was €45 788 (see Table 24 in part 7.3.1). This cost is in agreement with the costs from a previous Belgian study on a limited sample of patients: based on a sample of 6 patients, the Belgian study calculated an average cost of €45 453 for the initial hospitalisation to implant an LVAD in destination therapy. In a sample of 13 patients, this was on average €47 526 to implant an LVAD as BTT.[25]

Anno 2016, LVADs are reimbursed as BTT at a price of €67 106.57.[h] This cost is also included in the economic evaluation.

In our sample of 148 patients, a second LVAD was charged in three patients. This additional cost is not included in the current analysis. Also costs generated before the LVAD implantation were not included making the analysis rather optimistic.

In a scenario analysis, the costs for the year 2013 were selected, being the most optimistic cost data (see Table 27 in part 7.3.1). In 2013, the costs for an LVAD implantation were about €10 000 lower than the global average for all continuous-flow LVAD implantations in Belgium (see Table 39).

Table 39 – Costs for LVAD implantation

	Mean	Min - max (SD)	Probability distribution
Reference case (based on all continuous-flow LVADs in the Belgian sample)			
LVAD implantation cost	€45 788	€386 - €200 063 (€30 177)	Gamma(2.26; 20 057) + 386
NIHDI	€45 139	€221 - €198 698 (€29.990)	
Co-payment	€649	€0 - €1819 (€279)	
LVAD device	€67 106.57		Fixed
Scenario analysis (based on continuous-flow LVADs implanted in 2013)			
LVAD implantation cost	€35.784	€386 - €109 036 (€18 457)	Gamma(3.68; 9623.55) + 386

[h] HeartMate II (Thoratec): €67 106.57 (since 1 July 2011); HeartWare Ventricular Assist System (HeartWare GmbH): €82 298.05 (1/07/2011 - 31/08/2012); €79 763.27 (1/09/2012 - 30/06/2014); €67 106.57 (since 1/07/2014).(source: RIZIV)

9.1.10.2 Rehospitalisation costs

In the original analysis for the Netherlands, costs per repeat hospitalisation were included in the model. These costs were based on real-world cost data from the identified repeat hospitalisations (N = 69) in the real-world sample, excluding hospitalisations for LVAD replacements (N= 3) and explantation (N = 3). The cost amounted on average to about €8100.

In the current analysis, a different approach is applied. After the initial LVAD implantation, patients are hospitalised on average for 4.92% of their time (see Table 37 in part 9.1.8). During the 2105 days in hospital, they generated costs for the healthcare payer and patients of €1 827 915, or a cost of about €26 431 per month being hospitalised (see Table 37). Only the uncertainty around the percentage of time being hospitalised is included in the model.

Table 40 – Monthly in-hospital costs (exclusive the initial LVAD implantation)

	Mean
Cost per month being in hospital	€26 431
NIHDI	€26 160
Co-payment	€271

9.1.10.3 Out of hospital costs

In the original analysis, costs for renting the power base unit (PBU), LVAD accessories, physiotherapy, dietetics, medication and examinations were included. For further details, we refer to the original report.[21, 56]

In the current analysis, patients were not hospitalised for 95.08% of their time (see Table 37 in part 9.1.10.2). Costs for the healthcare payer and patients for all days out of hospital were €1 742 515. Distributed over the 40 644 days out of hospital, this is a cost of about €1305 per month (Table 41).

Table 41 – Monthly out-of-hospital cost

Original analsyis	LVAD
Costs out of hospital	€1305
NIHDI	€1235
Co-payment	€70

NIHDI: National Institute for Health and Disability Insurance (RIZIV – INAMI)

As a validation of the data in our current report, we compared the costs in and out of hospital with the data from a previous Belgian publication.[25] In that article, the total treatment cost per month was on average €2621 (€2200 re-hospitalisation/month + €343 follow-up cost/month + €78 medication cost/month).[25] In the current study, the average costs per month are €2541 (4.92% x €26 431 + (1 - 4.92%) x €1305).

9.1.10.4 Medication and follow-up cost in OMT group

For the LVAD group, costs for medication and follow-up were already included by including out-of-hospital cost information. For the OMT group, we had no sample at our disposal. Therefore, this cost was included in a theoretic way by including the costs for a combination of drugs and follow-

up investigations, based on information from the original Dutch report (see Table 42 and Table 43).

Following the Belgian guidelines for economic evaluations,[67] the cheapest alternative was taken into account. If the dose per tablet was different than the dose in the original Dutch report, then the nearest dose was selected. This is the case for perindopril and potassium chloride.

Table 42 – Monthly drug costs OMT group

Drug	Dose		Price per tablet	Price per month
Furosemide	160mg/day (80-240)	tablet 40mg	€0.20 (€11.27/56)	€24.15
Perindopril	8mg/day	tablet 10mg	€0.45 (€40.74/90)	€13.58
Spironolactone	25mg/day	tablet 25mg	€0.10 (€9.78/100)	€2.93
Carvedilol	2x25mg/day	tablet 25mg	€0.24 (€23.92/98)	€14.64
Simvastatin	40mg/day	tablet 40mg	€0.20 (€20.27/100)	€6.08
Acenocoumarol	2mg/day	tablet 1mg	€0.07 (€6.72/100)	€4.03
Amiodarone	200 mg/day	tablet 200mg	€0.13 (€13.24/100)	€3.97
Potassium chloride	2x600mg/day	tablet 746mg	€0.82 (€8.2/10)	€49.20
TOTAL				€118.59/month

Table 43 – Monthly follow-up costs OMT group

	Nomenclature code	Value (2015)	1st year protocol (week) 1	4	8	12	18	24	38	52	After first year protocol (month) 3	6	9	12	1st year	After 1st year
Consultation cardiologist	102594	€ 36,74	x	x	x	x	x	x	x	x	x	x	x	x	€ 293,92	€ 146,96
ECG	475075	€ 17,77	x	x	x			x	x	x	x	x	x	x	€ 106,62	€ 71,08
Chest x-ray	463691	€ 12,57	x					x				x		x	€ 25,14	€ 25,14
Echocardiogram	460456	€ 63,21	x			x				x				x	€ 189,63	€ 63,21
Exercise ECG	475812	€ 35,67						x		x					€ 214,00	
with VO2 measurement	471391	€ 71,33														
Cardiac catheterization	476081	€ 355,72								x					€ 838,88	
and coronary angiography	453585	€ 483,16														
Total (per year)															€ 1.668,19	€ 306,39
Total (per month)															€ 139,02	€ 25,53

9.1.10.5 LVAD replacement costs

In the original Dutch model, the costs for an LVAD replacement were assumed to be the same as for an initial LVAD implantation. In the Dutch analysis, it was assumed that devices were replaced on average after 4 years (changed in scenario analyses from 3 up to 7 years). According to current expert opinion, this assumption was not appropriate and hence abandoned in the current analysis. In addition, since in our model rehospitalisations (part 9.1.8) and related costs (part 9.1.10.2) were already included, replacements, which inevitably require rehospitalisation, did not need to be included separately.

9.1.11 Sensitivity and scenario analyses

One-way and probabilistic sensitivity analyses were performed. The probability distributions included in the current analysis are already presented in the above tables. Survival, utilities and the in/out of hospital ratio were modeled as beta distributions and cost variables as gamma distributions. The parameters of these probability distributions are presented transparently in the above tables in this chapter. Results of the probabilistic model are shown on the cost-effectiveness plane and the cost-effectiveness acceptability curve (CEAC).

The variables changed in the one-way sensitivity analyses are presented in the following table. Next to the scenarios explained in the previous parts, we also added a scenario in which the costs in the LVAD group were reduced with €10 000, €20 000, €30 000, €40 000 or €50 000, which refers to several potential scenarios: future price reduction of the LVAD device, decreasing costs in the LVAD group due to a shorter initial hospitalisation or less rehospitalisations, higher costs in the OMT group, etc..

Table 44 – Overview of scenario analyses

Variable	Reference case	Sensitivity analyses	More information
Quality of life	OMT: 0.53 LVAD 1st month: 0.51 LVAD after 1st month: 0.72	• Scen. 1: OMT: 0.548; LVAD: 0.809 • Scen. 2: OMT: 0.36; LVAD after 1st month: 0.67 • Scen. 3: OMT: 0.32; LVAD after 1st month: 0.71 • Scen. 4: LVAD after 1st month reduced from 0.72 to 0.62	Part 9.1.9
Probability of rehospitalisation OMT versus LVAD	20% more per month survived	• Scen. 1: equal • Scen. 2: 40% more • Scen. 3: 16% of their time in the OMT group versus 4.92% of their time in the LVAD group (excl. initial hospitalisation)	Part 9.1.8
Discount rate	Costs: 3% Effects: 1.5%	Three scenarios with equal discount rate for costs and effects: 0%, 3% and 5%.	Part 9.1.5

Variable	Reference case	Sensitivity analyses	More information
Survival LVAD population	30-day mortality: 10.1% 1-year survival: 68% 2-year survival: 58%	• Scen. 1: 1-year survival: 77%; 2-year survival: 62% • Scen. 2: 1-year survival: 76%; 2-year survival: 63% • Scen. 3: 30-day mortality: 6%; 1-year survival: 80.77%; 2-year survival: 64.93%	Part 9.1.7
Cost LVAD implantation	€45 788 (exclusive device cost of €67 107)	Scenario with lower cost of €35 784	Part 9.1.10.1
Reduction in costs	NA	Five scenarios with a reduction in costs of €10 000, €20 000, €30 000, €40 000 or €50 000.	Part 9.1.11

LVAD: left ventricular assist devices; NA: not applicable; OMT: optimal medical therapy

9.1.12 Validation of the model

The input variables were validated by comparing the results of the analysis of the Belgian data with outcomes from a previous analysis (i.e. both the Dutch HTA report[21, 56] and cost data published by Droogne et al.[25]) The model was validated by backward calculation, i.e. going back from the relevant output of the model (IC, IE, ICERs) to the input variables by checking all formulas. A check on the survival curves by checking the survival at 1, 2, 3, and 4 years and a visual check of the modelled survival curves were also performed. The logic of outcomes were also checked (e.g. better or worse results by decreasing or increasing discount rate, changing survival assumptions, etc.).

9.2 Results

9.2.1 Base case analysis

In our population of patients with end-stage heart failure, the (undiscounted) life expectancy of a patient in the OMT arm (without an LVAD) is 0.82 years versus 4.82 with an LVAD (Table 48). Adjusted for quality of life (QoL), this becomes 0.44 quality-adjusted life-years (QALYs) and 3.46 QALYs, respectively. The LVAD intervention creates thus an additional (undiscounted) 4 life years or 3 QALYs. Applying the 1.5% discount rate, this becomes 3.64 life years gained and 2.76 QALYs gained by implanting an LVAD. On the other hand, the extra costs are on average about €242 000. Discounted at 3%, these incremental costs are about €222 000, resulting in a relatively high ICER of about 62 000 per life year gained or about €82 000 per QALY gained. Since the disease and implantation of an LVAD clearly has an impact on quality of life, we focus on the results expressed in QALYs. The 95% confidence interval around the extra costs per QALY gained ranges from about €62 000 to €117 000 (see Table 45 and Figure 13).

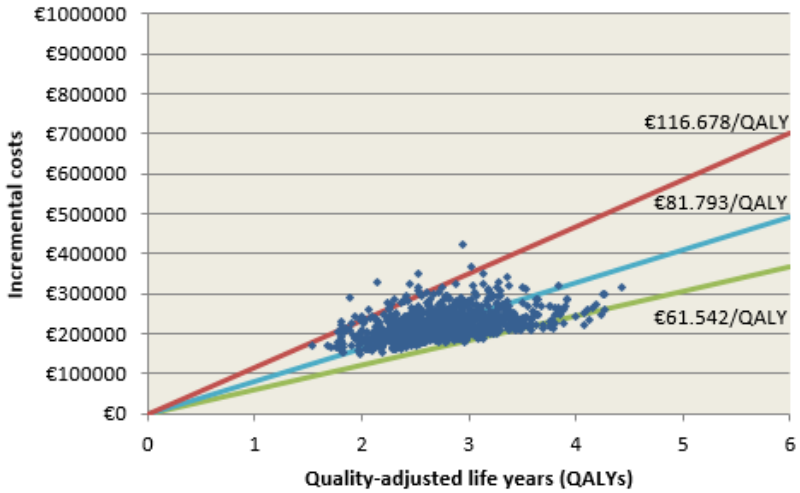
In Belgium, there is no clear cut-off value for the ICER threshold. Only NICE[69] has made this value explicit, being between £20 000 and £30 000 per QALY (or €26 352 – €39 529, exchange rate £1 = €1.31816 on 25 January 2016). If we apply this threshold to our results, then the probability of accepting the LVAD intervention as being cost-effective is 0% (see Figure 14). The lowest ICER being calculated in the 1000 simulations was higher then €54 000 per QALY. A much higher willingness-to-pay is thus necessary to consider this intervention cost-effective.

Table 45 – Results for the reference case

	Base case result mean (2,5% - 97,5%)
Life expectancy	
OMT (years)	0,81 (0,61 - 1,05)
LVAD (years)	4,46 (3,39 - 5,69)
Costs	
OMT	€ 17.228 (€13.000 - €22.266)
LVAD	€ 239.330 (€186.880 - €320.710)
IC	€ 222.101 (€168.452 - €303.791)
IE (LYG)	3,64 (2,54 - 4,93)
IE (QALY gained)	2,76 (1,93 - 3,81)
ICER (€/LYG)	€ 61.909 (€47.317 - €88.069)
ICER (€/QALY gained)	€ 81.793 (€61.542 - €116.678)

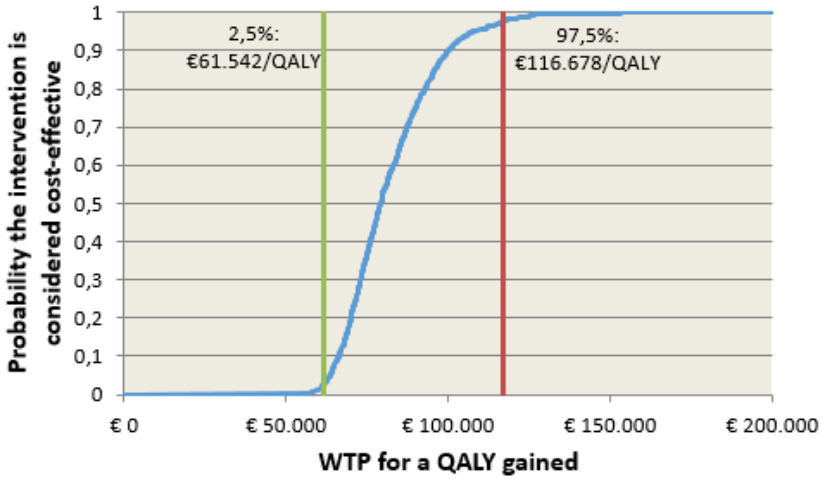
Remark: QALYs for the OMT and LVAD group are presented in Table 46.
IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years.

Figure 13 – Cost-effectiveness plane (reference case analysis)



QALY: quality-adjusted life year

Figure 14 – Cost-effectiveness acceptability curve (reference case analysis)



QALY: quality-adjusted life year; WTP: willingness to pay

9.2.2 Scenario analysis

Several scenario analyses were modelled to see how robust results were for changes in several variables. The following tables show the impact of changing quality of life values, rehospitalisations in the OMT group, discount rate for costs and effects, one- and two year survival, LVAD implantation costs, and overall difference in costs between the OMT and LVAD group. Results in the tables are mentioned in black or grey if they do or do not differ from the base case results.

The scenario with the most optimistic *QoL values* assumed a utility value of 0.809 during LVAD support, which remained stable during the extrapolation period. Even in this (over)optimistic scenario, the ICER remained relatively high with an average value of about 71 000 per QALY gained. The scenarios with UK and Belgian utility values provided ICERs close to the base case result, i.e. on average €78 000 (UK values) and €84 000 (Belgian values) (Table 46). Changing the QoL in the LVAD group to 0.62 instead of 0.72 (due to the possible bias in this value caused by a large proportion of missing information), results in a much higher ICER of about €97 000 per QALY gained.

The scenario with *more or less hospitalisations in the OMT group* did not have a major influence on the results (Table 47). The scenario in which OMT patients are hospitalised on average 16% of their time, versus 4.92% in the LVAD group, results in an average ICER of about €72 000 per QALY gained. Changes in costs per month in the OMT group do not have a major influence due to the relatively short survival time in this group. As a results, changes in both QoL and costs in the OMT group have a smaller impact on results than changes on these variables in the LVAD group, which is due to the higher life expectancy in the LVAD group.

The scenarios with a changing *discount rate for costs and effects* show that Belgian guidelines apply a beneficial discount rate for effects (1.5%) versus costs (3%). The scenario with a 0% discount rate for effects shows the four (undiscounted) life-years gained or three QALYs gained when implanting an LVAD versus OMT. With an undiscounted extra cost of on average about €242 000, the ICER remains on average about €82 000. Changing the discount rate for both costs and effects to 3% or 5% results in a worse ICER of on average about €89 000 or €94 000, respectively (Table 48).

Table 46 – Results of scenario analyses with changes in QoL

	Base case result	better QoL	QoL sampling (UK value set)	QoL sampling (Belgian value set)	Worse QoL
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy					
OMT (years)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)
LVAD (years)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)
QALYs					
OMT (years)	0,43 (0,28 - 0,62)	0,45 (0,29 - 0,64)	0,26 (0,13 - 0,42)	0,29 (0,15 - 0,46)	0,43 (0,28 - 0,62)
LVAD (years)	3,19 (2,37 - 4,21)	3,61 (2,70 - 4,73)	3,15 (2,34 - 4,15)	2,98 (2,20 - 3,93)	2,76 (2,03 - 3,65)
IC	€ 222.101 (€168.452 - €303.791)	€ 222.101 (€168.452 - €303.791)	€ 222.101 (€168.452 - €303.791)	€ 222.101 (€168.452 - €303.791)	€ 222.101 (€168.452 - €303.791)
IE (LYG)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)
IE (QALY gained)	2,76 (1,93 - 3,81)	3,16 (2,24 - 4,31)	2,89 (2,08 - 3,90)	2,68 (1,90 - 3,65)	2,32 (1,59 - 3,24)
ICER (€/LYG)	€ 61.909 (€47.317 - €88.069)	€ 61.909 (€47.317 - €88.069)	€ 61.909 (€47.317 - €88.069)	€ 61.909 (€47.317 - €88.069)	€ 61.909 (€47.317 - €88.069)
ICER (€/QALY gained)	€ 81.793 (€61.542 - €116.678)	€ 71.367 (€54.209 - €100.586)	€ 77.990 (€59.619 - €110.232)	€ 84.125 (€63.797 - €119.394)	€ 97.452 (€72.364 - €140.767)

Remark: in this table we also present the QALYs in the OMT and LVAD group, separately (instead of the costs in both groups since these values are exactly the same as in the reference case presented in the previous table). IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years; QoL: quality of life.

Table 47 – Results of scenario analyses with changes in rehospitalisations in the OMT group

	Base case result (20% more)	40% more	equal	16% (OMT) vs. 5% (LVAD)
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy				
OMT (years)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)
LVAD (years)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)
Costs				
OMT	€ 17.228 (€13.000 - €22.266)	€ 19.742 (€14.852 - €25.555)	€ 14.715 (€11.068 - €19.009)	€ 42.972 (€26.672 - €64.324)
LVAD	€ 239.330 (€186.880 - €320.710)	€ 239.330 (€186.880 - €320.710)	€ 239.330 (€186.880 - €320.710)	€ 239.330 (€186.880 - €320.710)
IC	€ 222.101 (€168.452 - €303.791)	€ 219.588 (€165.606 - €301.346)	€ 224.615 (€171.094 - €306.236)	€ 196.357 (€137.019 - €281.122)
IE (LYG)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)
IE (QALY gained)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)
ICER (€/LYG)	€ 61.909 (€47.317 - €88.069)	€ 61.198 (€46.747 - €87.124)	€ 62.621 (€47.821 - €89.013)	€ 54.620 (€40.524 - €79.349)
ICER (€/QALY gained)	€ 81.793 (€61.542 - €116.678)	€ 80.854 (€60.694 - €115.753)	€ 82.731 (€62.338 - €117.603)	€ 72.182 (€52.754 - €106.250)

IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years.

Table 48 – Results of scenario analyses with changes in discount rate

	Base case result (E: 1.5%; C: 3%)	E: 0%; C: 0%	E: 3%; C: 3%	E: 5%; C: 5%
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy				
OMT (years)	0,81	0,82	0,80	0,79
	(0,61 - 1,05)	(0,61 - 1,07)	(0,60 - 1,04)	(0,59 - 1,02)
LVAD (years)	4,46	4,82	4,14	3,79
	(3,39 - 5,69)	(3,62 - 6,23)	(3,19 - 5,23)	(2,96 - 4,73)
Costs				
OMT	€ 17.228	€ 17.648	€ 17.228	€ 16.965
	(€13.000 - €22.266)	(€13.257 - €22.899)	(€13.000 - €22.266)	(€12.829 - €21.869)
LVAD	€ 239.330	€ 260.030	€ 239.330	€ 228.554
	(€186.880 - €320.710)	(€199.830 - €343.048)	(€186.880 - €320.710)	(€179.638 - €308.309)
IC	€ 222.101	€ 242.382	€ 222.101	€ 211.589
	(€168.452 - €303.791)	(€181.604 - €326.097)	(€168.452 - €303.791)	(€160.992 - €291.886)
IE (LYG)	3,64	4,00	3,34	3,00
	(2,54 - 4,93)	(2,76 - 5,47)	(2,35 - 4,48)	(2,13 - 3,98)
IE (QALY gained)	2,76	3,02	2,54	2,29
	(1,93 - 3,81)	(2,09 - 4,20)	(1,79 - 3,47)	(1,64 - 3,10)
ICER (€/LYG)	€ 61.909	€ 61.521	€ 67.452	€ 71.536
	(€47.317 - €88.069)	(€48.155 - €85.604)	(€52.005 - €95.283)	(€54.565 - €101.669)
ICER (€/QALY gained)	€ 81.793	€ 81.588	€ 88.785	€ 93.695
	(€61.542 - €116.678)	(€62.783 - €113.936)	(€67.352 - €126.209)	(€70.380 - €134.267)

C: costs; E: effects; IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years.

Changing the one- and two-year *survival* did not improve the cost-effectiveness of the LVAD implantation. The modelled gain in life expectancy was never larger than in the base case scenario. This was even not the case in scenarios with a better one- and two-year survival. This might sound counterintuitively, but is completely logical if one takes into account the extrapolation of survival after the second year. The extrapolation is determined by the increase in mortality between the first and second year. Although survival was lower in the base case scenario (one-year survival: 68%, two-year survival: 58%), the increase in mortality was higher in the alternative scenarios (10% in absolute values versus up to 16%, see Table 50). The scenarios that have the best survival at one year seem to lose part of this advantage in the second year. The reason for this reduction in benefit after the first year is unclear. Nevertheless, as a result, the ICERs increase in the alternative survival scenarios to an average of about €82 000 up to €87 000 per QALY gained (Table 49).

The model includes the published 1- and 2- year survival and extrapolates for the following years. The INTERMACS study provided survival data up to 4 years. In order to validate our extrapolation, we compared the modelled survival and the published data. As shown in Table 50, the extrapolation provided the same survival after 3 years (i.e. 52%) and approached the published information very good at 4 years (i.e. 43% survival in the model versus 42% in the literature).

The scenario reflecting the impact of *lower LVAD implantation costs* (i.e. the costs of CF LVAD implantations in the year 2013) shows that even applying a €10 000 decrease in implantation costs still results in relatively high ICERs of on average about €78 000 per QALY.

Finally, several scenarios reflect the impact of a possible *decrease in incremental costs*, no matter what the reason for this decrease might be (lower LVAD implantation costs, less rehospitalisations in the LVAD group, higher costs in the OMT group, etc.). Even after a major decrease in costs of €50 000 the incremental costs are still about €172 000, resulting in an ICER of on average about €63 000 (Table 52). If we would apply the UK ICER threshold of £20 000 - £30 000 (€26 352 – €39 529, see part 9.2.1), the probability that an LVAD implantation is cost-effective remains 0%. Even in a scenario with a €70 000 cost decrease (e.g. because the device would be provided for free), the average ICER would be about €56 000 per QALY gained.

An overview of all above scenario analyses is provided in a tornado graph in Figure 15. Results seem to be robust and a possible underestimation of costs in the OMT group and an overestimation of QoL in the LVAD group might counterbalance each other. While higher costs in the OMT group might favour the ICER, this is the contrary for lower QoL values in the LVAD group.

Table 49 – Results of scenario analyses with changes in survival curves

	Base case result	Alternative survival Long et al. (2014)	Alternative survival DT Intermacs	Alternative survival Belgian BTT population
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy				
OMT (years)	0,81	0,81	0,81	0,81
	(0,61 - 1,05)	(0,61 - 1,05)	(0,61 - 1,05)	(0,61 - 1,05)
LVAD (years)	4,46	4,04	4,40	4,21
	(3,39 - 5,69)	(3,19 - 4,98)	(3,46 - 5,48)	(3,37 - 5,17)
Costs				
OMT	€ 17.228	€ 17.228	€ 17.228	€ 17.228
	(€13.000 - €22.266)	(€13.000 - €22.266)	(€13.000 - €22.266)	(€13.000 - €22.266)
LVAD	€ 239.330	€ 228.895	€ 238.698	€ 233.846
	(€186.880 - €320.710)	(€181.224 - €307.607)	(€189.414 - €318.859)	(€186.319 - €312.276)
IC	€ 222.101	€ 211.666	€ 221.469	€ 216.617
	(€168.452 - €303.791)	(€162.761 - €291.262)	(€170.327 - €302.025)	(€167.816 - €295.931)
IE (LYG)	3,64	3,22	3,59	3,39
	(2,54 - 4,93)	(2,34 - 4,22)	(2,61 - 4,70)	(2,51 - 4,39)
IE (QALY gained)	2,76	2,46	2,72	2,58
	(1,93 - 3,81)	(1,78 - 3,28)	(1,98 - 3,64)	(1,88 - 3,42)
ICER (€/LYG)	€ 61.909	€ 66.555	€ 62.454	€ 64.576
	(€47.317 - €88.069)	(€50.923 - €94.070)	(€48.376 - €87.230)	(€49.973 - €89.714)
ICER (€/QALY gained)	€ 81.793	€ 87.389	€ 82.481	€ 85.057
	(€61.542 - €116.678)	(€65.755 - €125.102)	(€62.817 - €117.128)	(€64.650 - €120.724)

BTT: bridge to transplantation; DT: destination therapy; IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years.

Table 50 – Validation of the modelled survival in comparison with published data

	Base case result			Alternative survival Long et al. (2014)[49]			Alternative survival DT INTERMACS			Alternative survival Belgian BTT population		
survival	Literature		Model	Literature		Model	Literature		Model	Literature		Model
1 year	68%	Δ10%	68.00%	77%	Δ15%	77.00%	76%	Δ13%	76.00%	80.77%	Δ16%	80.77%
2 year	58%		58.00%	62%		62.00%	63%		63.00%	64.93%		64.93%
3 year			49.38%			49.83%	52%		52.13%			52.10%
4 year			42.05%			40.06%	42%		43.14%			41.82%

BTT: bridge to transplantation; DT: destination therapy; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.

Table 51 – Results of scenario analyses with changes in costs for initial LVAD implantation

	Base case result	lower cost LVAD implantation
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy		
OMT (years)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)
LVAD (years)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)
Costs		
OMT	€ 17.228 (€13.000 - €22.266)	€ 17.228 (€13.000 - €22.266)
LVAD	€ 239.330 (€186.880 - €320.710)	€ 229.326 (€188.994 - €280.794)
IC	€ 222.101 (€168.452 - €303.791)	€ 212.098 (€171.788 - €264.694)
IE (LYG)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)
IE (QALY gained)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)
ICER (€/LYG)	€ 61.909 (€47.317 - €88.069)	€ 59.132 (€47.898 - €78.900)
ICER (€/QALY gained)	€ 81.793 (€61.542 - €116.678)	€ 78.116 (€61.403 - €102.702)

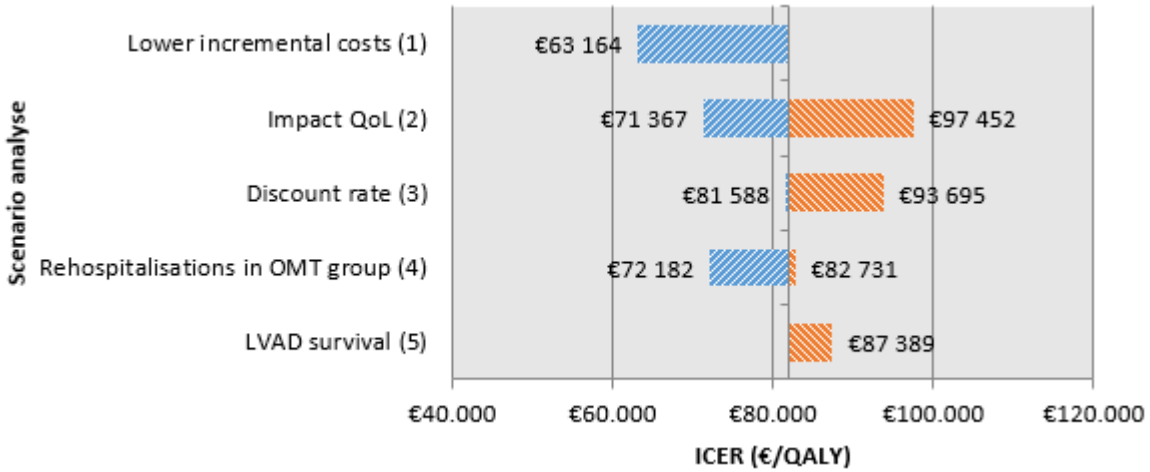
IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years.

Table 52 – Results of scenario analyses with changes in costs

	Base case result	lower cost -€10 000	lower cost -€20 000	lower cost -€30 000	lower cost -€40 000	lower cost -€50 000
	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)	mean (2,5% - 97,5%)
Life expectancy						
OMT (years)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)	0,81 (0,61 - 1,05)
LVAD (years)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)	4,46 (3,39 - 5,69)
Costs						
OMT	€ 17.228 (€13.000 - €22.266)	€ 17.228 (€13.000 - €22.266)	€ 17.228 (€13.000 - €22.266)	€ 17.228 (€13.000 - €22.266)	€ 17.228 (€13.000 - €22.266)	€ 17.228 (€13.000 - €22.266)
LVAD	€ 239.330 (€186.880 - €320.710)	€ 229.330 (€176.880 - €310.710)	€ 219.330 (€166.880 - €300.710)	€ 209.330 (€156.880 - €290.710)	€ 199.330 (€146.880 - €280.710)	€ 189.330 (€136.880 - €270.710)
IC	€ 222.101 (€168.452 - €303.791)	€ 212.101 (€158.452 - €293.791)	€ 202.101 (€148.452 - €283.791)	€ 192.101 (€138.452 - €273.791)	€ 182.101 (€128.452 - €263.791)	€ 172.101 (€118.452 - €253.791)
IE (LYG)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)	3,64 (2,54 - 4,93)
IE (QALY gained)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)	2,76 (1,93 - 3,81)
ICER (€/LYG)	€ 61.909 (€47.317 - €88.069)	€ 59.088 (€45.054 - €84.463)	€ 56.267 (€42.781 - €80.851)	€ 53.446 (€40.461 - €77.367)	€ 50.625 (€38.249 - €74.114)	€ 47.803 (€35.899 - €70.571)
ICER (€/QALY gained)	€ 81.793 (€61.542 - €116.678)	€ 78.067 (€58.777 - €112.204)	€ 74.341 (€55.841 - €107.267)	€ 70.615 (€52.843 - €103.111)	€ 66.889 (€49.720 - €99.646)	€ 63.164 (€46.613 - €94.847)

IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life-years gained; OMT: optimal medical therapy; QALY: quality-adjusted life years.

Figure 15 – Tornado graph



ICER: incremental cost-effectiveness ratio; OMT: optimal medical treatment; QALY: quality-adjusted life year; QoL: quality of life.

9.3 Discussion and conclusion

In an economic evaluation we combine the incremental costs and benefits of a new intervention versus alternative interventions. The strength of this evaluation depends on the strength of the underlying evidence. Several limitations apply to the present study.

In the first place, there are no studies that directly compare OMT with CF LVADs. The indirect comparison as used in the present report may underestimate survival in the OMT as well as in the CF LVAD group. However, scenario analyses changing the modelled 1- and 2-year survival in the LVAD group did not indicate that the intervention's cost-effectiveness would improve much by applying other survival assumptions.

A second limitation is that we had no OMT sample for analysis of costs. They were determined theoretically and may have underestimated the costs in the OMT group. In a scenario analysis, we increased the costs in this group by applying a higher hospitalisation rate (patients being hospitalised for 16% of their time in the OMT group versus 4.92% after the initial hospitalisation in the LVAD group) still resulting in relatively high ICERs. Furthermore, experts argued that new and more expensive drugs may come on the market that would increase the treatment cost in this group. However, such evolutions might also improve survival in this group and/or impact the treatment costs of the LVAD group.

Furthermore, the sample of LVAD patients for which we had data was not perfect. We tried to model the cost data as correctly as possible by selecting only the CF LVADs and by also modelling a scenario with the lowest available LVAD implantation costs, i.e. those derived from the year 2013. This happened to be the most recent year at our disposal and it is not clear if the lower value was due to a trend towards lower CF LVAD implantation costs, or to random variation over time (since there were also lower costs in the year 2009). Nevertheless, even with these lower costs, the ICER of the intervention remained unfavourable. It is also possible that we underestimated costs, e.g. because those generated before the LVAD implantation were not taken into account.

The CF-LVAD information is also based on a mainly BTT population, while the economic evaluation is performed for a DT population. It is not clear whether this might have a big impact on costs. Currently, no better information is available and using the information from the Belgian BTT population, receiving a CF LVAD, seems to be justified.

Other elements might also increase or decrease the incremental costs of CF LVAD implantation versus OMT for patients with end-stage heart failure. For example, the experts mentioned that the follow-up protocol of DT patients is different from that of BTT patients and might be less intensive and thus less expensive. They also mentioned that the patients for whom we had data available might be quite different than the DT patients for which reimbursement is requested based on a better selection of patients. For example, it is possible that patients with a better INTERMACS score are included which might have less costs after an LVAD implantation than the BTT patients. It was not possible to check this assumption. Probably, the life expectancy of such patients would also be different if they do not receive an LVAD. However, to see the possible impact on the ICER, scenario analyses were performed decreasing the cost difference between CF LVAD and OMT, whatever the reason might be for this. As shown in the results, the ICERs remained relatively high. Even after a further reduction in incremental costs of €50 000 to €70 000, the average ICERs remain relatively high at €63 000 and €56 000 per QALY, respectively.

Finally, there is also uncertainty on the impact on QoL because of methodological problems in the studies that reported them. QoL is not always measured with generic utility instruments or results are not expressed in utilities which are necessary to transform life years to QALYs. Studies that gathered QoL are often confronted with missing data (see also 4.3.3). For example, in our reference case, we use the QoL data as applied in the study of Long et al..[49] They refer to the INTERMACS study (Kirklin et al., 2013[41]) to include a utility value of 0.72 more than one month after the LVAD implantation. The figure in the original publication mentions there were 1694 CF LVAD patients. EQ-5D-3L VAS scores were only available for 852 patients before implantation. And worse, 12 months after implantation, results were available for only 281 patients, i.e. less than half of the survivors for which there was a baseline observation.[41] In the study of Grady et al.[34], 73% (n=1072) of data were available for patients before implant, including 203 patients who were too sick to respond and for whom the VAS score was assigned a 0. After one year, of the 1033 patients, 58% (n=599) completed the questionnaire and according to the authors, only 8 were too sick to respond the survey and received a VAS score of 0. The authors mention

that lacking information was primarily due to administrative reasons (e.g. no consent or no contact) or patient's refusal to participate.[34] However, missing data on more than 40% of the sample is very problematic. It is very probable that these data are not missing at random, but related to the disease state of the patients, with more missing data in sicker patients. This could result in too optimistic QoL values. Furthermore, utility values were assumed to remain constant during extrapolation. This might also be optimistic. Changing this assumption would only decrease the number of QALYs gained and disfavour LVAD's cost-effectiveness.

In conclusion, based on the results of this Belgian context-specific economic evaluation, the implantation of a CF LVAD results in a clear improvement of life years and QoL. Unfortunately, the incremental costs due to this intervention are also very high, resulting in relatively high ICERs (on average €82 000 per QALY) with a 0% probability of considering this intervention as being cost-effective if the willingness/ability-to-pay is lower than €54 000 per QALY.

Key points

- **A cost-utility analysis was performed for the Belgian context in which the Belgian pharmacoeconomic guidelines were followed.**
- **There is no direct comparison available between OMT and CF LVAD implantation. An indirect comparison combining the results of two RCTs (the REMATCH and the HeartMate II Destination Therapy Trial study) was used. Based on this indirect comparison, and extrapolating results to a lifetime horizon, an average incremental benefit of 3 QALYs (not discounted) was generated. Applying a discount rate of 1.5%, this was on average 2.76 QALYs.**
- **Belgian cost data concerning LVAD as destination therapy are limited. As an alternative, cost data on continuous-flow (CF) LVADs for all indications were used. Our sample of 156 CF LVAD implantations includes mainly BTT patients. Cost estimates of the initial implantation cost for an LVAD implantation of €45 800 were in line with previous (Belgian) estimates. Together with a device cost of about €67 000, this results in an initial LVAD implantation cost of about €113 000.**
- **Taking into account other costs for rehospitalisations and follow-up, the non-discounted incremental costs are on average about €242 000 (or €222 000 discounted at 3%). In combination with the QALYs gained, this results in an incremental cost-effetiveness ratio (ICER) of €82 000 per QALY.**
- **In Belgium, there is no explicit ICER threshold. If we would apply the UK ICER threshold value of £20 000 – £30 000 per QALY (or €26 352 – €39 529), then the probability that an CF LVAD implantation as destination therapy would be considered as being cost effective is 0%. Based on our scenario analyses, this result was robust.**
- **In conclusion, in line with previous economic evaluations, the cost-effectiveness of CF LVADs remains relatively high and further improvements (better survival, less adverse events, more pronounced QoL improvement, lower implantation costs, etc.) are needed to make this technique acceptable from a medical/economic point of view.**

10 SUMMARY, DISCUSSION AND CONCLUSION

10.1 Clinical aspects

Selected patients with end stage heart failure who remain symptomatic despite optimal standard treatment can be considered for heart transplantation. Because of a decreasing number of potential organ donors, there has been a marked decline in the number of transplantations. Over the last years, a fairly constant number of about 80 transplantations are performed in one of 7 heart transplant centres in Belgium.

The shortage of donor hearts has encouraged the development of artificial mechanical devices that can assist or replace the function of the failing heart. These left ventricular assist devices (LVAD) were first introduced as a “bridge to transplant” (BTT) in patients with rapidly deteriorating heart failure who were on the heart transplant waiting list. LVADs have been reimbursed for this clinical indication in Belgium since 1999.

With increasing international clinical experience, LVADs were subsequently promoted to be implanted as a permanent solution (“destination therapy” - DT) or as a “bridge to candidacy” (BTC) in patients in whom it is not yet clear at the time of LVAD implantation whether they are good transplantation candidates. Since 2014, the RIZIV – INAMI provides reimbursement for a yearly total number of 50 LVADs to be used for patients on the waiting list for transplantation (BTT) and in patients in whom transplantation could be anticipated (BTC). There is presently no reimbursement for LVADs as destination therapy (DT). Because of an increasing demand by Belgian practitioners for LVAD as a BTC and DT, the present report has been initiated with the aim to assess the clinical and cost-effectiveness of LVADs used as DT or as BTC.

An LVAD is implanted with the patient under general anaesthesia and involves open heart surgery. An inflow pipe towards the pump is inserted into the left ventricle of the heart and an outflow pipe is inserted into the aorta. A power cable is brought through the abdominal wall and attached to a control system and battery outside of the body. Patients need to carry this equipment with them at all times. It requires a thorough understanding of the LVAD system by the patient and companion to ensure safety. Aseptic maintenance of the exit site by the patient is critical to prevent infection of the device via the power cable that penetrates the skin. To prevent pump thrombosis, patients require systemic anticoagulation.

In comparison with standard treatments, randomized trials have shown an improvement in survival and in quality of life in patients with end stage heart failure in whom an LVAD is implanted as DT. This has particularly been demonstrated with the newer continuous-flow LVADs. No RCTs have been conducted on the use of LVADs as a BTC.

The benefit of LVADs as DT is counterbalanced by a range of common complications. Bleeding is the most commonly reported adverse event. Most patients experience some type of bleeding. The greatest risk of bleeding is within the first weeks postoperatively and is reported in 8 to 100% of patients. Late bleeding occurs in 12 to 23% of patients and is predominantly from gastro-intestinal origin. Ischaemic and haemorrhagic stroke occur in 8% and 11% of patients respectively in the first 2 years after LVAD placement. Infections after LVAD implantation may occur locally, at the driveline, or systemically. Local infections are reported in 20 to 49% of patients, driveline infections in 12 to 22%, and sepsis in 20 to 36% of patients. Right heart failure requiring inotropic support is reported in 5 to 25% of patients. Device failure rates at 12 and 24-months post-implantation are 2.9% and 6.5% respectively.

10.2 Economic considerations: a necessity for an accessible, high quality and sustainable health care system

In an article entitled “*The importance and added value of Health Technology Assessment and economic evaluations of medical interventions to support reimbursement decisions: the TAVI experience*”[70], we try to explain why it is desirable to take economic considerations into account. The same reasoning, which we explain here, is relevant for the reimbursement decision on LVADs.

Everybody will agree that resources are limited and that there are many more interventions that (might) provide benefit to patients than society can afford. Choices have to be made. Only looking at benefits without taking into account the costs might result in more harm than good for the health of the Belgian population due to the opportunity cost of every decision.[70] The opportunity cost is the value of the best alternative forgone, or according to the dictionary: “*the loss of potential gain from other alternatives when one alternative is chosen*” (The New Oxford American Dictionary). Although, the

opportunity cost is almost never made explicit, every policy maker will agree that every reimbursement decision has its opportunity costs. With the same budget, other services might not be reimbursed or existing services might be cut to provide this money.

"*Health technology assessment (HTA) aims at providing support to decision makers in taking good decisions to keep the health care system accessible, of the highest quality as possible and durable. Not taking into account costs runs the risk of having a negative impact on the health care system's accessibility or quality, e.g. by increasing patients' contributions or taking away other interventions that provide more value for money to fund the interventions that are relatively too expensive.*"[70]

"*Efficiency measures the effect of an intervention in relation to the resources it consumes ("Is it worth it?")*".[71] Economic evaluations of interventions are performed to support the efficient use of limited resources. They "*tend to guide decision makers towards the maximisation of health gains within a resource constraint, regardless of which individuals or population groups may benefit from a health intervention or perhaps be penalised by that intervention*".[72] An advice for **a negative reimbursement decision should thus not be seen in the first place as decision against a specific intervention, but rather as a decision to support a health healthcare system in which as many as possible life years and QoL are generated by making efficient use of limited resources**.

In practice, economic evaluations compare alternative interventions for a specific indication in terms of both their costs and consequences. As such, ICERs are calculated (being the ratio of: 1) the extra costs of an intervention versus its comparator and 2) the extra benefits, preferably expressed in QALYs, of this intervention versus this comparator). An ICER that is 'too high' means that its benefits are not high enough in relation to the extra costs (and thus we would do more harm than good due to the opportunity cost of this 'investment').

The main question then becomes when an ICER is 'too high'. When is an intervention too expensive in relation to its benefits? KCE already made a report on this issue.[73] As explained, the theoretical health maximisation model to determine this ICER threshold value cannot be applied in real life due to several reasons, the most important one being lack of full information on the ICERs of all possible health care interventions, which is utopian. As concluded in that KCE report "*The ICER threshold value against which the ICERs of interventions should be compared is unknown and is variable over time. This is not, however, an argument against the use of economic considerations in health care decision making. Neglecting economic considerations is unethical as spending resources on one health programme reduces the resources available for other health programmes.*"[73]

Only the guideline of the UK National Institute for Health and Care Excellence (NICE) defines an explicit threshold, ranging from £20 000 to £30 000 per QALY gained. The value depending a.o. on the degree of uncertainty about the ICER, whether the assessment of QoL has adequately been captured, the innovative nature of the technology, and whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life', as well as aspects that relate to non-health objectives of the NHS.[69] Recent research in the UK indicated that their threshold should not be increased (but rather lowered).[74] Thresholds of up to three times GDP per capita, as suggested more than 10 years ago by WHO,[75] are very probably unrealistic. People should be aware of the difference between stated willingness-to-pay and actual ability to pay. If policy makers say that displaced services (to fund the new interventions) are more cost effective than their threshold, then that threshold is too high[76] (and vice versa).

10.3 (Willingness to consider the economic argument for) LVADs as DT

There is no doubt that CF LVADs improve survival and QoL in patients with end-stage heart failure. From an individual physician's or patient's point of view, omitting costs, this intervention should be considered or even recommended. However, from a societal/governmental point of view, costs cannot be neglected and are (as explained above) linked to the health of our population.

That this is a challenging message to bring and that other non-economic arguments might be used is clear from the Dutch situation. In the Netherlands, the National Health Care Institute (ZIN) favoured reimbursing LVADs as destination therapy.[77, 78] It seemed that the argument prevailed that an LVAD as DT for most patients is the only treatment option, and that economic considerations were not taken into account.

Based on previous economic evaluations and the current context-specific economic evaluations, we estimate that the cost-effectiveness of CF LVADs as destination therapy in patients with end-stage heart failure is on average about €82 000 per QALY gained. In other words, **based on the results of this HTA report, considering both medical and economic arguments, LVADs as DT is very probable no efficient use of the limited resources**.

In the short term, one might say that one can and will find the money to finance this intervention. If it is argued that we 'let people die' if we do not reimburse this intervention, then the counterargument is that we try to do the best for our population and that in the long-term we are doing more harm than good by spending our limited budgets to interventions that have unfavourable incremental cost-effectiveness ratios. In the end, we want a health care system that is accessible, of the highest quality as possible and financially sustainable.

10.4 Legal liability

Patients have the right to high-quality service that meets their needs from the physician who treats them (Art. 5, Law on Patients' Rights). This however does not imply that all possible individual wishes of a patient in any situation in which he/she finds him/herself must be met. Moreover this also does not mean that no conditions could be set under which the high-quality service is made available. It was established in the Parliamentary Committee in preparation of the law on patients' rights that the right of the patient to the best possible treatment is not always possible for financial reasons.[i] The Minister of Public Health in fact also commented in this connection that "the role of social security consists of ensuring the right to healthcare insofar as possible." The right to high-quality service thus does not grant the patient the right to the very latest techniques.[j]

In any event, the entitlement of the insured does not extend to the point that if there is an indication for a procedure, any possible procedure that is available on the market, regardless of costs, must be provided when less expensive alternatives are also medically justified.[k] However, in principle obsolete techniques cannot be resorted to on the basis of cost considerations when a new method has become established as medically standard. When a physician, whether or not for economic reasons, treats below the standard of care and thereby does not provide high-quality care to the patient, he can be held liable.

Where exactly the boundary should be drawn between allowed and prohibited economic considerations is not always clear, in either the medical or the legal field.[l] In Dutch jurisprudence there are in fact calls that there is scope for accepting less effective or less safe options if the better option is accompanied by disproportionate costs.[m]

10.5 And what about LVADs for BTC patients?

The scope of this report also includes LVADs as BTC. Although there is no evidence to support strong conclusions, the cost-effectiveness of an LVAD as BTC can already be predicted based on the outcomes for DT. Increasing the number of LVADs (BTT, BTC or DT) will not increase the number of heart transplantations. It might only result in a different person receiving the heart transplant. The opportunity cost of selecting person A for a heart transplantation is that you cannot select person B to receive this donor heart. In the end, increasing the number of LVADs as BTC (or as BTT) will eventually only create more patients with an LVAD as DT since the number of heart donors is not increasing. Since the cost-effectiveness of DT is not favourable, it is very questionable that LVAD implantation as BTC can be considered to make efficient use of limited resources.

Experts might argue that BTC patients are another type of patients with other cost implications. Nevertheless, based on the high costs of the initial procedure and device, the above argument that DT patients are "created", and the results of the extensive scenario analyses in DT patients with large

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i Bill on patients' rights, Explanatory Memorandum, Parliamentary Documents, Chamber, 2001-02, 1642/001, 18

j Bill on patients' rights, Parliamentary Documents, Chamber, 2001-02, 1642/012, 64

k Rb. Haarlem [*Haarlem District Court*], 17 September 1993, Dutch Journal of Health Law, 1994/25

l Callens, S., Volbragt, I. and Nys, H., Cost-reducing measures, quality care and medical liability, Antwerp, Intersentia, 2006, 283 p.

m JKM Gevers and MCIH Biesaart, "Medical decisions, cost considerations and guidelines for clinical practice; comment from the legal point of view", Dutch Journal of Medicine 1999, 143, 2630

cost reductions, **there is currently no justification to consider LVADs as bridge to candidacy being a cost-effective intervention**.

APPENDICES

APPENDIX 1. SEARCH STRATEGIES FOR CLINICAL EFFECTIVENESS

Appendix 1.1. Electronic reference databases: Medline (through OVID), EMBASE and the Cochrane Library

Table 53 – Search strategy Medline

Date	2015-08-21		
Database	**Medline (OVID)**		
Search Strategy	#	Query	**Results**
	1	exp Heart Failure/	**93060**
	2	exp Cardiomyopathies/	**76710**
	3	Myocarditis/	**12003**
	4	exp Ventricular Dysfunction/	**28562**
	5	Shock, Cardiogenic/	**6684**
	6	cardiomyopath*.ab,ti.	**52342**
	7	((End-stage* or endstage* or end stage* or advance* or acute*) adj4 heart* adj4 failur*).ab,ti.	**12310**
	8	Myocardit*.ab,ti.	**11727**
	9	(ventricul* adj4 dysfunct*).ab,ti.	**20226**
	10	(Cardiogenic* adj4 shock*).ab,ti.	**7997**
	11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	**219566**
	12	Assisted Circulation/	**3252**
	13	Heart-Assist Devices/	**9604**
	14	((device? or pump? or system?) adj4 (assist or support) adj4 (heart or ventricular or ventricl*)).ab,ti.	**7997**
	15	(LVAD or LVAS or VAS or HVAD).ab,ti.	**31810**
	16	(Heart* adj4 assist* adj4 (device* or system* or pump* or treat* or therap* or surg*)).ab,ti.	**1253**
	17	(Heart* adj4 fail* adj4 (device* or system* or pump*)).ab,ti.	**2355**
	18	ventricular device?.ab,ti.	**70**
	19	(continuous-flow adj3 device?).ab,ti.	**361**

	20	(Assis* adj4 circulat*).ab,ti.	**1745**
	21	circulatory support device?.ab,ti.	**278**
	22	mechanical support system?.ab,ti.	**22**
	23	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	**45835**
	24	heartmate.ab,ti.	**804**
	25	heartware.ab,ti.	**238**
	26	thoratec.ab,ti.	**423**
	27	novacor.ab,ti.	**280**
	28	abiomed.ab,ti.	**165**
	29	cardiowest.ab,ti.	**67**
	30	"Berlin EXCOR".ab,ti.	**10**
	31	"DeBakey Child".ab,ti.	**1**
	32	ventrassist.ab,ti.	**44**
	33	(DuraHeart or Terumo).ab,ti.	**491**
	34	jarvik 2000.ab,ti.	**145**
	35	"Heart Excor".ab,ti.	**108**
	36	"Heart Incor".ab,ti.	**13**
	37	medos.ab,ti.	**161**
	38	PVAD?.ab,ti.	**117**
	39	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	**2486**
	40	23 or 39	**46483**
	41	11 and 40	**9028**
	42	((Destinat* or permanent*) adj4 (therap* or treat* or surg*)).ab,ti.	**5906**
	43	DT.ab,ti.	**20609**
	44	((long-term or longest-term) adj4 (LVAD or outcome? or device?)).ab,ti.	**48337**
	45	((long-term or longest-term) and (device? or LVAD)).ab,ti.	**13606**
	46	42 or 43 or 44 or 45	**85550**
	47	41 and 46	**1442**

	48	limit 47 to ed=20100630-20151231	**654**
	49	limit 48 to animals	**33**
	50	limit 48 to human	**608**
	51	49 not 50	**11**
	52	48 not 51	**643**
	53	52 not (editorial or news or newspaper or interview or letter).pt.	**632**
	54	52 and comment.pt.	**7**
	55	53 or 54	**639**
	56	remove duplicates from 55	**613**
	57	"bridge to decision".mp.	**69**
	58	"bridge to transplant".mp.	**544**
	59	"bridge-to-decision".mp.	**69**
	60	"bridge to transplantation".mp.	**942**
	61	"bridge to recovery".mp.	**396**
	62	"bridge to candidacy".mp.	**13**
	63	57 or 58 or 59 or 60 or 61 or 62	**1756**
	64	41 and 63	**992**
	65	limit 64 to yr="2005 -Current"	**712**
	66	limit 65 to animals	**26**
	67	limit 65 to humans	**648**
	68	65 not (66 not 67)	**703**
	69	68 and (editorial or news or newspaper or interview or letter).pt.	**14**
	70	68 and comment.pt.	**8**
	71	68 not (69 not 70)	**694**
	72	remove duplicates from 71	**670**
	73	72 not 56	**467**
Notes		**Destination therapy: Line 56; Bridge to decision: Line 73** **We remove from bridge to decision the results found in destination therapy**	

Table 54 – Search strategy Embase

Date	2015-08-21		
Database	**Embase**		
Search Strategy	#	Query	Results
	1	'heart failure'/exp	**344267**
	2	'cardiomyopathy'/exp	**107630**
	3	'myocarditis'/exp	**20284**
	4	'ventricular dysfunction'/exp	**12755**
	5	'cardiogenic shock'/exp	**16514**
	6	cardiomyopath*:ab,ti	**74993**
	7	myocardit*:ab,ti	**15282**
	8	(ventric* NEAR/4 dysfunction*):ab,ti	**31336**
	9	(cardiogenic* NEAR/4 shock*):ab,ti	**12447**
	10	(('end stage' OR 'end stages' OR 'end stage' OR 'end stages' OR advanc* OR acute*) NEAR/4 heart* NEAR/4 failur*):ab,ti	**20411**
	11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	**459076**
	12	'assisted circulation'/exp	**8900**
	13	'heart assist device'/exp	**23686**
	14	((device* OR pump* OR system*) NEAR/4 (assist OR support) NEAR/4 (heart OR ventricular OR ventricl*)):ab,ti	**12384**
	15	lvad:ab,ti OR lvas:ab,ti OR vas:ab,ti OR hvad:ab,ti	**52131**
	16	(heart* NEAR/4 assist* NEAR/4 (device* OR system* OR pump* OR treat* OR therap* OR surg*)):ab,ti	**1853**
	17	(heart* NEAR/4 fail* NEAR/4 (device* OR system* OR pump*)):ab,ti	**3277**
	18	'ventricular device':ab,ti OR 'ventricular devices':ab,ti	**135**
	19	('continuous flow' NEAR/3 device*):ab,ti	**549**
	20	(assis* NEAR/4 circulat*):ab,ti	**2386**
	21	'circulatory support device':ab,ti OR 'circulatory support devices':ab,ti	**427**
	22	'mechanical support system':ab,ti OR 'mechanical support systems':ab,ti	**37**

23	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	**81105**
24	heartmate:ab,ti	**1672**
25	heartware:ab,ti	**738**
26	thoratec:ab,ti	**644**
27	novacor:ab,ti	**366**
28	abiomed:ab,ti	**258**
29	cardiowest:ab,ti	**99**
30	'berlin excor':ab,ti	**17**
31	'debakey child':ab,ti	**1**
32	ventrassist:ab,ti	**131**
33	duraheart:ab,ti OR terumo:ab,ti	**1244**
34	'jarvik 2000':ab,ti	**229**
35	'heart excor':ab,ti	**233**
36	'heart incor':ab,ti	**37**
37	medos:ab,ti	**240**
38	pvad:ab,ti OR pvads:ab,ti	**198**
39	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	**4820**
40	#23 OR #39	**82436**
41	#11 AND #40	**18035**
42	((destinat* OR permanent*) NEAR/4 (therap* OR treat* OR surg*)):ab,ti	**8114**
43	dt:ab,ti	**27571**
44	(('long term' OR 'longest term') NEAR/4 (lvad OR outcome* OR device*)):ab,ti	**71687**
45	'long term':ab,ti OR 'longest term':ab,ti AND (device*:ab,ti OR lvad:ab,ti)	**20026**
46	#42 OR #43 OR #44 OR #45	**122499**
47	#41 AND #46	**2839**
48	#47 AND [30-6-2010]/sd NOT [31-12-2015]/sd	**1841**
49	#48 NOT [medline]/lim	**1246**

	50	#49 NOT ([animals]/lim NOT [humans]/lim)	**1229**
	51	#50 NOT [editorial]/lim	**1227**
	52	#51 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	**1052**
	53	#51 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	**175**
	54	'bridge to decision':ab,ti	**149**
	55	'bridge to transplant':ab,ti	**1118**
	56	'bridge-to-decision':ab,ti	**149**
	57	'bridge to transplantation':ab,ti	**1330**
	58	'bridge to recovery':ab,ti	**583**
	59	'bridge to candidacy':ab,ti	**36**
	60	#54 OR #55 OR #56 OR #57 OR #58 OR #59	**2853**
	61	#41 AND #60	**1775**
	62	#61 AND [2005-2015]/py	**1445**
	63	#62 NOT [medline]/lim	**816**
	64	#63 NOT ([animals]/lim NOT [humans]/lim)	**812**
	65	#64 NOT [editorial]/lim	**811**
	66	#65 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	**674**
	67	#65 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	**137**
	68	#66 NOT #52	**357**
	69	#67 NOT #53	**88**
Notes		**Destination therapy: Line #53; Bridge to decision: Line #69** **We remove from bridge to decision the results found in destination therapy**	

Table 55 – Search strategy Cochrane Database of Systematic Reviews

Date	2015-08-21		
Database	**Cochrane Database of Systematic Reviews**		
Search Strategy	**#**	**Query**	**Results**
	1	[mh "Heart Failure"]	**5871**
	2	[mh Cardiomyopathies]	**1374**
	3	[mh Myocarditis]	**87**
	4	[mh "Ventricular Dysfunction"]	**1844**
	5	[mh "Shock, Cardiogenic"]	**166**
	6	cardiomyopath*:ab,ti	**1555**
	7	((End-stage* or endstage* or end stage* or advance* or acute*) near/4 heart* near/4 failur*):ab,ti	**1249**
	8	Myocardit*:ab,ti	**935**
	9	(ventricul* near/4 dysfunct*):ab,ti	**1799**
	10	(Cardiogenic* near/4 shock*):ab,ti	**391**
	11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	**11440**
	12	[mh "Assisted Circulation"]	**385**
	13	[mh "Heart-Assist Devices"]	**195**
	14	((device? or pump? or system?) near/4 (assist or support) near/4 (heart or ventricular or ventricl*)):ab,ti	**79**
	15	(LVAD or LVAS or VAS or HVAD):ab,ti	**10710**
	16	(Heart* near/4 assist* near/4 (device* or system* or pump* or treat* or therap* or surg*)):ab,ti	**100**
	17	(Heart* near/4 fail* near/4 (device* or system* or pump*)):ab,ti	**354**
	18	ventricular device?:ab,ti	**263**
	19	(continuous-flow near/3 device?):ab,ti	**5**
	20	(Assis* near/4 circulat*):ab,ti	**36**
	21	circulatory support device?:ab,ti	**21**

22	mechanical support system?:ab,ti	**259**
23	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	**11841**
24	heartmate:ab,ti	**24**
25	heartware:ab,ti	**7**
26	thoratec:ab,ti	**11**
27	novacor:ab,ti	**0**
28	abiomed:ab,ti	**8**
29	cardiowest:ab,ti	**2**
30	"Berlin EXCOR":ab,ti	**0**
31	"DeBakey Child":ab,ti	**0**
32	ventrassist:ab,ti	**0**
33	(DuraHeart or Terumo):ab,ti	**65**
34	jarvik 2000:ab,ti	**3**
35	"Heart Excor":ab,ti	**2**
36	"Heart Incor":ab,ti	**0**
37	medos:ab,ti	**6**
38	PVAD?:ab,ti	**0**
39	#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38	**115**
40	#23 or #39	**11917**
41	#11 and #40	**507**
42	((Destinat* or permanent*) near/4 (therap* or treat* or surg*)):ab,ti	**313**
43	DT:ab,ti	**618**
44	((long-term or longest-term) near/4 (LVAD or outcome? or device?)):ab,ti	**2279**

	45	((long-term or longest-term) and (device? or LVAD)):ab,ti	**427**
	46	#42 or #43 or #44 or #45	**3558**
	47	#41 and #46	**45**
	48	#41 and #46 Publication Year from 2010 to 2015	**25**
	49	"bridge to decision":ab,ti	**0**
	50	"bridge to transplant":ab,ti	**13**
	51	"bridge-to-decision":ab,ti	**0**
	52	"bridge to transplantation":ab,ti	**20**
	53	"bridge to recovery":ab,ti	**3**
	54	"bridge to candidacy":ab,ti	**0**
	55	#49 or #50 or #51 or #52 or #53	**35**
	56	#55 and #41	**21**
	57	#55 and #41 Publication Year from 2005 to 2015	**16**
Notes		**Destination therapy: Line #48** **Bridge to decision: Line #57**	

APPENDIX 2. STUDY SELECTION AND QUALITY APPRAISAL

Appendix 2.1. Study selection

Table 56 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Adzic A, et al. - Impact of adverse events on ventricular assist device outcomes	Focus on pulsatile devices.
Aggarwal A, et al. - Incidence and management of gastrointestinal bleeding with continuous flow assist devices	Retrospective analysis of 101 patients implanted with the Heart Mate II from January 2005 to August 2011. Excluded because a more recent SR was identified (Draper et al).
Attisani M, et al. - Advanced heart failure in critical patients (INTERMACS 1 and 2 levels): ventricular assist devices or emergency transplantation?	Limited series on 49 patients. Selection bias.
Bielecka A, et al. - The ventricular assist device: a bridge to ventricular recovery, a bridge to heart transplantation or destination therapy?	Design (narrative review).
Birks EJ, et al. - Long-term outcomes of patients bridged to recovery versus patients bridged to transplantation	Population and design: retrospective analysis of 40 pts that could be explanted vs 52 that were transplanted. Out of scope: no DT.
Boothroyd LJ et al. Challenge of informing patient decision making: what can we tell patients considering long-term mechanical circulatory support about outcomes, daily life, and end-of-life issues? Circ Cardiovasc Qual Outcomes. 2014 Jan;7(1):179-87.	Summary of small series
Bryant R, 3rd, et al. - Current use of the EXCOR pediatric ventricular assist device	Excor is extracorporeal and excluded because of this.
Bunte MC, et al. - Major bleeding during HeartMate II support	Less than 200 patients (n=139).
Dang NC, et al. - Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure	Less than 200 patients (n=108)
de By TM, et al. - The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first annual report	In contrast to INTERMACS, this register is not mandatory and prone to selection bias. Only 2 Belgian centres (Aalst, Gent) participate according to this publication.
D'Udekem Y, et al. - Recurrent or prolonged mechanical circulatory support: Bridge to recovery or road to nowhere?	Intervention (short-term).

Reference	Reason(s) for exclusion
Dunlay SM, et al. - Frailty and outcomes after implantation of left ventricular assist device as destination therapy	Considers patient selection, not outcomes.
Forest SJ, et al. - Readmissions after ventricular assist device: etiologies, patterns, and days out of hospital	Less than 200 patients (n=71)
Genovese EA, et al. - Early adverse events as predictors of 1-year mortality during mechanical circulatory support	Less than 200 patients (n=163).
Goldstein D.J, et al. - Gastrointestinal Bleeding in Recipients of the HeartWare Ventricular Assist System	Bleeding events from 382 patients. More comprehensive SR identified (Draper; n=1839).
Hayes, et al. - HeartMate II (Thoratec Corp.) Left Ventricular Assist Device (LVAD) for destination therapy in adult patients with chronic heart failure (Structured abstract)	Only abstract. Full article not retrievable through ILL or KUL.
Ibrahim M, et al. - Bridge to recovery and weaning protocols	Retrospective selection of recovery patients.
Kalavrouziotis D, et al. - Percutaneous lead dysfunction in the HeartMate II left ventricular assist device	This paper selectively considers LVAD lead dysfunction whih we consider out of scope.
Kormos RL, et al. - Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes	Large series that is included in McIlvennan's SR.
Lowry AW, et al. - The potential to avoid heart transplantation in children: outpatient bridge to recovery with an intracorporeal continuous-flow left ventricular assist device in a 14-year-old	Case report.
Menon AK, et al. - Low stroke rate and few thrombo-embolic events after HeartMate II implantation under mild anticoagulation	Intervention = anticoagulation scheme.
Morgan JA, et al. - Stroke while on long-term left ventricular assist device support: incidence, outcome, and predictors	Series less than 200 (n=100).
Naik A, et al. - Acute kidney injury and mortality following ventricular assist device implantation	Series less than 200 (n=157).
Najjar SS, et al. - An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial	Large series that is included in McIlvennan's SR.
Patel AM, et al. - Renal failure in patients with left ventricular assist devices	Narrative review.

Reference	Reason(s) for exclusion
Pawale A, et al. - Implantable left ventricular assist devices as initial therapy for refractory postmyocardial infarction cardiogenic shock	Very selected population.
Petrucci RJ, et al. - 2009 Neurocognitive assessments in advanced heart failure patients receiving continuous-flow left ventricular assist devices	No outcome of interest
Petrucci RJ, et al. 2012 -- Neurocognitive function in destination therapy patients receiving continuous-flow vs pulsatile-flow left ventricular assist device support	No outcome of interest
Sharma V, et al. - Driveline infections in left ventricular assist devices: implications for destination therapy	Less than 200 cases.
Smedira NG, et al. - Unplanned hospital readmissions after HeartMate II implantation: frequency, risk factors, and impact on resource use and survival	Only 20 DT patients.
Starling RC, et al. - Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support).	Less than 200 cases.
Struber M, et al. - HeartMate II left ventricular assist device; early European experience	Less than 200 cases (n=101).
Takeda K, et al. - Incidence and clinical significance of late right heart failure during continuous-flow left ventricular assist device support	Scope limited to late right heart failure.
Takeda K, et al. - Long-term outcome of patients on continuous-flow left ventricular assist device support	Less than 200 cases (n=140)
Tsiouris A, et al. - Factors determining post-operative readmissions after left ventricular assist device implantation	Observational, less than 200 patients (138, of which 63 DT).
Tsiouris A, et al. - Lessons learned from 150 continuous-flow left ventricular assist devices: A single institutional 7 year experience	Less than 200 cases (n=150).
Weitkemper H.-H, et al. - "Bridge to Transplant" using two different VAD (ventricular assistance device) systems	case report
Westaby S, et al. - Cardiogenic shock in ACS. Part 2: Role of mechanical circulatory support	Very selected population.

Reference	Reason(s) for exclusion
Wu L, et al. - Outcomes of HeartWare Ventricular Assist System support in 141 patients: a single-centre experience	Less than 200 cases (n=141)
Ziemba EA, et al. - Mechanical circulatory support for bridge to decision: which device and when to decide	Narrative review.

Appendix 2.2. Quality appraisal of systematic reviews

Table 57 – Amstar evaluation of included systematic reviews

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion		List of in- and excluded studies		Characteristics of included studies provided
Boothroyd et al., 2014	Y	N	Y	Y	Non-published documents also looked for (e.g. INTERMACS documents)	N		N
Draper et al., 2014	Y	Y	Y	N	only indexed papers were considered	N		Y
McIlvennan et al., 2014	Y	Y	Y	Y	Manual search of reference list of retrieved articles	N	No list of excluded studies	N
Xie et al., 2014	Y	Y	Y	Y	The references of retrieved articles were also reviewed in order to identify further relevant studies.	N		Y

Systematic review	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed		Conflict of interest stated
Boothroyd et al., 2014	N	N	NA	N	?	Only for SR, not for primary studies

Draper et al., 2014	Y	Quality assessment of the studies by using the Newcastle-Ottawa Scale	N	NA	Y	?	Only for SR, not for primary studies
McIlvennan et al., 2014	N		N	NA	N	?	Only for SR, not for primary studies
Xie et al., 2014	N		N	NA	Y	?	Only for SR, not for primary studies

Appendix 2.3. Quality appraisal of RCTs

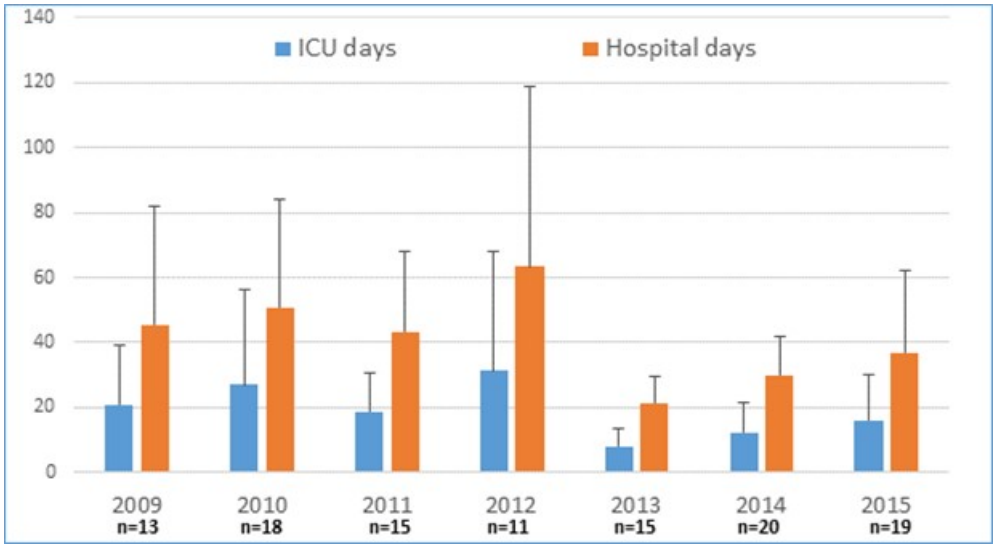
Table 58 – Critical appraisal of RCTs (Source: Neyt et al.[21])

Selection criteria	Level of evidence (EBRO, Evidence Based Richtlijnontwikkeling)	Critical appraisal
Rose et al., 2001 [26]	A2 (i.e. Good quality randomized double blind comparative clinical trial with sufficient sample size)	Randomization with block design No clear information on allocation concealment, but the trial was executed by an independent coordinating centre No blinding of patients nor clinicians Blinding of investigators (except for statisticians) ITT analysis No mention of median follow-up
Slaughter et al., 2009[7]	B (Comparative clinical trial, but not all characteristics essential for level A2 are fulfilled)	No clear information on allocation concealment No blinding of patients nor clinicians Independent data and safety monitoring board and clinical events committee ITT analysis for primary endpoint

APPENDIX 3. LENGTH OF STAY

Figure 16 shows the length of stay after implantation of a CF LVAD in one university hospital in Belgium over the last 7 years. In every year, there is a high variability. On the other hand, there is a shorter hospitalization time (and thus lower costs) in 2013-2015 compared to 2009 – 2012.

Figure 16 – Length of stay in one university hospital (2009-2015)



ICU: intensive care unit
Source: personal communication UZLeuven

APPENDIX 4. SEARCH STRATEGIES ECONOMIC PART

Appendix 4.1. Literature search (cost-effectiveness)

In August-October 2015, the websites of HTA institutes (Table 59) and following databases were searched: Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)), Medline, and Embase. Table 60 up to Table 64 provide an overview of the applied search strategies.

Table 59 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
ASSR	Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care)	Italy
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CDE	Center for Drug Evaluation	Taiwan
CEDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques	France
CEM	Inspection générale de la sécurité sociale (IGSS), Cellule d'expertise médicale	Luxembourg
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CONITEC	National Committee for Technology Incorporation	Brazil
CMeRC	Department of Internal Medicine	South Africa
CRD	Centre for Reviews and Dissemination	United Kingdom
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil

ETESA	Department of Quality and Patient Safety of the Ministry Health of Chile	Chile
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
G-ba	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesundheit Österreich	Austria
HAD-MSP	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HCT-NHSRC	Division of Healthcare Technology, National Health Systems Resource Center	India
HealthPACT	Health Policy Advisory Committee on Technology	Australia
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HQO	Evidence Development and Standards Branch	Canada
HSAC	Health Services Assessment Collaboration	New Zealand
HTA-HSR/DHTA	HTA & Health Services Research	Denmark
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IHE	Institute of Health Economics	Canada
INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NHC	New Zealand National Health Committee	New Zealand
NHMRC CTC	NHMRC Clinical Trials Centre	Australia
NIHR	National Institute for Health Research	United Kingdom
NOKC	Norwegian Knowledge Centre for Health Services	Norway
OSTEBA	Basque Office for Health Technology Assessment	Spain

RCHD-CS	Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development, Centre of Standardization, HTA department	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UCEETS	The National Coordination Unit of Health Technology Assessment and Implementation	Argentina
UVT	HTA Unit in A. Gemelli University Hospital	Italy
VASPVT	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	Lithuania
ZIN	Zorginstituut Nederland	The Netherlands
Selection of ex or non-member websites		
CHE	Centre for Health Economics	United Kingdom
CMT	Center for Medical Technology Assessment	Sweden
EUnetHTA	European Network for HealthTechnology Assessment	Europe
NICE	National Institute for Health and Care Excellence	United Kingdom
PHARMAC	Pharmaceutical Management Agency	New Zealand

Table 60 – Search strategy and results for CRD: HTA

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Heart-Assist Devices EXPLODE ALL TREES	83
	2	* IN HTA	15446
	3	#1 AND #2	**48 references**
Note	In comparison with the previous search, **5 extra references** were identified.		

Table 61 – Search strategy and results for CRD: NHS EED

Date			
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Heart-Assist Devices EXPLODE ALL TREES	83
	2	* IN NHSEED	17613

	3	#1 AND #2	**20 references**
Note	In comparison with the previous search, **4 extra references** were identified.		

Table 62 – Search strategy and results for Medline (OVID) (part I)

Date			
Date covered	1996 to July Week 5 2015		
Search Strategy	1	economics/	6139
	2	exp "Costs and Cost Analysis"/	128016
	3	"Value of Life"/ec [Economics]	227
	4	Economics, Dental/	188
	5	exp Economics, Hospital/	11777
	6	Economics, Medical/	1779
	7	Economics, Nursing/	554
	8	Economics, Pharmaceutical/	2210
	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	140062
	10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	380501
	11	(expenditure$ not energy).tw.	13333
	12	(value adj1 money).tw.	16
	13	budget$.tw.	12587
	14	10 or 11 or 12 or 13	393195
	15	9 or 14	446218
	16	letter.pt.	545992
	17	editorial.pt.	278831
	18	historical article.pt.	137448
	19	16 or 17 or 18	950594
	20	15 not 19	424627
	21	Animals/	2919099

	22	human/	8256932
	23	21 not (21 and 22)	1887893
	24	20 not 23	386114
	25	(metabolic adj cost).ti,ab,sh.	639
	26	((energy or oxygen) adj cost).ti,ab,sh.	1711
	27	24 not (25 or 26)	384307
	28	exp Heart-Assist Devices/	7763
	29	(HeartMate or HeartWare or HeartAssist$ or Jarvik or "AB-180 iVAD" or Abiomed or LionHeart or AxiPump or "Berlin Heart" or "Berlin Incor" or BP-80 or "Cora valveless pulsatile pump" or CorAide or DeltaStream or "Gyro pump" or "Heart Quest" or Heartquest or Hemopump or Medos or "MicroMed DeBakey" or "Baylor/NASA" or "Nippon-Zeon" or Novacor or "Pierce-Donachy" or "Rotodynamic pump" or "Sun Medical/ Waseda/Pittsburgh" or Evaheart or DuraHeart or Thoratec or Toyobo or Ventrassist or HeartSaver or AbioCor or Akutsu or Biomedicus or "Gyro pump" or Impella or Levitronix or Liotta or Medos or "Bio-Pump" or "Model-7 ALVAD" or TandemHeart).mp.	2366
	30	28 or 29	8209
	31	27 and 30	290 references
Note	In comparison with the previous search, 37 extra references were identified.		

Table 63 – Search strategy and results for Medline (OVID) (part II)

Date			
Date covered	In process & other non-indexed citations August 05, 2015		
Search Strategy	1	cost$.mp.	48494
	2	economic$.mp.	21068
	3	budget$.mp.	2655
	4	expenditure$.mp.	3729
	5	1 or 2 or 3 or 4	68566

	6	(((vad or vads) and (heart or cardiac)) or (lvas$ or lvad$) or ((ventric$ adj3 assist$) and (left or heart or cardiac)) or (ventric$ adj3 support system$) or (assist$ adj device$ adj (ventric$ or heart or cardiac))).mp.	733
	7	(HeartMate or HeartWare or HeartAssist$ or Jarvik or "AB-180 iVAD" or Abiomed or LionHeart or AxiPump or "Berlin Heart" or "Berlin Incor" or BP-80 or "Cora valveless pulsatile pump" or CorAide or DeltaStream or "Gyro pump" or "Heart Quest" or Heartquest or Hemopump or Medos or "MicroMed DeBakey" or "Baylor/NASA" or "Nippon-Zeon" or Novacor or "Pierce-Donachy" or "Rotodynamic pump" or "Sun Medical/ Waseda/Pittsburgh" or Evaheart or DuraHeart or Thoratec or Toyobo or Ventrassist or HeartSaver or AbioCor or Akutsu or Biomedicus or "Gyro pump" or Impella or Levitronix or Liotta or Medos or "Bio-Pump" or "Model-7 ALVAD" or TandemHeart).mp.	258
	8	6 or 7	817
	9	5 and 8	**26 references**
Note	In comparison with the previous search, **18 extra references** were identified.		

Table 64 – Search strategy and results for EMBASE

Date			
Date covered	All		
Search Strategy	1	socioeconomics'/exp	192,925
	2	cost benefit analysis'/exp	67,756
	3	cost effectiveness analysis'/exp	107980
	4	cost of illness'/exp	15,087
	5	cost control'/exp	52,584
	6	economic aspect'/exp	1,212,957
	7	financial management'/exp	325,079
	8	health care cost'/exp	220,162
	9	health care financing'/exp	11,786
	10	health economics'/exp	658,559
	11	hospital cost'/exp	28000
	12	finance'/exp OR 'funding'/exp OR fiscal OR financial	202,999

	13	cost minimization analysis'/exp	2,681
	14	cost*:de,cl,ab,ti	728,769
	15	estimate*:de,cl,ab,ti	784,877
	16	variable*:de,cl,ab,ti	740,967
	17	unit:de,cl,ab,ti	459,463
	18	#14' NEAR/1 '#15' OR '#15' NEAR/1 '#14'	94,742
	19	#14' NEAR/1 '#16' OR '#16' NEAR/1 '#14'	233,857
	20	#14' NEAR/1 '#17' OR '#17' NEAR/1 '#14'	46,044
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	1,604,886
	22	heart assist device'/exp	23,602
	23	#21 AND #22	1,012
	24	heartmate OR heartware OR heartassist* OR jarvik OR 'ab-180 ivad' OR abiomed OR lionheart OR axipump OR 'berlin heart' OR 'berlin incor' OR 'bp 80' OR 'cora valveless pulsatile pump' OR coraide OR deltastream OR 'heart quest' OR heartquest OR hemopump OR 'micromed debakey' OR 'baylor/nasa' OR 'nippon-zeon' OR novacor OR 'pierce-donachy' OR 'rotodynamic pump' OR 'sun medical/ waseda/pittsburgh' OR evaheart OR duraheart OR thoratec OR toyobo OR ventrassist OR heartsaver OR abiocor OR akutsu OR biomedicus OR 'gyro pump' OR impella OR levitronix OR liotta OR medos OR 'bio-pump' OR 'model-7 alvad' OR tandemheart	12,971
	25	#21 AND #24	534
	26	#23 OR #25	**1299 references**
Note	In comparison with the previous search, **281 extra references** were identified.		

After removal of all duplicates, a total of 315 extra references were identified (Table 65).

Table 65 – Results of search strategy

Database	August-October 2015	Extra references versus December 2013
CRD HTA	48	5
CRD NHS EED	20	4
Medline	290	37
Medline In-Process & Other	26	18
Embase	1299	281
Total (incl. duplicates)	**1683**	**345**
Duplicates		30
Total (excl. duplicates)		**315**

Appendix 4.2. Data extraction sheet

Table 66 – Data extraction sheet

1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question
5	Type of analysis (analytic technique) e.g. cost-effectiveness analysis, cost-utility analysis, …
6	Design e.g. Markov model, decision tree, …
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate For costs and/or effects
12	Perspective
13	Costs Cost items included Measurement of resource use Valuation of resource use Data sources Currency and cost year Other aspects…
14	Outcomes Endpoints taken into account and/or health states Valuation of health states

	Treatment effect and Extrapolation Utility assessment (Quality of Life) Data sources for outcomes Other aspects…
15	Uncertainty Scenario analysis Sensitivity analysis
16	Assumptions
17	Results Cost-effectiveness and/or cost-utility (base case) Scenario analysis Sensitivity analysis Other aspects…
18	Conclusions The conclusion of the authors (which can be discussed in the actual critical appraisal)
19	Remarks e.g. limitations of the study

APPENDIX 5. THE CHEERS CHECKLIST

The aim of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is to provide recommendations, in the form of a checklist, to optimise reporting of health economic evaluations.[65] The 24 items checklist is provided in Table 67.

Table 67 – CHEERS checklist

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title of Chapter 9 (page 69)
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	No separate abstract is provided for the economic evaluation in this HTA report.
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Chapter 1 (page 12)
		Present the study question and its relevance for health policy or practice decisions.	Chapter 2 (page 18)
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Chapter 9, part 9.1.2 (page 69)
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Chapter 1, part 1.2.6 (page 17)
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Chapter 9, part 9.1.1 (page 69)
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Chapter 9, part 9.1.3 (page 69)
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Chapter 9, part 9.1.5 (page 69)
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Chapter 9, part 9.1.5 (page 69)
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Chapter 9, part 9.1.4 (page 69)
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	See 11b

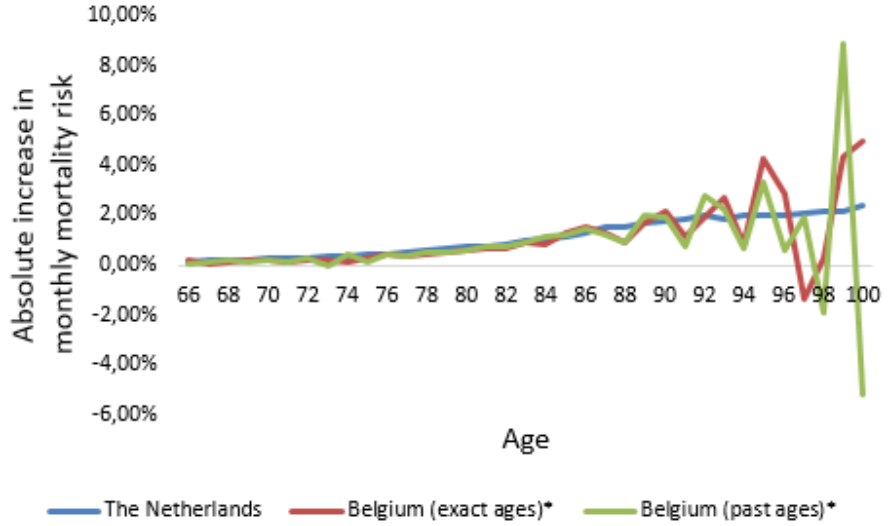
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Identification: Chapter 3 (page 18) Synthesis: Chapter 4 (page 24)
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Chapter 4 part 4.3.3 (page 37) and chapter 9 part 9.1.9 (page 74)
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Chapter 7 part 7.2.1 (page 50) and part 7.3.1 (page 51) and chapter 9 part 9.1.8 (page 73) and part 9.1.10 (page 76)
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Chapter 9, part 9.1.10 (page 76)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Chapter 9, part 9.1.6 (page 70)
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Assumption are mentioned in chapter 9 part 9.1.1 (p69), 9.1.7 (p71), 9.1.8 (p73), 9.1.9 (p74), 9.1.10 (p76), and 9.1.11 (p80)
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Chapter 9, part 9.1.6 (p70), 9.1.7.2 (p73), and 9.1.11 (p80)
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Chapter 9, Table 36 - Table 44 (p72 – 80)

Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Chapter 9, part 9.2.1 (p81)
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Chapter 9, part 9.2.1 (p81) and 9.2.2 (p83)
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Chapter 9, part 9.3 (p92)
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Study performed by KCE (independent federal agency providing advice to our policy makers)
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	
For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist			

APPENDIX 6. DUTCH VERSUS BELGIAN LIFETABLES

The absolute increase in mortality risk is similar between the Netherlands and Belgium. Only at very high ages, there are differences (see Figure 17). However, in the modelled LVAD population with an average age of 64 and starting the extrapolation at the age of 66, there are no survivors beyond the age of 90. Using data from the Dutch or Belgian lifetables results in about the same discounted life expectancy of 4.40 or 4.46, respectively.

Figure 17 – The absolute increase in monthly mortality risk (Belgium vs the Netherlands)



Sources: http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/sterfte_leven/tafels/ (Belgium) and www.ag-ai.nl/download/7693-AG-tafel+2003-2008DEF.pdf (the Netherlands).

The data are sex-adjusted: 82.7% men. * Statistics Belgium provides two tables with mortality risks. This risk can be calculated at 1 January of two consecutive years (which is referred to as “past ages”) or between two anniversaries (which is referred to as “exact ages”).

APPENDIX 7. CORRECTION OF THE ORIGINAL DUTCH MODEL

In the formulas of the original model for the Netherlands, we found two erroneous references to cells in the Excel file, which have no major impact on the results, and thus also do not influence the initial conclusions or recommendations.

First, in the original model, outcomes were validated by checking the mortality at 30 days, 1 year and 2 years. Also, a visual inspection of the survival curves was carried out. However, updating the model for the current report, we identified that a 10% absolute reduction in mortality was not only modelled after the 1st year (from 68% to 58%), but (wrongly) also after the 2nd year (from 58% to 48%). This also influenced the extrapolation of survival data. Visually, this error was not visible (Figure 18), but the estimated gain in life was thus underestimated (4.04 versus 4.4 discounted life years, see Table 68). Secondly, the monthly follow-up costs in the model were set at €1261 and €1047 for the LVAD and OMT group, respectively. This should have been €1192 and €984, respectively, during the first year and €1116 and €842, respectively, in the following years.

Eventually, the ICER should have been €101 800 per QALY gained instead of €107 600 per QALY (Table 68), not changing the original results of the study. The cost-effectiveness acceptability curves also show the minor impact on the results of the economic evaluation (Figure 19).

Figure 18 – Survival curves in the Dutch HTA report (original versus corrected)

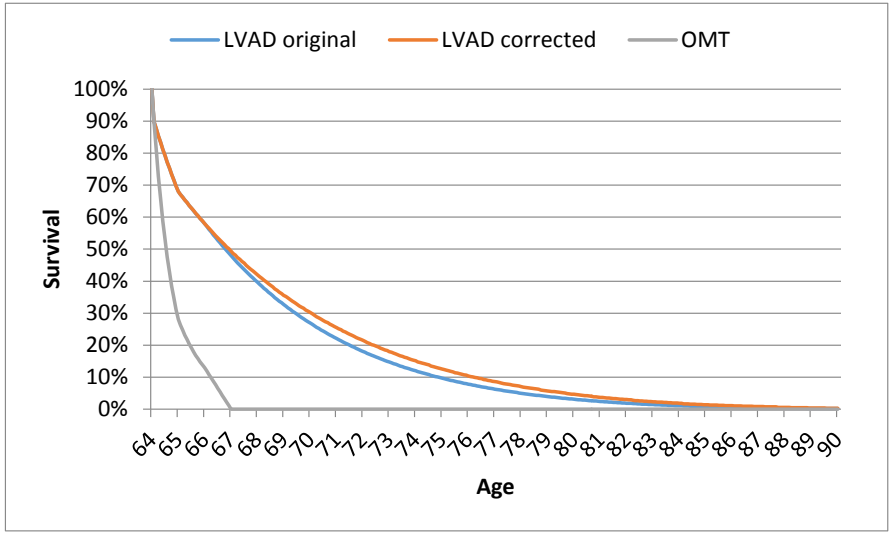
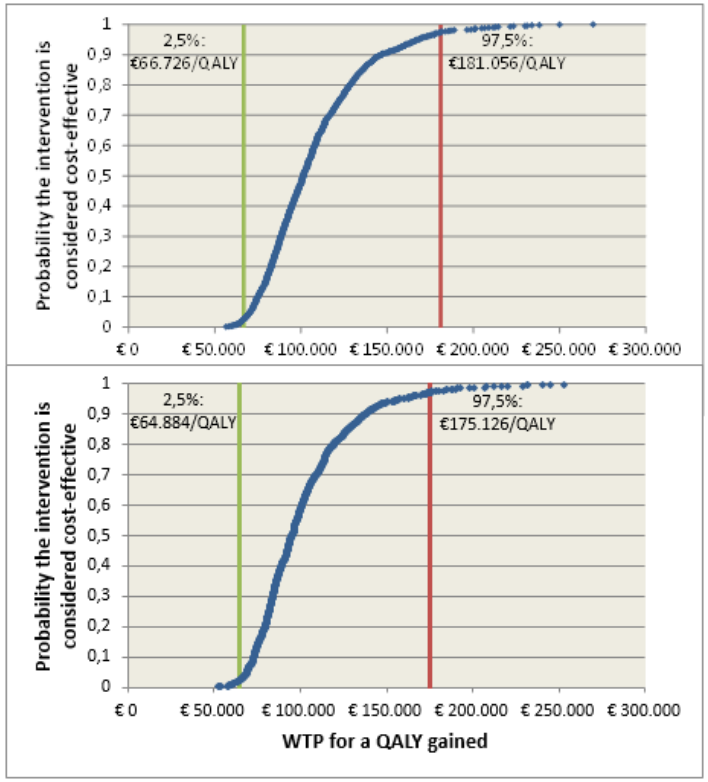


Table 68 – Results of the Dutch HTA report (original versus corrected)

	Original results	Corrected results
	mean (2,5% - 97,5%)	**mean (2,5% - 97,5%)**
Life expectancy		
OMT (years)	0,81 (0,65 - 0,98)	0,81 (0,61 - 1,05)
LVAD (years)	4,04 (3,00 - 5,26)	4,40 (3,36 - 5,62)
Costs		
OMT	€ 30.878 (€9.962 - €98.278)	€ 29.704 (€9.723 - €96.252)
LVAD	€ 330.017 (€204.992 - €609.132)	€ 343.077 (€214.382 - €622.385)
IC	€ 299.139 (€190.464 - €521.014)	€ 313.374 (€200.182 - €543.919)
IE (LYG)	3,23 (2,18 - 4,49)	3,59 (2,50 - 4,86)
IE (QALY gained)	2,83 (1,91 - 3,90)	3,12 (2,21 - 4,12)
ICER (€/LYG)	€ 94.127 (€59.056 - €160.124)	€ 88.314 (€57.465 - €150.094)
ICER (€/QALY gained)	€ 107.554 (€66.726 - €181.056)	€ 101.769 (€64.884 - €175.126)

IC: incremental costs; ICER: incremental cost-effectiveness ratio; IE: incremental effects; LVAD: left ventricular assist device; LYG: life years gained; OMT: optimal medical treatment; QALY: quality-adjusted life year

Figure 19 – Cost-effectiveness acceptability curve (original versus corrected)



Top: original CEA-curve; bottom: corrected CEA-curve. CEA-curve: cost-effectiveness acceptability curve; QALY: quality-adjusted life year; WTP: willingness-to-pay

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