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"Cost-effectiveness analysis of Left Ventricular Assist Devices (LVAD): a preliminary study on the interventions carried out at the Cardiac Surgery Department of the Padua University Hospital"

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1.1. Advanced heart failure (AHF)

1.1.1. Definition and aetiology of HF and AHF

Heart failure (HF) is a pathologic condition characterized by heart inability to provide adequate amount of blood to meet the metabolic demand of the organism or to do that by incrementing one or more cardiac chambers and venous circulation pressure. HF distinguishes from other circulatory failures as the inability of transporting enough oxygen depends on the myocardia (Rugarli and Cappelli, 2021).

Most of the times HF results from insufficient myocardial function. This condition can be determined primarily by relevant loss in myocardial tissue (as for myocardial infarction) or by structural and functional myocardial alterations (as for some dilatative cardiomyopathy both ischemic and non-ischemic, and myocarditis). Another primary cause of HF is the chronic excessive work of myocardia, which can be caused by pressure overload (due to pulmonary or systemic arterial hypertension and pulmonary or aortic valve stenosis) or by volume overloads (due to atrioventricular and semilunar valves insufficiencies). Cardiac diseases such as hypertrophic and restrictive cardiomyopathy, may result in HF due to impairment of the diastolic function (Rugarli and Cappelli, 2021).

Often, HF patients appear asymptomatic because of endogenous compensation mechanisms and pharmacologic treatment. The causes that can alter this equilibrium and require prompt identification to prevent worsening of the illness are the following: psycho, physio and environmental stress, hypertension, arrythmias, systematic infections, augmented cardiac output, kidneys diseases, pulmonary embolism, inappropriate reduction in therapy and assumption of contraindicated substances. The treatments must address the primary cause of HF and try to prevent or eliminate worsening in patients' symptoms causes. Some patients characterized by debilitating HF symptoms, who are refractory to therapy, ultimately progress to advanced FH (Rugarli and Cappelli, 2021).

'Advanced', 'refractory', and 'end-stage' heart failure (HF) are all interchangeable terms, reflecting HF patients who should be evaluated for advanced heart failure (AHF) therapies,

encompassing cardiac transplantation, long-term mechanical circulatory support (MCS), and palliative therapies.

Nevertheless, no unique definition of AHF is available. The definitions adopted by the main HF organizations focus on marked HF symptoms interfering with daily life and recurrent hospitalizations, underscoring the need for an optimized medical therapy (Garascia *et al.*, 2023).

1.1.2. Classification of HF: identification of AHF patients

The New York Heart Association (NYHA) classification has been widely used to categorize the severity of symptoms in patients with HF on the basis of their physical activity (Figure 1.1). Nevertheless, the inter- and intra-observer variability in the NYHA class have been shown to be large, and validity and reproducibility to be low. Moreover, the NYHA classification has been found to correlate poorly with objective measures of cardiac function, such as peak oxygen consumption and 6-minute walk distances, often required to confirm the diagnosis of AHF (Garascia *et al.*, 2023).

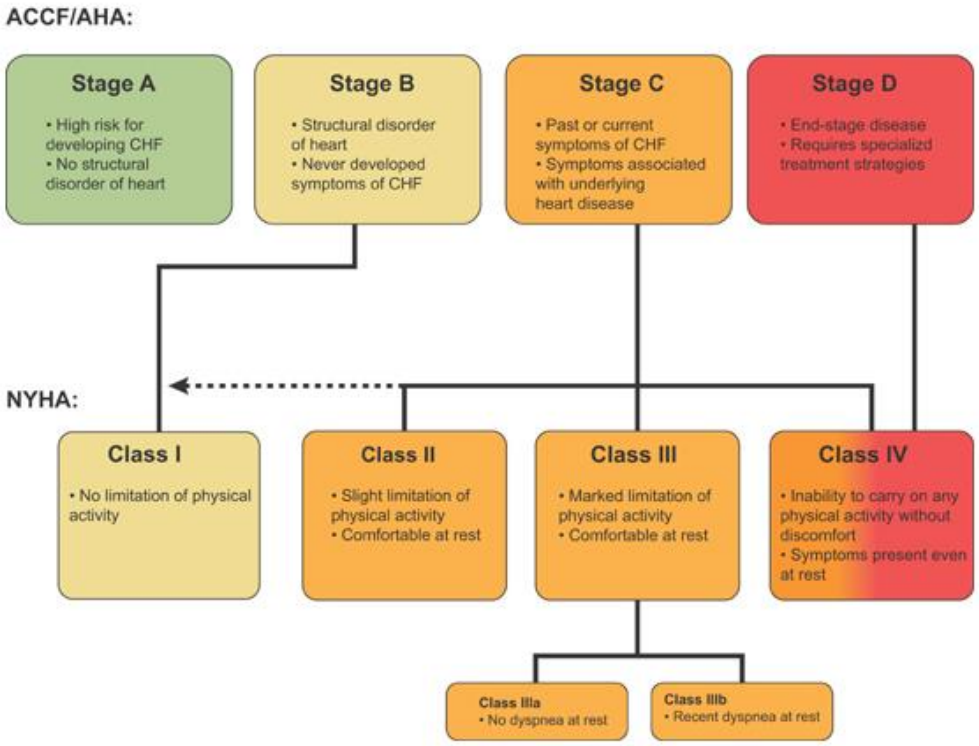

Figure 1.1. American College of Cardiology and AHA stages of HF in comparison with New York Heart Association (NYHA) functional classification.

Since no single event or parameter alone can define AHF, the European Society of Cardiology (ESC) and the American Heart Association (AHA) adopted in their guidelines of HF (2018) a different definition for AHF. In order to define AHF, all the following criteria have to be present despite optimal guideline-directed treatment (GDMT):

1) Severe and persistent symptoms of HF (NYHA class III [advanced] or IV)
2) Severe cardiac dysfunction defined by ≥1 of these:
   - left Ventricular Ejection Fraction (LVEF)≤ 30%
   - isolated RV failure
   - non-operable severe valve abnormalities
   - non-operable severe congenital heart disease
   - LVEF ≥40%, elevated natriuretic peptide levels, and evidence of significant diastolic dysfunction
3) Hospitalizations or unplanned visits in the past 12 months for episodes of:
   - congestion requiring high-dose intravenous diuretics or diuretic combinations
   - low output requiring inotropes or vasoactive medications
   - malignant arrhythmias
4) Severe impairment of exercise capacity with inability to exercise or low 6-minute walk test distance (<300 m) or peak VO2 (<12–14 mL/kg/min) estimated to be of cardiac origin.

Note that patients with recurrent ventricular dysrhythmias, especially those who have failed ventricular tachycardia ablation, are at very high risk for mortality and might be considered for advanced HF referral regardless of ventricular ejection fraction, renal function, blood pressure, or NYHA class (McDonagh *et al.*, 2021).

1.1.3. Epidemiology of HF and AHF

Globally, HF is estimated to affect approximately 64 million people worldwide (Savarese *et al.*, 2023), accounting for 6.2 million people in US (2.4% of the US population over 20 years) and more than 15 million in Europe (Figure 1.2). The prevalence of HF is between 1-2% of the adult population in industrialized high-income countries, rising to 10% in population over 70 years. At the age of 55 years the risk to develop HF over the remaining lifetime it is estimated to be 33% for men and 28% in women (Hessel, 2021).

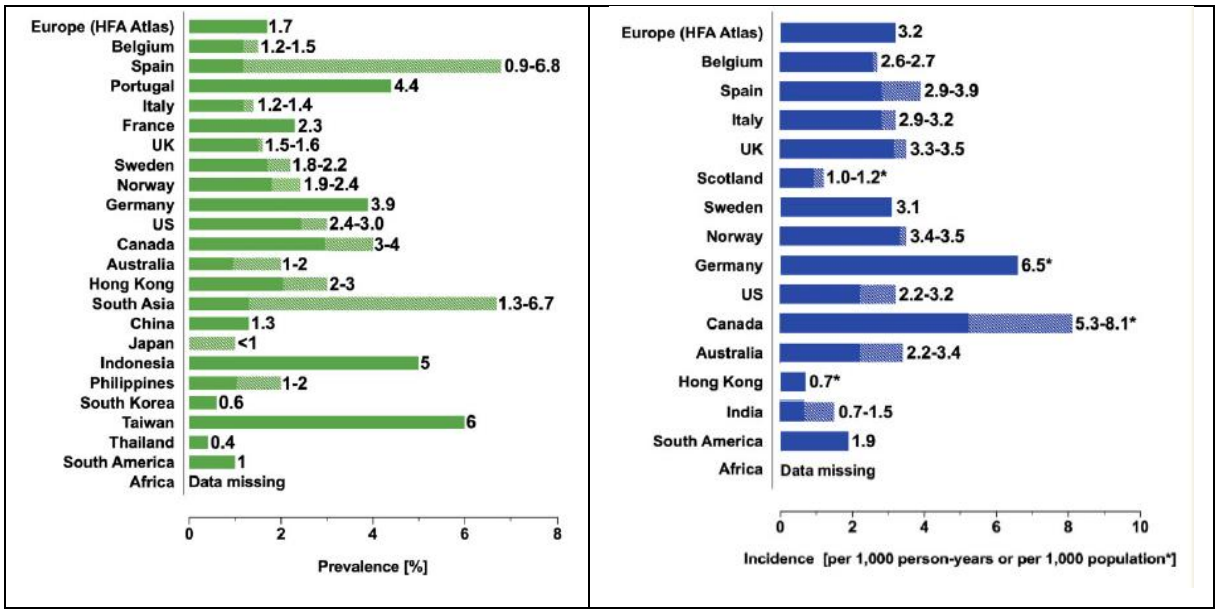

Figure 1.2. Estimated prevalence (left) and incidence (right) of HF worldwide. Image from (Savarese et al., 2023).

Incidence is relatively stable over time with 500.000 to 600.000 newly diagnosed cases per year, testifying a successful primary prevention of risk factors associated with HF. Prevalence instead grew in the last decades in association with the increasing proportion of elderly people and improvements in diagnosis and therapy.

In US the prevalence of HF is estimated to further increase by 46% from 2012-2030, such that, by 2030, 8 million American will be affected by HF (Bhatnagar *et al.*, 2022).

However, it is challenging to identify advanced HF subpopulation, since no single criterion for advanced HF exists and therefore, referring to ESC guidelines, a medical record review of the patient is needed. As a result, the prevalence of advanced HF and population characteristics are unknown. Most of our knowledge of advanced HF come from LVAD clinical trials and referral populations. However, those patients may not be representative of the "true" AHF population, as cardiologists and HF specialists referral varies by patient characteristics, resulting in a highly selected population of young, predominantly male, patients with AHF with reduced ejected fraction (HFrEF) (Dunlay *et al.*, 2021).

To fill this gap of knowledge, 2018 ESC AHF was applied to the population of Olmsted Country Minnesota (US). This population-based cohort study on 6,836 adults with HF found that 13.7% of the population met criteria for advanced HF. The prevalence of AHF increased with age and was higher in men. Diagnoses for AHF were 42.3% HFrEF, 14.3% HFmrEF (mid-range ejection fraction) and 43.4% HFpEF (preserved ejection fraction). No differences in risks of all-cause

mortality or hospitalization were correlated to EF, but HFpEF resulted at lower risk for cardiovascular mortality in comparison with patients with reduced EF (Dunlay *et al.*, 2021).

Nonetheless, there is still no epidemiologic study focused only on AHF. Estimates set the percentage of patients with AHF between 1–10% of the overall HF population and their prevalence is increasing due to the growing number of patients with HF, ageing of the population, and the improvement of survival provided by GDMT (Guideline-Directed Medical Therapy) (Garascia *et al.*, 2023).

It is important to notice that the vast majority of the studies analysing the epidemiology of HF has been performed in western industrialized high income country populations. Disparities between countries, sex, place of diagnosis and socioeconomic status determine relevant differences in long term outcomes and often in the lack of scientific evidence on HF epidemiology (Hessel, 2021).

1.1.4. Survival of AHF patients

Survival in patients with severe systolic HF is on average poor, but patient phenotypes are highly heterogenous, leading to marked patient-level variability in survival.

According to the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (2001), stage D patients medically treated experienced a 75% chance of mortality at 1 year, while no patient survived the 2 years follow-up (Rose *et al.*, 2001).

These data might be obsolete because of current more efficient and safer treatments and classifications increased survival for this population. A real-world study on restricted AHF population found a median time from AHF diagnosis to death of 12.2 months (3.7-29.9 months) (Dunlay *et al.*, 2021).

Patients with cardiogenic shock, with or without use of temporary circulatory support, have uniformly poor survivals of 35–50% at discharge, while those who are less critically ill but dependent on home inotropes have marginally better survivals of 25–50% at 1 year (Mandawat and Rao, 2017).

Ambulatory patients with severe left ventricular dysfunction without an inotrope requirement are the most challenging patients to prognosticate risk for. These patients are most commonly grouped into the stage C category (systolic dysfunction with present or past HF clinical signs and symptoms). However, some of them within the stage C HF category have very poor short-

term survival, and for others the transition to the “refractory” HF stage D category is often unclear. In the ROADMAP study (2017), ambulatory outpatients on optimal medical management with NYHA Class IIIb/IV systolic (ejection fraction ≤ 25%) HF, ≥ 1 hospitalization in a year for HF, and 6-min walk distance < 300 m had a 1-year survival of 63%. At 2 years, only 41% were alive on medical therapy and 22% received an LVAD implant (Starling *et al.*, 2017).

1.1.5. Therapeutic options for ADH patients

According to ACC/AHA studies, prevention and progressive therapy of HF start with the reduction of risk factors and the treatment of hypertension, diabetes and dyslipidaemia for stage A patients. As HF progresses to stage B, ACE-inhibitors or ARB, and β-blockers are recommended. In stage C, diuretics are introduced to address hydric retention. ARB and/or MR antagonists have to be augmented, ventricular resynchronization is indicated when the QRS complex > 120ms and implantable cardiac defibrillator (ICD) might be implanted if ejection fraction (EF)<30-35%. In most severe stage C patients, surgery of the mitral valve is suggested. Stage D or AHF patients treatment begins with inotropes. If despite GDMT, HF progression can no longer be adequately managed severely affecting the quality of life of patients or compromising end-organ function, the “long-term” therapeutic options are palliative care, HTx, LVADs and total artificial heart (TAH) (Rugarli and Cappelli, 2021).

Once excluded the reversibility of the primary cause of HF, therapies providing prognostic benefits in AHF patients are heart transplant (HTx) and long-term mechanical circulatory support (MCS). However, when the clinical condition deteriorates, or end-organ damage prevails, short-term therapies may be needed, until prognostic therapies become available or feasible. These short-term therapies are inotropes and vasopressors, diuretics and renal replacement therapy, and temporary mechanical circulatory support (T-MCS), usually indicated after cardiogenic shock, such as intra-aortic balloon pump, impella ventricular support system, ECMO and Tandem Heart (Garascia *et al.*, 2023).

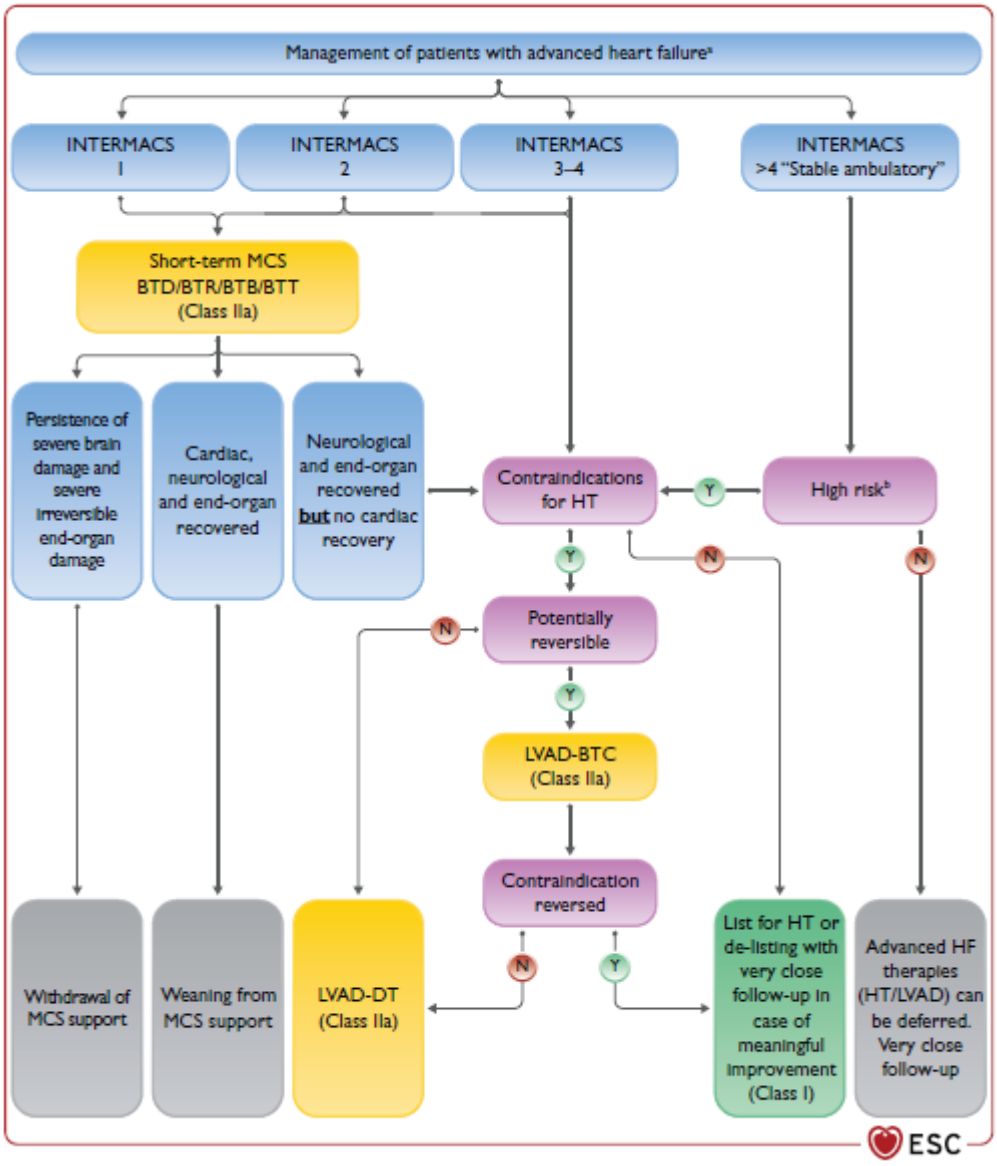

Figure 1.3. Algorithm for the treatment of patients with advanced heart failure. Modified for (McDonagh et al., 2021).

For general practitioners, the most imperative step in managing patients with advanced HF is to assess their risk of death with ongoing medical management of HF so that appropriate and timely advanced HF referral can be initiated. Estimating mortality risk in the diffuse systolic HF population requires careful (re)assessment of patient functional capacity, laboratory values, vitals, and clinical history. Several clinical trials, registries, and cohort studies have identified risk factors for mortality in patients with symptomatic systolic HF. Using this data, the ACC has developed the acronym "I NEED HELP" to suggest practitioners when advanced HF consultations should be considered (Michaels and Cowger, 2019).

1.1.6. INTERMACS profiles

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles are commonly used descriptors of disease severity in patients with AHF, which are used to define candidate selection and timing for durable MCS, but also performing in prognosis estimation (Figure 1.4) (McDonagh *et al.*, 2021).

Selected INTERMACs 1–2–3 profiles represent the most severely ill patients. These typologies of patients are generally treated with intravenous inotropes and eventually may require temporary-MCS during hospitalization. They should be considered for MCS over a short period of time (hours, days, or weeks) but no firm indication exists regarding patient selection and surgical timing for LVAD implantation or HTX.

INTERMACs 4-7 profiles represents a large variety of conditions, which are less critical with respect to 1-3 profiles. These patients might experience limitations in their everyday activity dealing with congestive symptoms and need for diuretics. The time frame for intervention depends on the maintenance of nutrition, organ function and activity level.

Factors that might determine a rapid worsening of patients' health conditions are frequent arrythmias episodes and frequent episodes of HF decompensation requiring emergency visits or hospitalization (McDonagh *et al.*, 2021).

The accessibility for INTERMACS 4–7 population (ambulatory patient) to advanced treatments such as LVAD implantation was investigated by the ROADMAP trial. In this context, the study importantly showed a reduced chance of identifying advanced patients who might greatly benefit from LVAD therapy if timely treated. Hospitalizations for HF are currently being replaced by outpatient visits, with infusions of loop diuretics and/or other vasoactive medications, so that illness might deteriorate possibly reducing the effectiveness of more advanced treatments or ineligibility.

NYHA II patients with 'red flags' or NYHA III/IV patients, despite optimal medical therapy, should be at least 'discussed' with the AHF specialists (Starling *et al.*, 2017).

INTERMACs profiles are insufficient to quantify the patient's risk and prognosis as countless factors must be taken into consideration, including end-organ function, age, sex, frailty, and need for concomitant procedures (Garascia *et al.*, 2023).

Profile	Time frame for intervention
Profile 1. Critical cardiogenic shock Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. "Crash and burn."	Definitive intervention needed within hours.
Profile 2. Progressive decline Patient with declining function despite i.v. inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance. "Sliding on inotropes." Also describes declining status in patients unable to tolerate inotropic therapy.	Definitive intervention needed within few days.
Profile 3. Stable on inotrope or inotrope-dependent Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous i.v. inotropic support (or a temporary circulatory support device or both) but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. "Dependent stability."	Definitive intervention elective over a period of weeks to few months.
Profile 4. Frequent Flyer Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over a period of weeks to few months.
Profile 5. Housebound Comfortable at rest and with activities of daily living but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4, and require definitive intervention.	Variable urgency, depends upon maintenance of nutrition, organ function, and activity.
Profile 6. Exertion limited Patient without evidence of fluid overload, comfortable at rest and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with haemodynamic monitoring, to confirm severity of cardiac impairment. "Walking wounded."	Variable, depends upon maintenance of nutrition, organ function, and activity level.

Profile	Time frame for intervention
Profile 7. Advanced NYHA class III symptoms Patient without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Heart transplantation or MCS may not be currently indicated.
Modifiers for profiles	**Possible profiles that can be modified**
Temporary MCS can modify profile only in hospitalized patients. They include IABP, ECMO, TandemHeart, LVAD, Impella.	1, 2, 3
Arrhythmia can modify any profile. They include recurrent ventricular tachyarrhythmias that have recently contributed substantially to clinical compromise, frequent ICD shocks or requirement for external defibrillation, usually more than twice weekly.	1–7
Frequent episodes of HF decompensation characterize patients requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary i.v. vasoactive therapy. Frequent episodes may be considered as at least two emergency visits/admissions in the past 3 months or three in the past 6 months.	3 if at home, 4, 5, 6. Rarely for profile 7.

ECMO = extracorporeal membrane oxygenation; HF = heart failure; IABP = intra-aortic balloon pump; ICD = implantable cardioverter-defibrillator; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; i.v. = intravenous; LVAD = left ventricular assist device; MCS = mechanical circulatory support; NYHA = New York Heart Association. Modified from [381].

Figure 1.4. Interagency Registry for Mechanically Assisted Circulatory Support profile descriptions of patients with advanced heart failure. From (McDonagh et al., 2021).

1.1.7. Timing of referral and prognostic tools

One of the most debated issues associated with the consolidation of LVADs as a common practice lifesaving treatment, is the timing to indicate patients to LVAD therapy, so that they can take the highest benefit from the cure (Figure 1.5).

The clinical course of AHF patients varies dramatically across the spectrum of disease severity and is relatively unpredictable for individual patients, being exacerbated by the contrast between sudden death and congestive symptoms with progressive pump failure. Moreover, several events might alter the prognostic trajectory, changing considerably the outcome of the disease.

Once a patient fulfils the definition of AHF, with the limitation provided, a deep characterization needs to be performed, to primarily exclude reversible causes of HF (Garascia *et al.*, 2023).

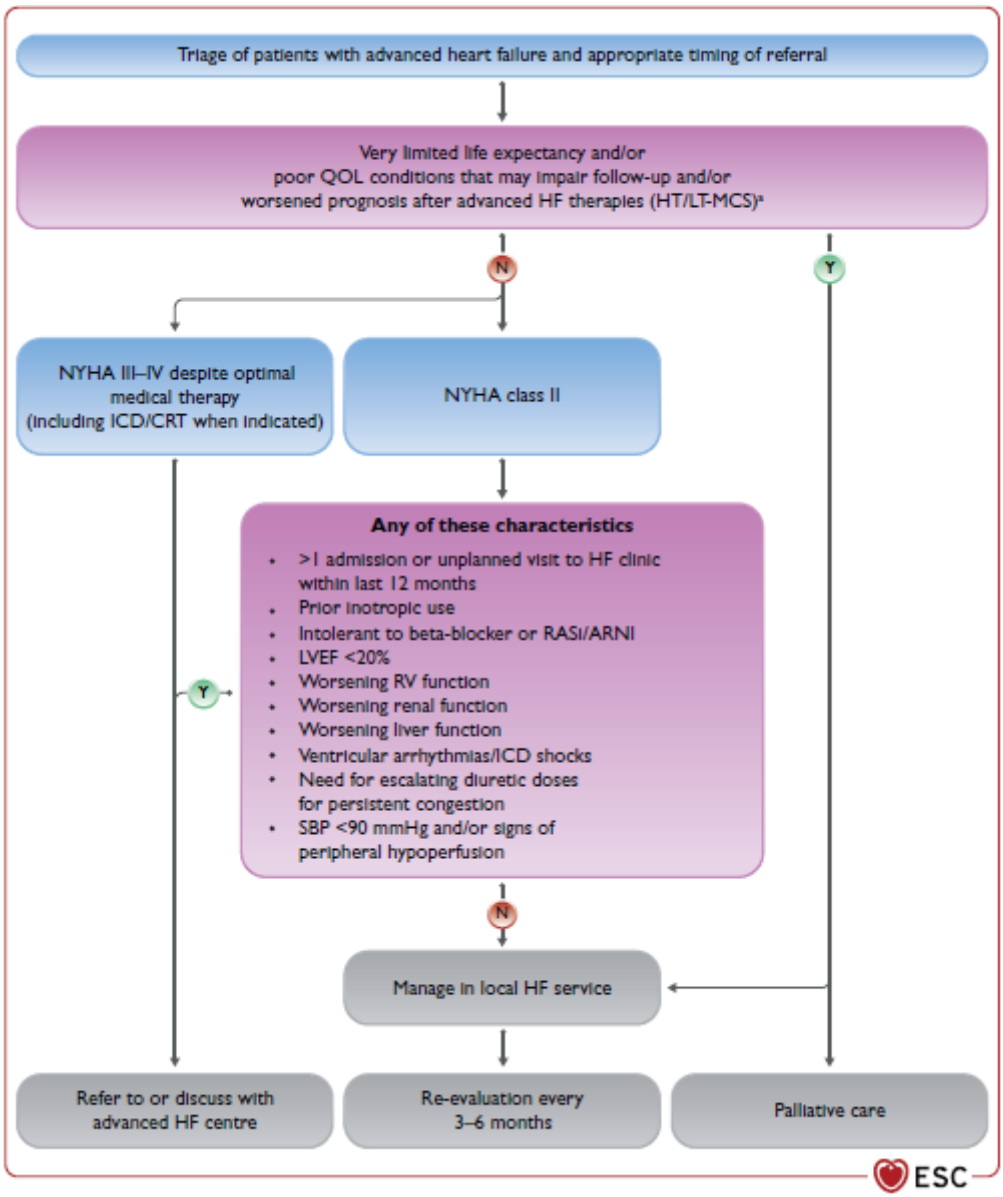

Figure 1.5. Triage of patients with advanced heart failure and appropriate timing of referral. Image from (McDonagh et al., 2021).

Since survival of AHF is poor, assess patients' risk of death with ongoing MM of HF is fundamental so that timely advanced HF referral can be initiated, and patients may access or obtain better outcomes from the more advanced treatment (Michaels and Cowger, 2019).

Patients with a predicted HF mortality of ≥ 7% at 1 year should be considered for advanced HF referral. This threshold is chosen because it approximates the risk associated with cardiac transplant surgery and promotes early advanced HF referral (Michaels and Cowger, 2019). In other studies, a risk score threshold of mortality higher than 20% in a year is considered valuable for patient recognition (Garascia *et al.*, 2023).

The timing of referral can modify the disease trajectory by itself. Late referral can allow the development of irreversible end-organ damage, right ventricle dysfunction, pulmonary hypertension, or cardiac cachexia, which could represent "high-risk features" or contraindication towards advanced therapies as MCS or HTx (Figure 1.6) (Morris *et al.*, 2021).

Timely referral effects might be:

a) to foster the development of a relationship with the advanced HF program that is necessary for assessing patient compliance for transplant/LVAD candidacy;
b) to allow the application of LVAD/transplant therapy prior to the onset of severe organ deterioration;
c) to ensure adequate opportunity for LVAD/transplant patient education as part of shared decision making prior to patient loss of decision capacity from HF;
d) to avoid futile or ineffective treatments with respect to patient health status;
e) to maximize the cost-effectiveness of the costly treatments delivered.

Therefore, to provide high-value care for patients with HF, an optimal approach would be to refer patients when they are approaching a level of illness that would warrant consideration of advanced therapies based on refractory symptoms yet are not too far advanced that progressive or irreversible end-organ damage has occurred, a time period that can be considered as "the golden window" (Morris *et al.*, 2021)

It is important to acknowledge that alarmistic referral may accrue additional costs and burden associated with travel or contribute to unnecessary anxiety for patients and their families with little additional advantage (Morris *et al.*, 2021).

Prognostic stratification is important to identify the ideal time for referral to an appropriate centre for more advanced treatments and, since no single parameter or parameter

combination can fulfil the task of precise profiling of AHF, some models were designed to help clinicians in the prognosis.

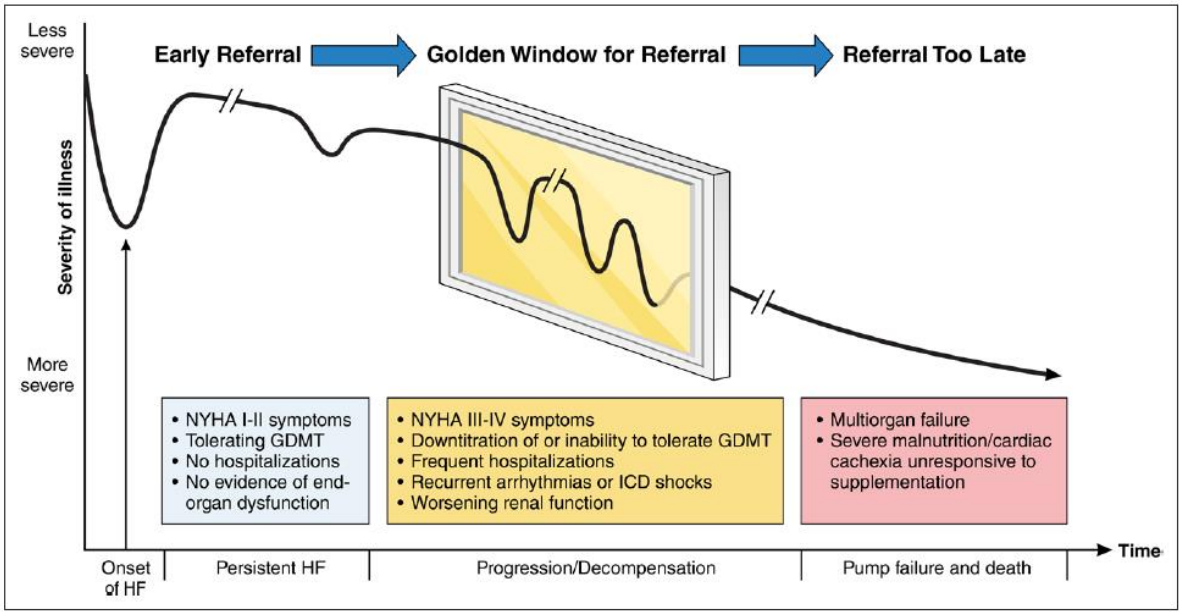

Figure 1.6. Golden window for referral for consideration of advanced heart failure (HF) therapies. From (Morris et al., 2021).

However no single HF model has excellent accuracy in risk prediction and, more importantly, they must be chosen in relation to patient's characteristics, which have to mirror the population from that the model was derived from. Therefore, the HF risk models might be useful to supplement—but not replace—clinical decision-making(Figure 1.7) (Garascia *et al.*, 2023).

Author	Risk model	*N*	Markers	Time horizon
Levy	Seattle Heart Failure Model	1125	SBP, age, gender, EF, weight, NYHA class, etiology, diuretic dose, use of statin, beta blocker, RAAS inhibition, allopurinol, metolazone, furosemide equivalence dosing, potassium sparing diuretic, defibrillator, BiV pacing, Na, cholesterol, Hgb, % lymphocytes, uric acid	3 years
Pocock	MAGGIC	39,372	Cr, SBP, age, gender EF, BMI, NYHA class, current smoker, DM, COPD, HF diagnosis > 18 months, use of B-blocker, ACEi/ARB	3 years
O'Connor	OPTIMIZE-HF	4402	Cr, SBP, age, weight, Na, lower extremity edema, reactive airway disease, depression, use of B-blocker, lipid lowering therapy	90 days
Fonarow	ADHERE	65,275	BUN, SBP, HR, age	In hospital
Peterson	GWTG-HF Risk Score	39,783	BUN, SBP, HR, Age, Na, Black race, COPD history	In hospital

ACEi, angiotensin-converting enzyme inhibitor; *ARB*, aldosterone receptor blocker; *Bi-V*, biventricular; *BMI*, body mass index; *BUN*, blood urea nitrogen; *COPD*, chronic obstructive airway disease; *Cr*, creatinine; *DM*, diabetes mellitus; *EF*, ejection fraction; *GWTG*, Get with the Guidelines; *HF*, heart failure; *Hgb*, hemoglobin; *HR*, heart rate; *Na*, sodium; *SBP*, systolic blood pressure

Figure 1.7. Heart failure risk prediction models and their variables. Modified from (Garascia et al., 2023).

1.1.8. Critical aspects of long-term VAD therapy

The decision pathway leading to HTx or LVAD is unique for each patient. Eligibility and outcomes may change over patients-related and un-related factors (McDonagh *et al.*, 2021). Patient unrelated factors might be time on HTx waiting list, centre's surgical experience, resources and policies can influence decision-making, surgical timing, and therapeutic strategies. Patients related factors such as evidence of preoperative renal dysfunction, hepatic congestion and/or right ventricular dysfunction, advanced age, poor functional capacity, and poor nutrition, may lead to higher operative mortality risk during LVAD surgery (Michaels and Cowger, 2019).

Mortality is greatly impacted by the coexistence of other concomitant medical conditions (e.g., pulmonary disease) as well as complications encountered during the perioperative period (e.g., pneumonia, bleeding, right ventricular failure) and those developed as a result of LVAD support (e.g., stroke).

Furthermore, the impact of living on LVAD support and LVAD-related complications (bleeding, stroke) on Quality of life (QoL) is critical for defining LVAD "success." Low preoperative QoL and functional capacity metrics along with multimorbidity were predictive of a patient's failure to clinically improve after LVAD and identified patients at increased risk of death after LVAD (Michaels and Cowger, 2019).

As global population is aging, especially in Europe, and HF as well as AHF patients are destined to increase in number, the economic burden on worldwide healthcare systems and economies related to HF and HF therapies is a serious issue that must be addressed to guarantee value healthcare for each individual (Bhatnagar *et al.*, 2022). As reported in the next chapters, this concern is particularly relevant for life saving treatments, such as LVADs, which are costly and relatively cost-effective depending on their therapeutic indication, hospitalization rate, reliability of the device and centre experience (Pagani *et al.*, 2021).

Table 1.1 illustrates the costs related to LVADs implantation; Figure 1.9 shows the Annual Health care costs of heart failure per patients per year worldwide.

	HeartMate 3 (n = 812)	HeartMate II (n = 1,840)	Other-VADs (n = 1,534)
Number of hospitalized patients N (%)	600 (73.9)	1,347 (73.2)	1,093 (71.3)
All-cause hospitalization[a], Events per patient year [95% CI]	2.8 [2.6 - 3.0]	3.0 [2.9 - 3.2]	3.2 [3.1 - 3.4]
Cumulative LOS for All-cause hospitalizations a, Days per patient year [95% CI]	25.2 [23.0 - 27.8]	28.5 [26.9 — 30.3]	31.3 [29.0 - 33.9]
Reimbursement for Index Implant Hospitalization, $ [95% CI]	$ 249,561 [$243,656- $256,383]	$ 266,752 [$261,767- $272,300]	$ 280,0128 [$272,902- $287,395]
Hospitalization cost while patients are ongoing on original device			
Average cost at 1-year (CPSY), $ [95% CI]	$ 52,583 [$47,970- $58,025]	$ 63,717 [$60,141 - $67,825]	$70,838 [$65,942 - $76,097]
Total cost conditional on survival (TCCS) at 1-year, $ [95% CI]	$ 50,885 [$46,371 - $56,359]	$ 61,607 [$57,993 - $65,545]	$ 68,832 [$64,215 - $74,100]
Hospitalization cost in the 1-year post discharge until death			
Average cost at 1-year (CPSY), $ [95% CI]	$ 71,846 [$64,438- $81,785]	$ 84,942 [$79,376 - $90,805]	$115,574 [$108,300 - $123,877]
Total cost conditional on survival (TCCS) at 1-year, $ [95% CI]	$ 70,566 [$63,465 - $78,964]	$ 83,975 [$78,895 - $89,659]	$ 115,382 [$108,617 - $123,968]

Abbreviations: EPPY, events per patient year; LOS, length of stay; CI, pivotal confidence intervals from non-parametric bootstrap model (x100,000); CPSY, cost per study year; TCCS, total cost conditional on survival

[a]Aggregate of hospitalizations in the 1-year post discharge - censored at VAD explant, heart transplant or death.

Table 1.1. Number of hospitalizations and costs related to LVADs devices in the contest of CLEAR-LVAD study. Table from (Pagani et al., 2021).

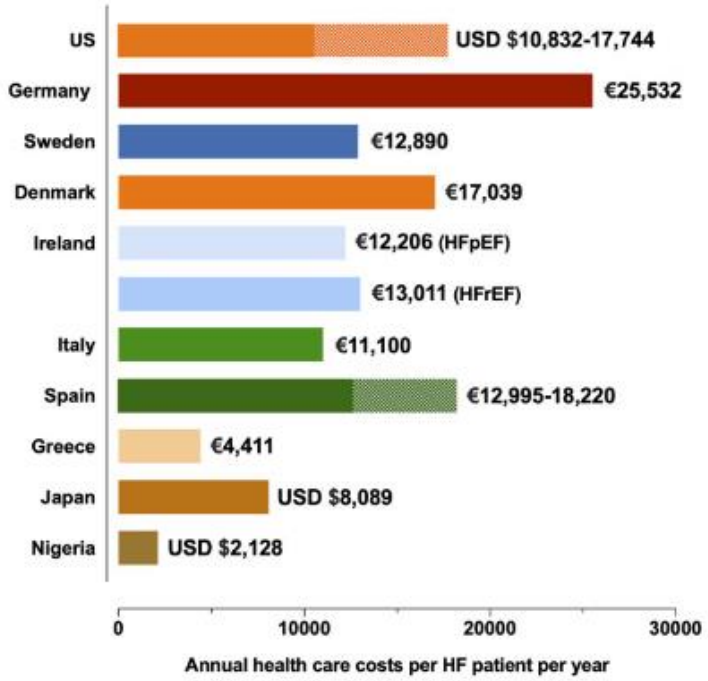

Figure 1.9. Annual Health care costs of heart failure per patients per year worldwide. Image from (Savarese et al., 2023).

1.2. Left ventricular assist device (LVAD) therapy

1.2.1. Demand for LVAD therapy

Left ventricular assist device (LVAD) was first prototyped in the late 50s by observing postoperative complication for patients undergoing open-heart surgery while supported by cardiopulmonary bypass machinery (CPM). Postoperative acute left ventricular failure risk was found to be related to the timing of weaning from extracorporeal circulation. In some cases, heart needed more time on slowly decreasing CPB pump speed support to restore its function. Other patients were not yet able to survive this weaning procedure asking for longer support. This issue generated the idea for the concept of durable Left Ventricular Assist Device (Figure 1.10) (Liotta *et al.*, 1963; DeBakey, 2003).

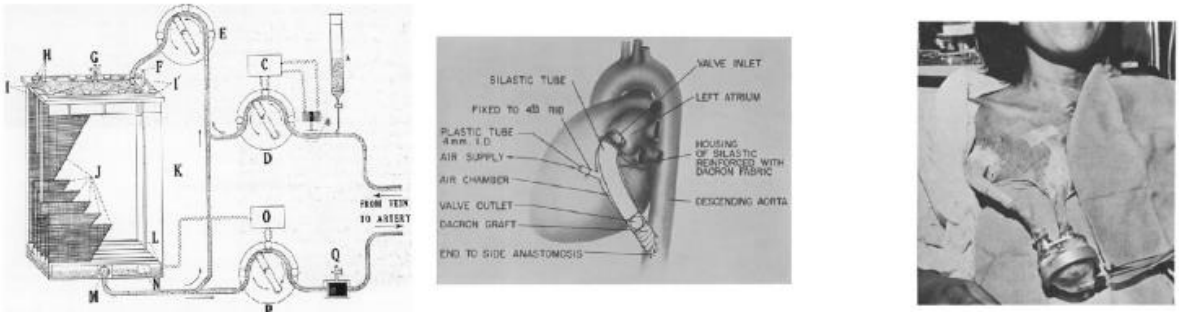

Figure 1.10. Dr John Gibbon's extracorporeal cardiopulmonary bypass circuit (left), Dr Liotta's implantable tube-type LVAD (centre) and Liotta-DeBakey spherical LVAD (Right). Image modified from (Goodman, Stulak and Rosenbaum, 2022).

Later in the 60s, the interest for LVAD technology was enhanced even further. As heart transplant became feasible, the idea of possibly using LVAD as bridge-to-transplant (BTT) could have been a solution for extending the life of patients on waiting list for a biological organ. In the same decade, the first case of LVAD therapy ended with cardiac recovery opened the doors for the possibility to use LVADs in treatments aiming to restore patients' myocardial function (Goodman, Stulak and Rosenbaum, 2022).

Nowadays, it is common to indicate LVADs therapeutic purposes as follows:

- BTT (bridge-to-transplant): the device is implanted in patients eligible for heart transplant in case they demand for left ventricular support while waiting for a donor;
- BTE (bridge-to-eligibility): the device is implanted in patients who are not eligible for heart transplant at the time of implantation, but they still have the possibility to reach eligibility;

- BTR (bridge-to-recovery): the device is implanted in patients asking for left ventricular support for a limited time as myocardial recovery is presumed;
- DT (destination-therapy): the device is implanted in patients asking for left ventricular support with no possibility neither to receive transplant or to recover.

The issues with early LVAD were both technological and practical. Major operation to install the device was considered very risky because of patients' contraindications to surgery at the time of requirement for the implant and the costs of both surgery and device, which were prohibitively high with respect to the therapeutic outcomes achieved at the time (Kadakia *et al.*, 2016).

1.2.2. Engineering questions of LVADs

As suggested above, LVADs apparatuses were conceived as pumps to support non efficient heart in effectively delivering oxygenated blood to the tissues. Already oxygenated blood had to be conveyed through an inflow canula into the pump and ultimately ejected through an outflow canula into one of the major arteries (e.g., aorta). These pumps need to be constantly and reliably working once positioned inside patients' body, while patients should be in the conditions to perform most of everyday life basic activity autonomously and ideally to restore myocardial function (Klotz, Jan Danser and Burkhoff, 2008).

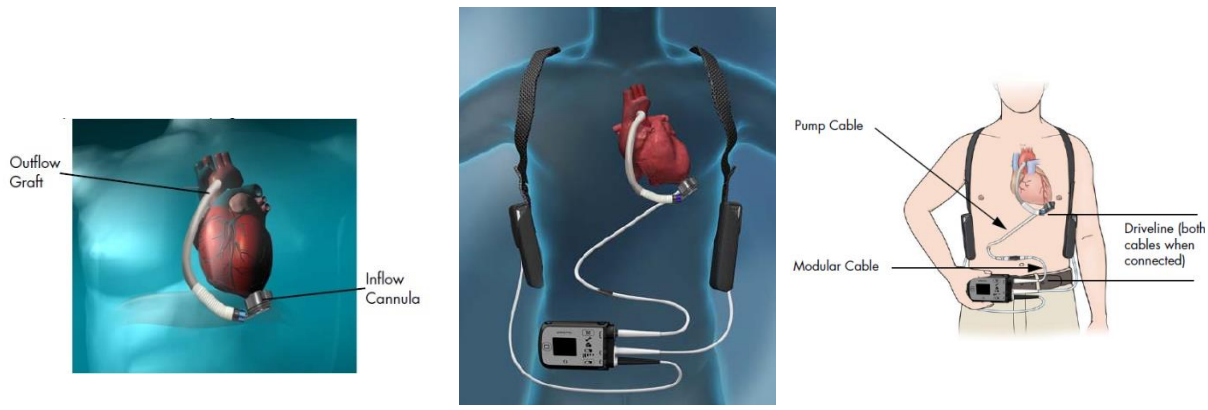

Figure 1.11. The latest HeartMate3 LVAD full implant consisting of inflow and outflow canula, pump, batteries (black pockets), unit control and driveline cables, one of which is percutaneous. Image from (United States & Canada Thoratec Corporation, 2017).

LVAD concept is straightforward, but many are the limitations related with actual implementation. The recurrent challenges engineers had to face in the refinement of this technology are the following:

i) hemocompatibility: the many surfaces exposed to blood contact have to be carefully designed, to avoid activation of platelets and to control embolization, or to promote intima-like tissue formation. Therefore, in the first case the device can be considered Bio-inert and in the second one Bio-mimetic;
ii) pump type: the mechanism that propels the flow must be efficient in terms of performances but also must guarantee limited blood trauma. In addition, minimization of pumps dimension makes possible less invasive interventions, and it is crucial for the application of the therapy on smaller patients;
iii) power delivery and sources of energy: the necessity of providing reliable sources of energy to the device must meet patients' needs for an acceptable quality of life. Therefore, power delivery systems, connecting the implanted LVAD with the extracorporeal power supply, are objective of continuous research and development.

1.2.3. A brief technological evolution of LVADs.

It took several years of crafting but finally FDA approved the first LVAD in 1994, for use as BTT. Since then, many LVADs models became available in the market, and it is common practice to distinguish them in three generations of devices. This distinction is motivated not only by timing of approval, but also by similarities in the issues each generation tried to address.

1.2.3.1. First Generation

The most notable LVADs belonging to this generation were the Novacor LVAD and the Thoratec HeartMate IP, VE, and XVE. They were all designed in the attempt to provide long-term circulatory support, to be used as BTT devices (Figure 1.12.).
The pumps of these devices remained pulsatile, as it was for pre-market LVADs, and the inflow and outflow canulas were both guarded with valves to induce unidirectionality in blood flux.

Figure 1.12. Novacor LVAD (Left), HeartMate XVE (Right). Image modified from (Goodman, Stulak and Rosenbaum, 2022)

Hemocompatibility was accessed adopting two opposing strategies, both intended to prevent the risk of thrombosis and infections inside the device. HeartMate systems tried to stimulate the formation of intima-like tissue layers on the blood-contacting surfaces of the pump by applying a sintered titanium microsphere layer to the titanium chamber of the pump and a fibrillar texture on the polyurethane diaphragm. Novacor LVAD installed a pump consisting of a mid-plane polyurethane sac collecting blood that was squeezed by two pushing plates. This approach meant to ensure continuous washing of the blood contacted surfaces and to shorten the fatigue life of the components involved.

The main change was in the energy delivery method. Since the birth of the first proto-LVADs, pumps were energized by compressed gas, which required extracorporeal compressors that were bulky, noisy, dependent on AC power supply and consequently inhibited patients' mobility. The first generation of LVADs introduced electromechanical actuation, allowing some to be energized by a battery worn on the waist. This new paradigm was crucial since it allowed some patients to be discharged from hospital as they were waiting for heart transplant (Goodman, Stulak and Rosenbaum, 2022).

1.2.3.2. Second Generation

The major features of second generation LVADs were their continuous, rather than pulsatile, rotatory pumps, which produced axial blood motion using a rotor. As blood delivers nutrition

to the organs at capillary level, where vessels radius is so small that the inertial influence of the blood dominates over the pulsatile component, eliminating the pulsatile engine was not considered an issue and continuous blood flowing could support end organ function.

Figure 1.13 depicts the sketches of the cardiovascular systemic circulation and of the constituents of blood tissue. (Battaglia Mayer et al., 2010; Goodman et al., 2022)

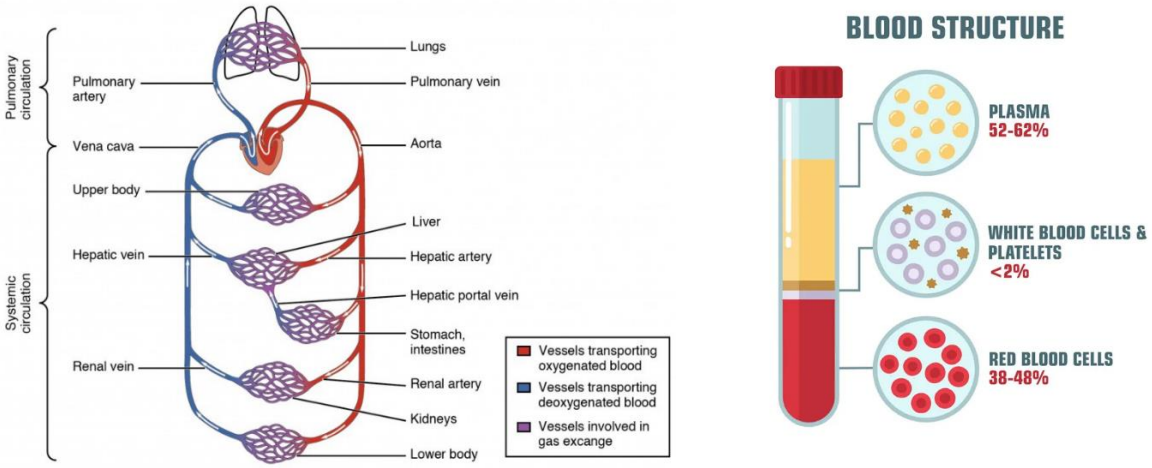

Figure 1.13. From fluid mechanics notions, the pulsatile character of the fluid flow depends on the frequency of the driving force (e.g. heart rate), on fluid viscosity and more importantly on the vessel radius. The figure schematized circulatory system and blood structure.

Commonly known devices embracing this approach were the HeartMate II, the Jarvik 2000 and the MicroMed DeBakey.

Figure 1.14. Heart Mate II (left) and Jarvik 2000 (centre). Basic pump design (right) consists of a rotor with a cylindrical magnet in it that is subjected to a spinning magnetic field created by motor coils in the housing. The rotor is mechanically suspended and generated momentum in the blood thanks to curved blades mounted on its body.

This radical change in the propulsion of the blood implied just one moving component, reducing the number of the parts subjected to mechanical stress and so increasing the durability of the device. There was no need for prosthetic valves to induce unidirectionality in the flux, which were subjected to wear and calcification.

Volume and weight were reduced so much that the device could be implanted above the diaphragm or even within the left ventricle (e.g., Jarvik 2000). The so called “miniaturization” not only paved the way for less impactful surgical techniques, but also extended the accessibility for treatment to smaller patients (Zucchetta *et al.*, 2014; Tarzia *et al.*, 2016).
Although it is difficult to compare the performances of different models, all studies confirmed successful reduction of mechanical failure, but complications related to blood trauma and thrombosis were still major issues of the devices. In particular, the continuous axial flow mechanism exposed blood to high shear while flowing in the pump, causing haemolysis (Slaughter *et al.*, 2009).

1.2.3.3. Third Generation

The third and latest generation LVADs, best represented by HeartMate III and HeartWare HVAD, were designed to address blood trauma encountered with the second generation axial pumps LVADs and to reduce even further dimensions and bearing of the pump (Figure 1.15).

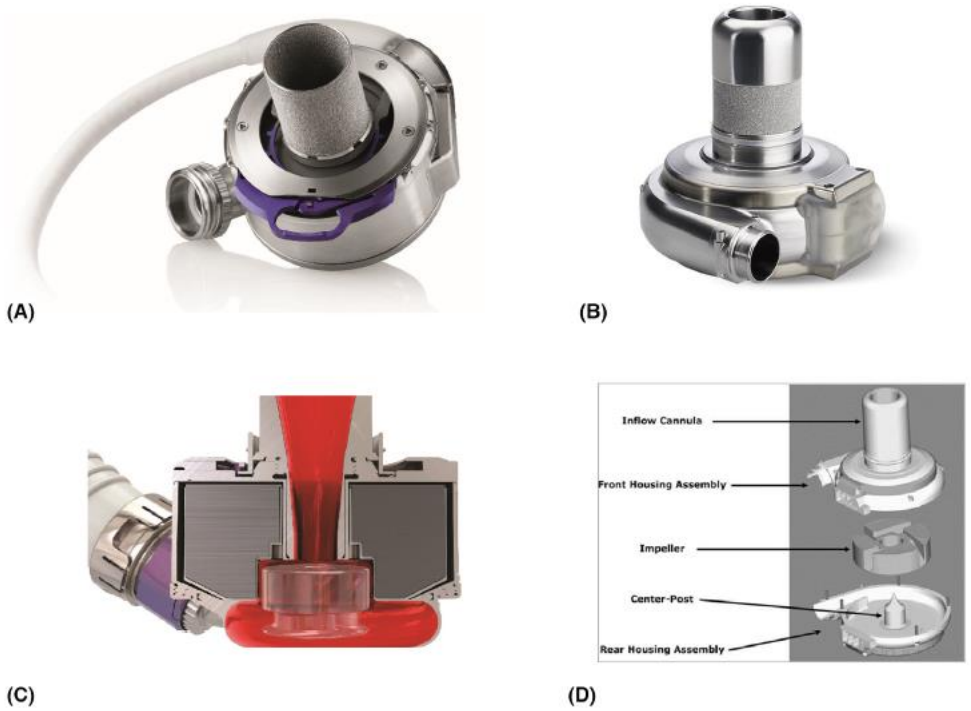

Figure 1.15. (A) HeartMate 3.(B) HeartWare HVAD. (C) Cross section of HM3. (D) Cross section of HeartWare HVAD presenting the components of the device. Image modified from (Goodman, Stulak and Rosenbaum, 2022).

Approximating blood as a Newtonian fluid (even if it is non-Newtonian, because of the dependence of viscosity from shear), the shear stress can be represented by the following equation:

$$\tau = \mu \frac{du}{dy}$$

where τ is the shear stress [Pa], μ is viscosity [Pa*s] and $\frac{du}{dy}$ [$^{1}/_{S}$] is the velocity gradient that describes the difference in velocity of two neighbouring infinitesimal fluid elements. The higher the difference in velocity $\frac{du}{dy}$ between one fluid element and the neighbouring one is, the higher the shear stress τ is . Since red blood cell can be thought as a droplet of one fluid suspended in another, which integrity depends on the equilibrium between surface tension (interaction within its molecules) and shear stress (interaction with surrounding fluid molecules), the most disruptive regions of the pump for red blood cells are the ones where high velocity surfaces or fluid abut low-velocity surfaces or fluid.

To solve this problem, engineers implemented a magnetically or hydrodynamically levitated, rather than mechanically suspended, rotors. These were centrifugal pumps propelling blood in a tangential direction rather than axially, while the pump chamber redirects the flux towards a single tangential outlet, providing continuous flow as in the previous generation. This method gave the possibility to widen the gaps between rotor blades and the pump chamber without risk for secondary flow paths. This could lead to reduce the velocity of the blades and consequently mitigate the shear stress applied to the blood as the velocity gradient between the chamber walls and the propeller is lower. However, the radius of the rotor is typically larger in centrifugal pumps than in axial ones, which can result in similar blade tip velocities and related shear rates depending on the design (Moazami *et al.*, 2013; Thamsen *et al.*, 2015).

Another new feature, incorporated both in HM3 and HW, was a flow modulating algorithm designed to simulate the cardiac cycle. In particular, HM3 “artificial pulse” program consists of increasing and decreasing the speed of the rotor with respect to an optimal value, usually around 4800-6000 rpm, set by the physician at the time of implantation (Figure 1.16).

The reasons of including an “artificial pulse” algorithm were to mitigate firstly the burden of microthrombi in the pump and, secondly, the cardiovascular and hematologic complications observed in clinical trials for second generation devices. These complications included

thromboembolic disease, increased production of matrix metalloproteinases, arteriovenous malformations (AVM), vascular dysfunction and aortic stiffening. AVMs were most notable in gastrointestinal tract and resulted in bleeding (Kapuria *et al.*, 2020).

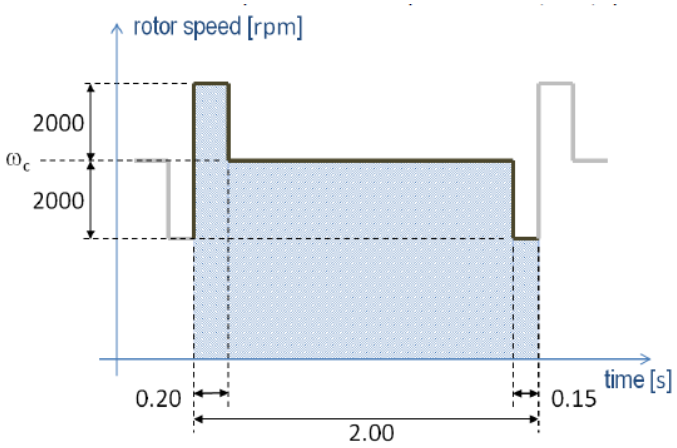

Figure 1.16. HM3 pump starts the cycle by increasing the speed by 2000rpm for 0.20s, decreases it to the optimal value for 1.65s, further decreases it by 2000rpm for 0.15s and then repeat the cycle. The overall cycle lasts 2.00s, which corresponds to a pulse of 30bpm. (United States & Canada Thoratec Corporation, 2017)

1.2.4. Major adverse events related to LVAD implants.

1.2.4.1. Survival

LVADs are life saving devices that are meant to give patients the possibility to survive until transplant or to mitigate advanced heart failure disease symptoms. Focusing on the last two generations, in MOMENTUM 3 clinical trial survival at 6 months in HM3 patients was compared to HM2 patients reporting significantly better outcomes (86.2% vs 76.8%). Survival at 2 years for patients treated with HM3 was comparable to survival after heart transplant, 82% (Teuteberg *et al.*, 2020).

The quality of life of LVADs patients is strictly related to adverse events related to the device, patients' conditions at the time of the implant, or centre experience with this kind surgical intervention and patient management. Actually, LVAD patients can experience frequent rehospitalizations and serious if not fatal injuries during LVADs treatment.

Leading causes of death common to both devices are right heart failure, stroke and infection. In HM3 patients, aortic insufficiency remained an important cause of morbidity and mortality (Kannojiya, Das and Das, 2021).

Some of the major device-related adverse events are presented in the following.

1.2.4.2. Gastrointestinal (GI) Bleeding

As mentioned above, high shear stress is disruptive for red blood cells, activates platelets, leading to potential thrombosis, and degrades high molecular weight multimers of von Willebrand factor (HMW vWF), which is related to bleeding (e.g., acquired von Willebrand disease).

To quantify how these phenomena occur when blood is exposed to shear stress for a certain time, a benchtop testing suggested the following threshold: a hemolysis threshold of 90 Pa at 600 s, a threshold for platelets activation of 50 Pa for 600 s, and 12 Pa for 900 s and a HMW vWF degradation threshold of 12 Pa at 300 s (Chan *et al.*, 2022).

Many studies reported the occurrence of gastrointestinal bleeding as a relevant cause of morbidity of patients since the introduction of continuous flow second generation LVADs, in direct relation to haemolysis. A single centre, American retrospective review of records performed for 79 patients who underwent LVAD implantation (HM2 80% and HVAD) between 2010 and 2015, rates GI bleeding at 34.1%, with a mean time to bleed of 267 days. Older patients were more exposed to the risk of bleeding. Arteriovenous malformations (AVM) were the source of bleeding in 74% bleeders and 80% of these patients had de novo AVM formation. Half of patients previously experiencing bleeding had a re-bleeding event. Thrombotic events were found to be 4.5 times more likely to occur in patients who also had a GI bleed (Kapuria *et al.*, 2020).

Besides the relevant rate of hospitalizations, GI bleedings are relatively mild adverse events, which on their own hardly impact on survival.

1.2.4.3. Pump thrombosis

Pump thrombosis (Figure 1.17.) is a relatively frequent complication with a reported incidence of 5.5%–12.2% but it is associated with significant morbidity. In Momentum 3 clinical trials, pump thrombosis at 2 years from the implant accounted for 1.4% for HM3 and 13.9% HM2 (Mehra *et al.*, 2019).

Numerous factors contribute towards this complication. They can be:

i) device-related, including outflow graft kinking, extrinsic compression, low pump speed and local heat generated by the pump;
ii) patient-related owing to pro-thrombotic conditions including elevated blood pressure, infection, congestive heart failure and hypercoagulable states;

iii) management-related factors resulting from subtherapeutic and inadequate anticoagulation.

Patients with bleeding events such as GI bleeding are predisposed to a higher risk of thrombosis owing to the need of decreasing or discontinuing anticoagulation. Pump thrombosis is associated with increased morbidity and mortality if not promptly and effectively managed (Malone *et al.*, 2023).

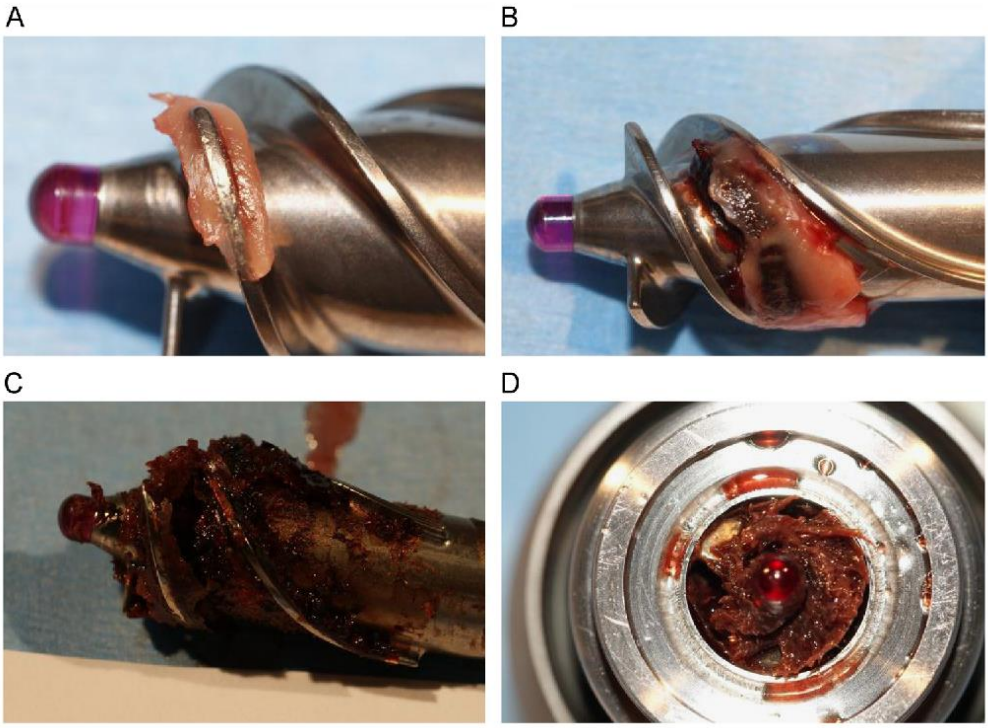

Figure 1.17. Examples of HeartMate II device thrombosis. (A–C) HeartMate II impeller with the ruby bearing and different types of clots in the same location. (A) Fibrin-only clot. (B) Fibrin and blood clot. (C) Blood-only clot. (D) Cross-section view of the HeartMate II motor with significant combined fibrin and blood clot. Image from (Uriel *et al.*, 2014).

1.2.4.4. Strokes

Reported rates of LVAD-associated stroke at 2 years post-implantation range from 10 to 30%, which is significantly higher than in age-matched controls (Figure 1.18.). There are approximately equal rates of ischemic and haemorrhagic strokes, and rates are highest during the peri-implantation period and in the first year of therapy. Risk factors associated with ischemic and haemorrhagic stroke can be grouped into: 1) treatment-related factors, including specific devices and antithrombotic/anticoagulation strategy, and 2) patient-related factors (Plecash *et al.*, 2022).

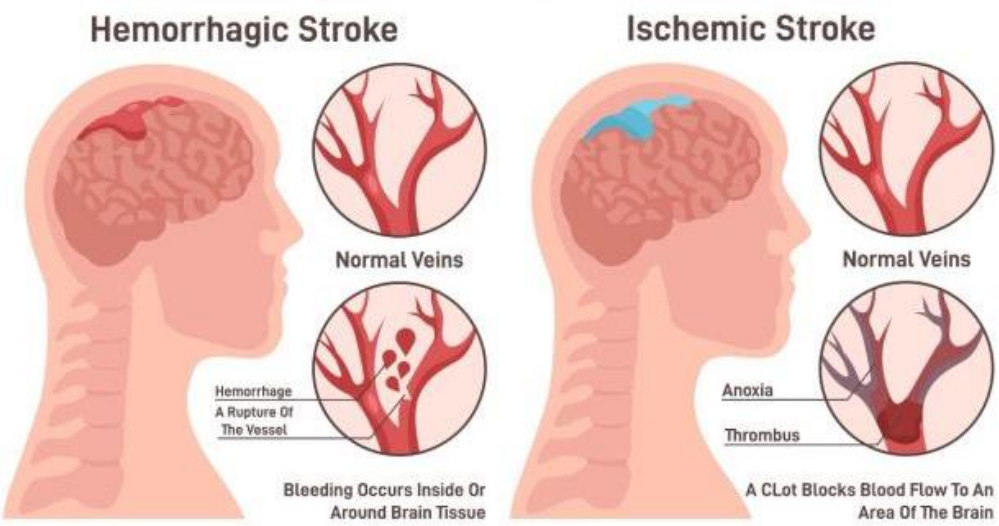

Figure 1.18. Differences between Hemorrhagic stroke (left) and Ischemic stroke (right).

Ischemic stroke can be a result of multiple elements contributing to thrombotic complications in LVADs related to activation of the extrinsic coagulation pathway:

i) foreign pump materials (hemocompatibility);
ii) shear stress: haemolysis caused by the shear stress produces ADP leakage from red cells, which in turn promotes platelet activation. Shear stress from altered flow may also promote endothelial damage on native vessels and accelerate atherosclerosis;
iii) stasis within a hypokinetic heart, pump circuit or graft site;
iv) concurrent inflammation and infection can also promote coagulation.

The risk of haemorrhagic stroke can be related to both exogenous use of antithrombotics in addition to endogenous factors contribution:

a) altered blood flow patterns may impair cerebral autoregulation and promote endothelial dysfunction through shear stress, reduced nitric oxide bioavailability and vascular smooth muscle proliferation;
b) systemic hemorrhagic complications may be precipitated by the acquired von Willebrand's disease. The breakdown of vWF is caused by the shear stress from continuous-flow devices, and results in an acquired deficiency that prevents normal platelet adhesion and leads to systemic bleeding complications. Normal vWF multimers are instead found in patients with pulsatile-flow LVADs.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS registry) is a large prospective observational registry of both adults and children with LVADs; it

monitored 9,489 patients receiving 10,285 continuous-flow LVADs between 2014 and 2017. Overall, 16% of patients had one (85%) or more (15%) strokes, with ischemic and hemorrhagic events occurring with equal frequency. While the risk of first ischemic stroke was associated with an increased risk of subsequent ischemic and hemorrhagic stroke, those with incident hemorrhagic strokes were not at increased risk for recurrent haemorrhagic events (Plecash *et al.*, 2022).

In the momentum 3 trial at 2years from implantation, rates of any type of stroke were around 9.9% for HM3 and 19.4% for HM2, making them comparable to the rates of stroke after heart transplantation, 13%. Rates for any bleeding were 43.7% for HM3 and 55.0% for HM2 (Uriel *et al.*, 2017; Mehra *et al.*, 2019).

1.2.4.5. Infections

Infections related to LVAD devices are of three types:

i) driveline infection: it is the most reported and frequent LVADs related infection. This kind of infection tends to occur relatively late in the treatment (190 days median) and it is successfully managed with a combination of local debridement and antimicrobial therapy, eliminating the need for LVADs removal in most cases. In the MOMENTUM3 study at 2years from implantation, rates of driveline infections were 23.3% and 19.4% for HM3 and HM2 patients respectively;

ii) pocket infection: pump pocket infection is usually the second most common infection reported in the literature. Even in this scenario, debridement and antimicrobial therapy is indicated and pump explant might be considered as a possibility;

iii) bloodstream infection: it is a serious complication of LVAD implantation less frequently reported. Bloodstream infection has been associated with increased risk of both haemorrhagic and ischemic stroke. The best approach for managing severe bloodstream infections in LVAD recipients is unclear. Bloodstream infections were found to take longer hospitalization than patients with driveline infections.

Infection incidence and mortality associated with LVAD infections appeared to decrease over time. This trend was associated with a Centre's increased experience in implanting and subsequently managing the devices, as well as with the use of smaller devices with better flow dynamics. Nonetheless, most of infections-oriented research in the literature come from secondary analyses of other LVAD studies, leaving certain areas unexplored (e.g., bloodstream

infections) as well as unstandardized management guidelines to treat these infections (O'Horo *et al.*, 2018; Patel *et al.*, 2020).

1.2.4.6. Right heart failure

Right heart failure after left ventricular assist device implantation remains a significant cause of morbidity and mortality, leading to hypoperfusion, end-organ dysfunction, prolonged hospital length of stay, and increased mortality (Figure 1.19). This issue is relevant nowadays more than ever since stricter heart transplant policies (i.e., UNOS allocation policy change in USA) have contributed to shift phenotype of patients receiving LVADs, with a larger proportion of destination therapy (DT) implants and an overall sicker population.

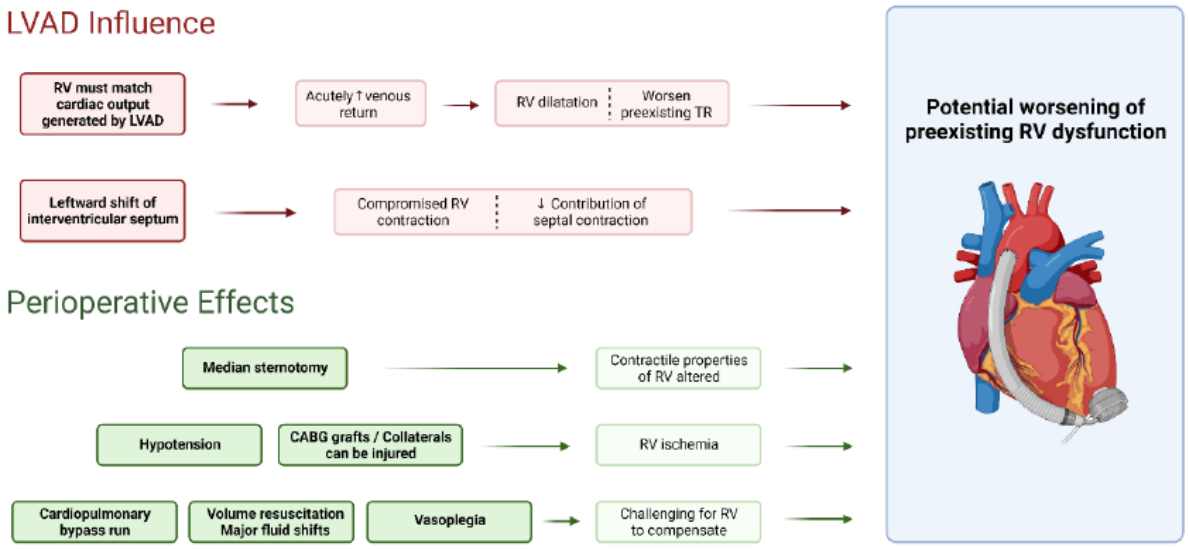

Figure 1.19. Influence of left ventricular assist device and perioperative factors on right heart function. CABG = coronary artery bypass graft; LVAD = left ventricular assist device; RV = right ventricle; TR = tricuspid regurgitation; ↑ = increased; ↓ = decreased. Image from (Wang *et al.*, 2022).

Early right heart failure (RHF) incidence estimates as high as 40% in second-generation devices and 34% in current third-generation devices. For patients with severe RHF requiring temporary right ventricular assist device (RVAD) placement, one-year mortality is as high as 41%. In this sicker contemporary population, RHF will continue to pose a significant obstacle despite technological innovation, and a comprehensive understanding of the timing, predictors, and treatment of RHF will be critically important in the ongoing success of LVADs (Wang *et al.*, 2022).

1.2.5. Comparison between HM3, Jarvik2000, and HVAD

As discussed above drawing comparisons between devices in terms of outcomes can be tough. LVAD therapy efficacy is influenced by the following factors:

i. device characteristics;
ii. patients' conditions at the time of the implant;
iii. centre experience with a certain device;
iv. surgical techniques;
v. patient management strategies.

Focusing on device characteristics, it is possible to compare three of the most notable LVAD devices: HeartMate3, HeartWare HVAD and Jarvik2000 (Table 1.2). The comparison is not to sort the best devices but to display their technical characteristics, which are relevant for further discussions.

Technical characteristics	Jarvik2000®	HeartWare® HVAD®	HarteMate 3®
Producer	Jarvik Heart	Medtronic	Abbott
Generation	2nd	3rd	3rd
Peso	85g	160 g	200g
Volume	2.5 cm wide 5.5 cm long	Diameter: 50mm Height: 33mm	Diameter: 50.3 mm. Height: 33.8 mm
Engine	Continuous axial flow	Continuous centrifugal flow	Continuous centrifugal flow
Displacement Volume	25 ml	50 ml	21 ml
Output	Pump speed of 8,000-12,000 rpm (Average flow rate of 5 L/min up to 7 L/min).	Pump speed of 1800 and 4000 rpm. (2,0 to 10 L/min)	Pump speed range: 3000-9000 rpm. (3,3-10L/min)
Speed control	Manual adjustment	Artificial pulse	Artificial pulse
Site of implantation	Inside left ventricle	Outside left ventricle apex	Outside left ventricle apex
Housing Material	Titanium	Titanium	Titanium
Outflow canula	Ascending aorta	Ascending or descending aorta	Ascending or descending aorta, arteria subclavian
Battery charge	8-10h less than two pounds	4-7h each of the two batteries	Max 17h
Availability	Still on the market	Recall 2021	Still on the market
Valve	No valves	No valves	No valves

Table 1.2. Comparison between Jarvik 2000, HeartWare HVAD and HeartMate 3. The specification reported refer to the time in which these devices were implanted at the University-Hospital of Padua.

Figure 1.20. depicts two different techniques of LVAD outflow canula grafting anastomosis in use at the Cardiac Surgery Department of the University Hospital of Padua.

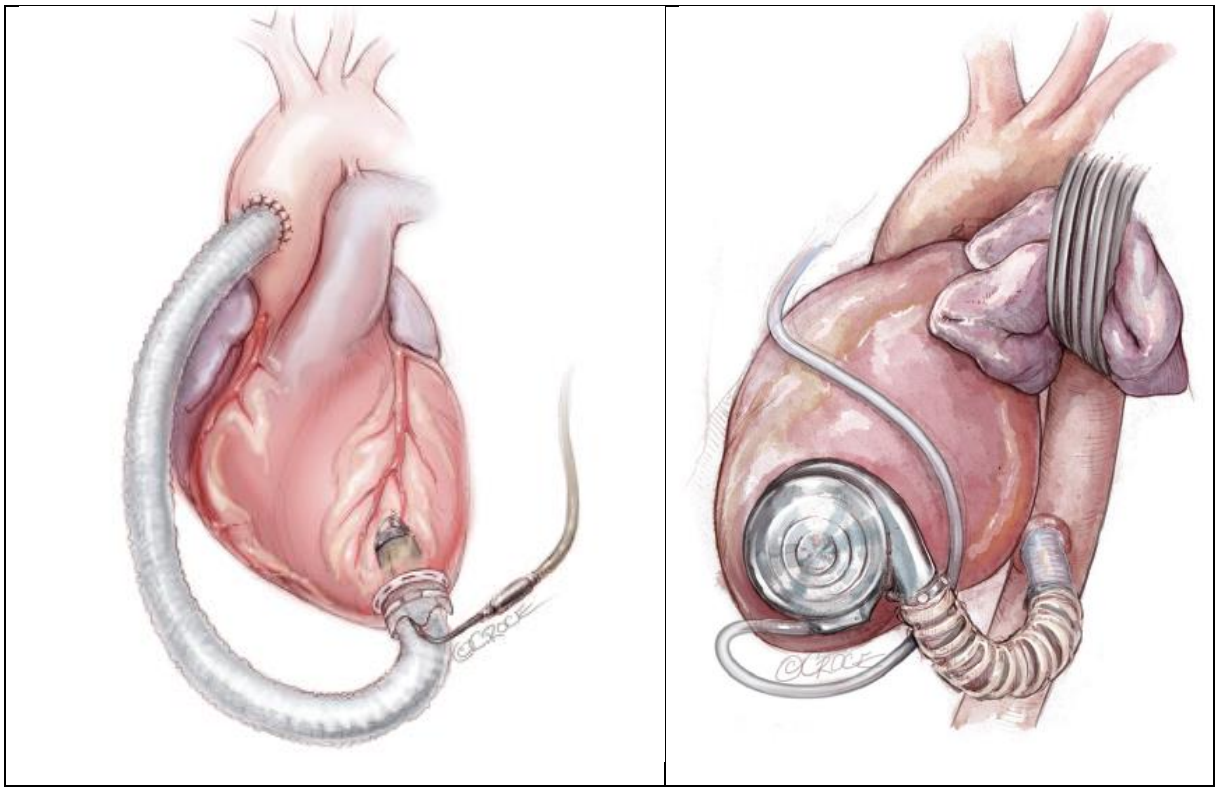

Figure 1.20. Implantation of the Jarvik pump into the left ventricular apex with distal outflow graft conduit anastomosis to ascending aorta (left). Implantation of not specified centrifugal continuous flow device with outflow graft anastomosis to the descending aorta (right) (Zucchetta *et al.*, 2014; Loforte *et al.*, 2021).

1.2.6. LVADs prospectives

Although LVADs have achieved very good results in terms of survival, adverse events related to the devices are still relevant both in terms of loss of patients' quality of live and in terms of costs. Besides LVADs are still the only alternative option to traditional medical management to treat advanced heart failure, the increasing interest for artificial heart (Figure 1.21.), tissue engineering and artificial organs will possibly represent future alternatives to LVADs.

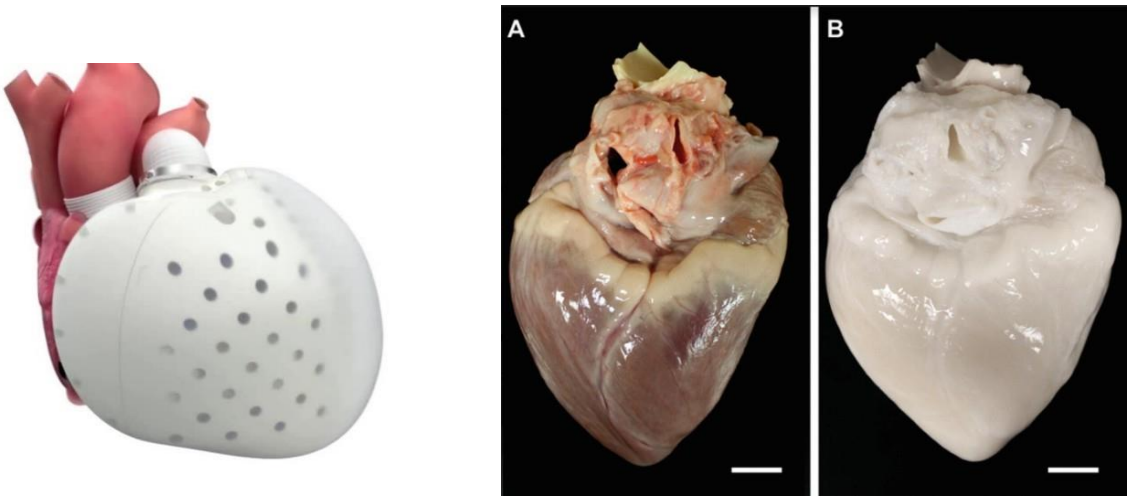

Figure 1.21. The Carmat total artificial heart (left), A porcine heart (A), the same porcine heart decellularized to be repopulated with human cells (B) (Hodgson *et al.*, 2018).

For these reasons, many research groups are still working on LVADs to address the issue highlighted above. One of the most famous recent examples is the first human use of coplanar energy transfer coupled with a continuous LVAD, which is meant to get rid of power driveline connecting the device to the external control system (Pya *et al.*, 2019).

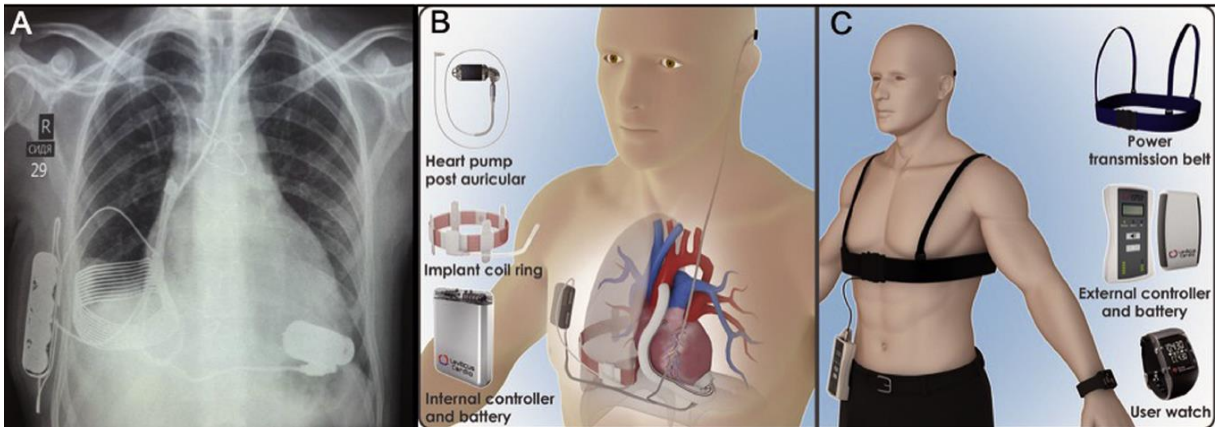

Figure 1.22. (A) Chest X-ray depicting implantable components topography. (B) Implantable components. (C) External components. Image from (Pya *et al.*, 2019)

In the context of Life Lab project, the University of Padova is now working on a new prototype of LVAD pump to address the haemolysis issues common to all continuous flow devices in use today.

2. Economic evaluation on LVADs

2.1. Economic Evaluation in Healthcare

2.1.1. Health demand and resource constraints in the healthcare sector

Grossman's theoretical approach to the relationship between the consumer and the demand for health and healthcare (HC) claimed that individuals use goods, services and time as input to produce other basic or primary goods that enter their utility functions. This idea can be used to explain the demand for healthcare as a derived demand. Healthcare goods and services are generally not demanded because of their utility *per se* rather as they might provide positive effects on health, which on its term influences the ability of the individual to participate in the labour market, to spend leisure time freely, to consume, etc.

The demand for health, and therefore for healthcare goods and services, clashes with the shortage of resources for healthcare and the necessity for healthcare systems to provide care at sustainable costs for the population. Imbalance between patients' demand and healthcare system offer under economic constrains leads to system difficulties in dealing with sanitary emergencies (i.e., Covid19 pandemic), patients selection mechanisms and social-economic discrimination accessing costly therapies. Hence, healthcare goods have to be considered as economic goods and they need to be addressed for basic economic question such as:

1) How much should be invested in HC with respect to other sectors of the economy?

2) Which particular type of HC should be produced (screening, treatments, palliative care)?

3) Which resources should be used to produce these HC services (staff, technology, researchers)?

4) Who should receive these services (equally, as a matter of priority)? (Bhattacharya J, Hyde T, and Tu P, 2014a)

2.1.2. HTA and Economic evaluation

Each time a new health technology, drug or campaign is designed, it should be necessary to investigate its effectiveness as well as its social, economic, organizational, and ethical issues. This systemic evaluation of properties, effects and impact of health technology is covered in the field of health technology assessment (HTA), whose main purpose is to inform policy decision makers and to create a connection between scientific research and policy. In Italy, HTA is performed at regional level and Azienda Zero is the agency operating in Veneto region.

A major component of HTA is the economic evaluation. Its main objective is to help decision-makers in understanding the possible ways in which limited healthcare resources might be used. Practically, a complete economic evaluation in healthcare is a comparative analysis of two or more alternative treatments in terms of their costs and their outcomes (Table 2.1) (Bhattacharya J, Hyde T, and Tu P, 2014a).

		Both costs and consequences		
		No		Yes
		Only consequences	Only costs	
Comparison of two or more alternatives	No	Outcome Description	Cost Description	Cost-Outcomes Description
	Yes	Evaluation of effectiveness (ex. Clinical Randomized Control Trial)	Cost Analysis	Complete economic evaluation (ex. CBA, CEA, CUA)

Table 2.1. Description of possible analysis with respect to costs and outcomes. In the following, the present manuscript mainly focuses on the evaluation highlighted in the red cell.

Costs are related to the prospective adopted for the evaluation, which may focus on national health care and hospitals expenditure, or on patients and society costs. For this reason, resources are attached to a value that is generally given by their prices on the market or in terms of their opportunity costs (the benefit lost by not investing the same amount of money on other resources).

Even though outcomes can be measured in monetary terms as money saved thanks to a certain treatment, it is complex to give a monetary value to health. It is more common to evaluate the effectiveness of a treatment or drug referring to various physical units: life years, early diagnosis and quality of life indicators such as quality adjusted life years (QALYs) or disability adjusted life years (DALYs) (Drummond M et al., 2015a).

2.1.3. Types of Analysis

Assuming to compare two treatments, where A is the innovative one and the Comparator is the standard one, the relationship between the outcomes of each therapeutic pathway determine which type of analysis can be performed. In case the two treatments have the same therapeutic effects, the analyses which can be performed are the following:

2.1.3.1. Cost Minimization Analysis

Cost Minimization Analysis is the analysis of choice as it is a simple search for the least expensive interventions among the ones available. Any choice does not have implications on patients' outcomes. In case the two treatments have different therapeutic effects, there are three possible types of analysis depending on how outcomes are valued.

2.1.3.2. Cost Benefit Analysis (CBA)

Cost Benefit Analysis (CBA) consider both costs and outcomes in monetary terms and compare the net benefits (benefits-costs) of each alternative in order to indicate the best one. Generally, this kind of evaluation is more likely to be performed for infrastructures or "pure economic scenarios" rather than for healthcare interventions as it is hard to value their outcome in monetary terms (Bhattacharya J et al., 2014a).

2.1.3.3. Cost Effectiveness Analysis (CEA)

Cost Effectiveness Analysis (CEA) still refers to costs in monetary terms while outcomes are treated for their health effects or physical units of effects such as years of life saved, avoided exacerbations, days without symptoms and others. Deciding for the best option in this analysis is not straightforward and possible scenarios are presented in the following evaluation matrix (Table 2.2).

	A effects < Comparator effects	A effects > Comparator effects
A cost > Comparator cost	A is rejected. (A is DOMINATED)	Trade off (is there the possibility to invest?)
A cost < Comparator cost	Trade off (is there the necessity to save?)	A is adopted. (A is DOMINANT)

Table 2.2. The evaluation matrix is used in CEA and CUA to describe all possible relationships of dominance between A and the comparator.

Treatment A is surely rejected if its costs are greater, and benefits are lower, with respect to the comparator treatment. In this case, A is DOMINATED by the Comparator. Treatment A is DOMINANT and then surely adopted as it is more effective and less expensive with respect to the standard one. Decision results in a trade off in case treatment A is more effective but more expensive with regard to the comparator and vice versa (A less expensive and less effective than the Comparator). The strategy adopted to suggest whether superior effectiveness justifies for extra costs or not, consists in an incremental approach and Incremental Cost-Effectiveness Ratio (ICER) is the index of choice for non-obvious results:

$$ICER = \frac{CostA - CostComp}{OutcomeA - OutcomeComp}$$

By definition, ICER is the ratio between the differences in costs and in outcomes between treatment A and the comparator. If we consider outcomes in terms of life years saved, ICER can be interpreted as the extra amount of money to spend, by choosing treatment A, in order to save 1 extra year of life with respect to the comparator [ICER]=[€/LY]. Once the ICER is calculated, the decision to prefer a new treatment depends on how much health system is willing to pay for this kind of treatment, which can be formalized as a threshold value for the ICER itself (Bhattacharya J et al., 2014a).

2.1.3.4. Cost Utility Analysis (CUA)

Cost Utility Analysis (CUA) improve CEA by taking into account for patients quality of life rather than survival only. Outcomes are commonly measured in QALYs, which try to estimate the number of years an individual is expected to live in perfect health by accessing some basic health characteristics (Figure 2.1). To calculate one of the many coefficients established to this purpose, means to assign an utility value to a multitude of patient's specific conditions (i.e., inability to walk without crutches, depression, focused pain) in a period of time usually elapsing between ambulatory visits after or/and before the intervention (Bhattacharya J et al., 2014).

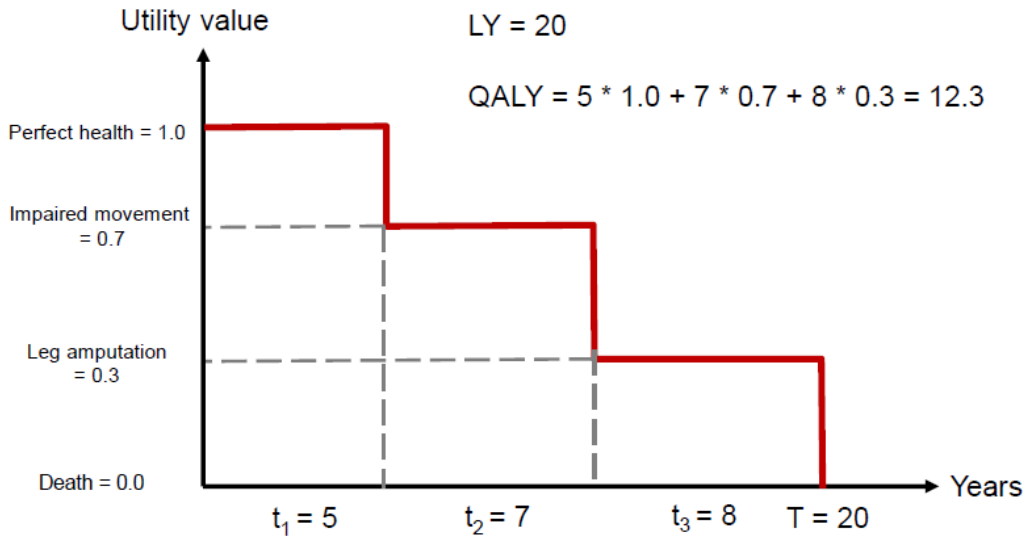

Figure 2.1. The graph describes the difference between life years (LY) and QALYs with respect to a patient last twenty years of life (T). Each health status is associated with an utility value and the total amount of years lived in perfect health is calculated as $\mathrm{QALYs}=\sum t_i \times \mathrm{Utility}_i$.

In this kind of analysis decisions for the best option relies on the same evaluation matrix used for CEA. In this case, the ICER is interpreted as the extra amount of money to spend, by choosing treatment A, in order to save 1 extra year of life in perfect health conditions with respect to the comparator [ICER]=[€/QALYs]. ICER's thresholds indicating the willingness to pay vary from country to country. While at first little theoretical or empirical justification advocated for the set threshold values, the way threshold should be calculated to better account for typology of intervention/illness and patient's health loss is now object of many studies (Neumann and Kim, 2023; Russo *et al.*, 2023). An example of how these benchmarks are usually set, is reported in Table 2.3.

	Likely to be accepted	Need for additional motivation to be accepted	Likely to be rejected
UK	ICER < 20.000 [£/QALYs]	20.000 - 30.000 [£/QALYs]	ICER> 30.000 [£/QALYs]
Europe	ICER < 30.000 [€/QALYs]	30.000 - 50.000 [€/QALYs]	ICER> 50.000 [€/QALYs]
Us	ICER < 50.000 [$/QALYs]	50.000 - 150.000 [$/QALYs]	ICER> 150.000 [$/QALYs]

Table 2.3. CUA threshold values adopted in Europe and UK.

It is worthy to notice that ICER values depend on QALY assignment to a specific condition of the patient. This means that the reliability of CUA analysis suffers from QALYs limitations.

QALYs do not account for effective trajectory of health status as they refer to a specific moment evaluation. Gradients in utility value of the same magnitude are considered equivalent whichever the severity or the course of the illness (e.g., 0.6->0.3 = 0.6->0.9). Utility value is not an objective measurement as it is affected by the type of the illness, age, sex, socioeconomics and many other factors (Drummond M et al., 2015a). For these reasons, CUA analysis is meaningful only while comparing alternatives for the same health condition and, furthermore, ICER values obtained from this evaluation are less precise indicators than ICERs obtained from CEA. Hence, sensitivity analysis is always indicated to verify the stability of the obtained results with respect to each input variable: this kind of analyses are of major importance especially when results are obtained through modelling strategies, as it will be mentioned later.

Finally, it is worthy to mention budget impact analysis that is always performed after every type of economic evaluation to estimate the financial impact deriving from the introduction of a new drug/treatment. Budget constraints, as much as willingness to pay, determine the affordability of a treatment for the eligible population. For this reason, costs are valued in terms of opportunity costs and outcomes are considered for their monetary value.

2.1.4. Decision Making – Modelling

As mentioned above, a complete economic evaluation in healthcare is a comparative analysis of two or more alternative treatments in terms of their costs and their outcomes. Ideally, the outcomes should be derived from a clinical trial study in which the population is randomly sampled in two or more homogeneous groups: the control or standard therapy group and the alternative approaches groups. Moreover, there is no clinical trial that is exhausting to the purposes of the study and can guarantee randomicity. This problem leads to the necessity of implementing models that schematize the scenarios of interest to the more relevant information. So, at the cost of incorporating uncertainty in the final estimations, essential data can be retrieved from different studies while outcomes and costs can be extrapolated beyond trials limited duration to fulfil the time horizon chosen for the analysis (Drummond M et al., 2015b).

Models used in this contest are decision trees, Markov models or a combination thereof.

2.1.4.1. Decision Trees

Decision trees are trees where each pathway from the decision node to the endpoints is a possible set of eventualities a patient can encounter undergoing a specific treatment (Figure 2.2).

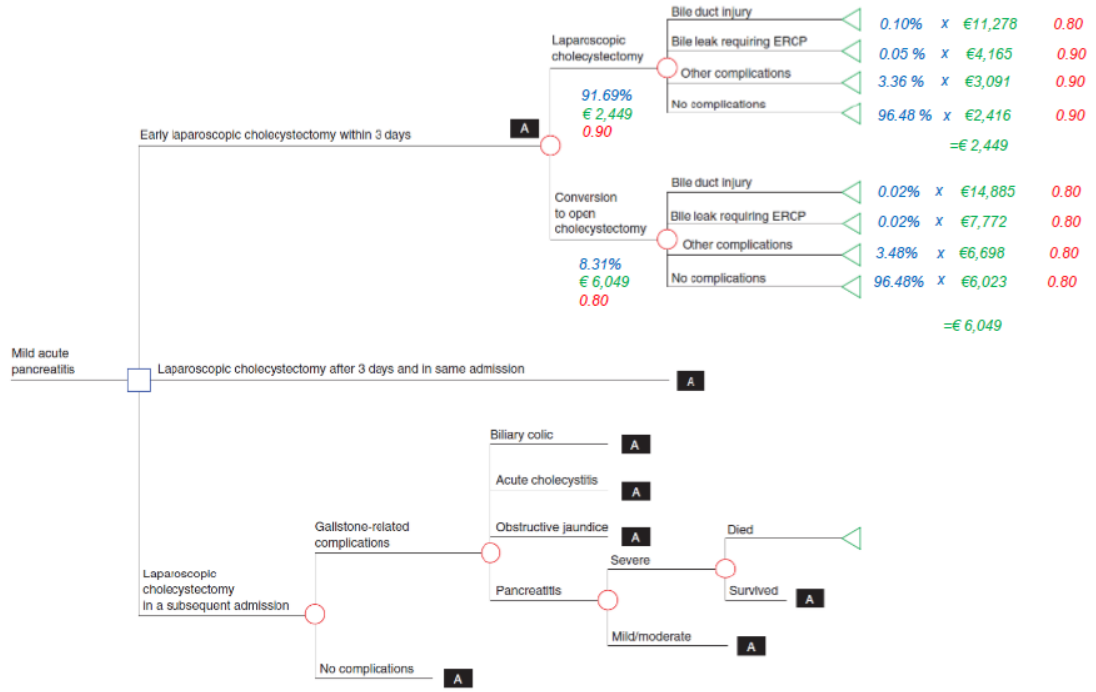

Figure 2.2. A decision tree with three alternative interventions for mild acute pancreatitis. In blue are the probabilities, in green the costs, in red the QALYs associated with each branch. The square-shaped node is the decision node, the round-ones are chance nodes, and the triangular ones are the end points. Imagine from (Morris et al., 2014)

From the decision node branch out all treatments to be compared. A possible course is described through successive levels of branches, each level referring to a single chance node. These nodes indicate more possible chances and each one is linked with a probability. The sum of probabilities of all branches exiting that kind of node is one. Every endpoint is attached to cost and outcome related to that specific pathway. Hence, the conditional probability associated with each endpoint is the product of all the probabilities encountered along that pathway. The expected costs and outcomes are the product of endpoints costs/outcomes and the conditional probabilities associated with them. The expected costs and outcomes of each treatment are simply the sum of the expected costs/outcomes related to the pathways originating from that treatment.

Decision trees are effective in modelling acute events, but as considered time lapses grow, more eventualities can occur, resulting in increasingly complex trees. That is why Markov

models have been introduced to deal with longer periods of time, recurring events and generally for chronic conditions.

2.1.4.2. Markov Models

Markov Models applied in this field take advantage of exhaustive and mutually exclusive compartments to represent the various health states (i.e., healthy, ill, death) a patient can experience. A unit of time (days, months, years) indicates the length of the cycle and therefore the frequency at which patients can change health state. The probability for patients' migration to another state depends only on the state they were in the previous cycle, and it is called transition probability. Hence, comparing two treatments means to create two Markov matrixes, each one attached to its own set of probabilities. Costs and Outcomes are associated to each health status so that it is trivial to calculate the total costs and outcomes at each cycle. Then, the total costs and outcomes for each cycle are summed to obtain the total cost and outcome of the treatment. Markov models can easily approximate complex problems and even recurrent conditions, but it is a memoryless method. This means that patients' specific pathways are lost; hence, the probability remains constant at every cycle not accounting for individual more/less risky condition. One possible solution to manage more realistic sets of probabilities, is to create multiple compartments for the same health state in order to account for the time a patient spent in a particular health condition (Briggs A et al., 2006a) .

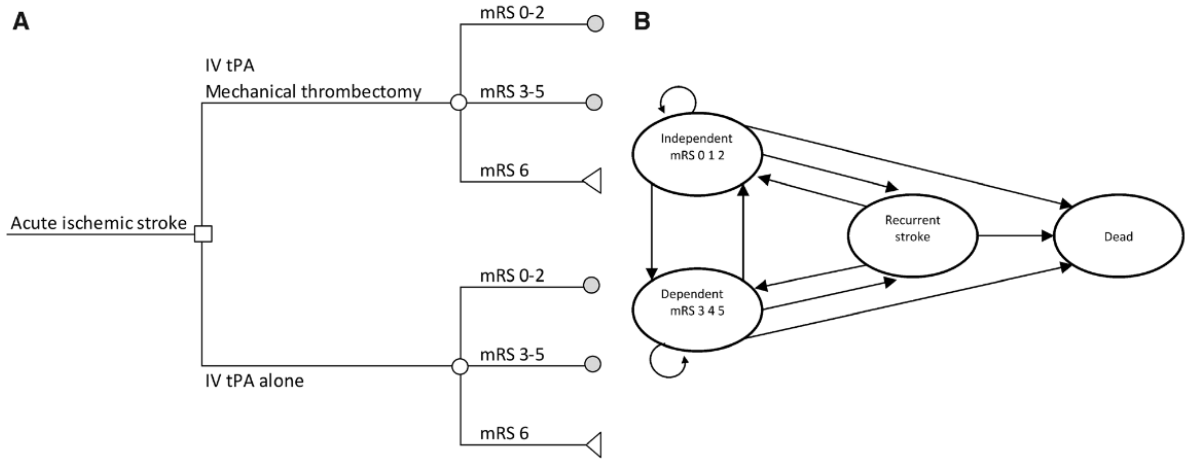

Figure 2.3. A decision model between two treatments for acute ischemic stroke. The Markov model (B) describes patients' heath status with respect to modified ranking scale (mRs). The Markov model is attached to grey round dots at the ends of the decision tree (A), to account for the two different treatments. Imagine from (Ganesalingam et al., 2015).

2.1.5. Decision Making – Sensitivity Analysis

Once the comparison between the new treatment and the standard one has been performed, it is fundamental to evaluate the robustness of the results just elaborated, especially with respect to the input parameters of the model. As costs vary from region to region and outcomes and probabilities derive from trials or evidence in the literature, therefore they all are sources of uncertainties (Briggs A et al., 2006b).

Here follows a brief overview of the sensitivity analysis types.

2.1.5.1. One Way

One Way sensitivity analyses investigate the behaviour of the results from an economic evaluation by varying just one input parameter at the time. In particular, univariate analysis is frequently performed by pharmaceutical companies to give a new treatment an appropriate price for the healthcare system.

One way sensitivity analysis is also used to understand which input parameter influences the most the variation of the ICER. In this case, TORNADO diagrams are the most effective representation of this phenomenon (Figure 2.4).

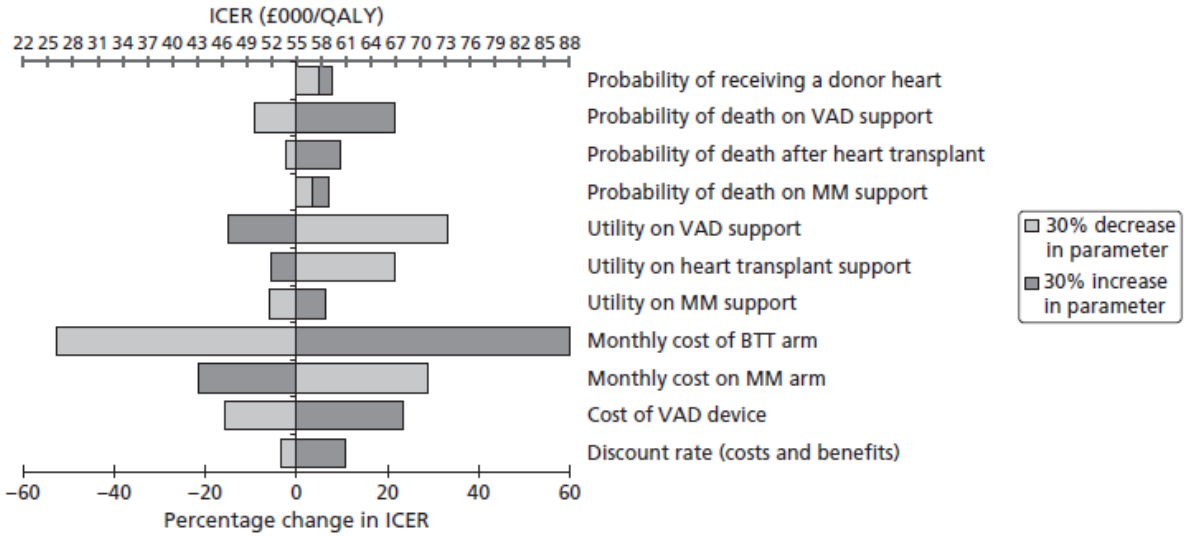

Figure 2.4. Tornado diagram indicates the effect on the ICER of a 30% increase or decrease in each input parameter listed on the right side of the figure. The base-case deterministic ICER is £55,173/QALY, and the parameter with the greatest impact on ICER is Monthly cost BTT arm (60% variation on the ICER). Imagine from (Sutcliffe et al., 2013).

2.1.5.2. *Multivariate Sensitivity Analyses*

Multivariate sensitivity analyses investigate the behaviour of the results from an economic evaluation by varying more than one input parameter at the time. Scenario analysis is a particular type of analysis aimed at describing the worst/best scenarios by setting extreme input value. Another purpose of this analysis might be to focus the economic evaluation on a specific subgroup of the population particularly interesting for their costs and/or outcomes.

2.1.5.3. *Probabilistic Sensitivity Analyses (PSA)*

Probabilistic sensitivity analyses (PSA) investigate the behaviour of the results from an economic evaluation by assigning a statistical distribution to each input parameter. The results of the models are recalculated a significant number of times, and a different value from parameters statistical distribution is randomly selected at each iteration of the model. The significant amount of ICERs coefficient generated from this procedure gives an indication on the likelihood of the cost effectiveness of the new treatment with respect to the set threshold (Figure 2.5) (Briggs A et al., 2006b).

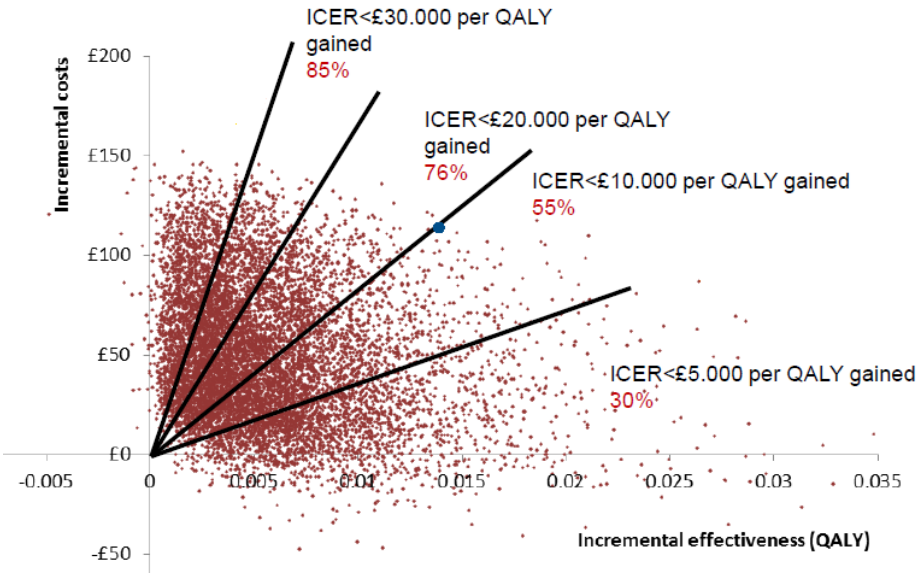

Figure 2.5. When the cloud of dots resulting from PSA is represented in the cost/effectiveness graph, it is possible to account for the percentage of results below the chosen threshold and therefore for acceptability of the new treatment.

Interestingly, PSA gives the possibility to relate the willingness to pay for new treatments and their possible cost effectiveness scores, even comparing more than two different treatments in the same graph (Figure 2.6 and Figure 2.7). It is important to notice that for every threshold

level in the graph, all probability curves values at that specific threshold add up to the unit (Drummond M et al., 2015b)

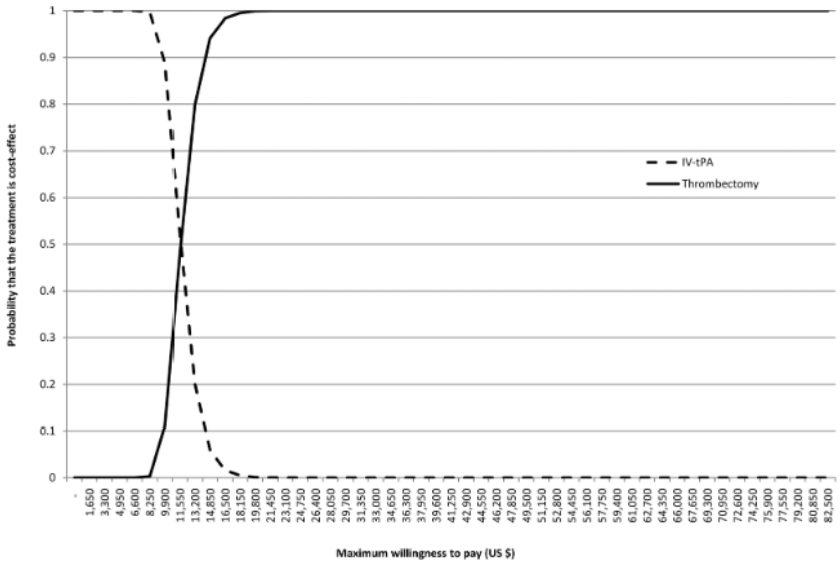

Figure 2.6. The results obtained from PSA are used to relate the probability that the treatment is cost effective to the maximum willingness to pay. Thrombectomy and IV-tPA balance their acceptability for around 11,550$. For lower values IV-tPA is preferable while thrombectomy becomes surely cost effective around 18,000$. Image from (Ganesalingam *et al.*, 2015).

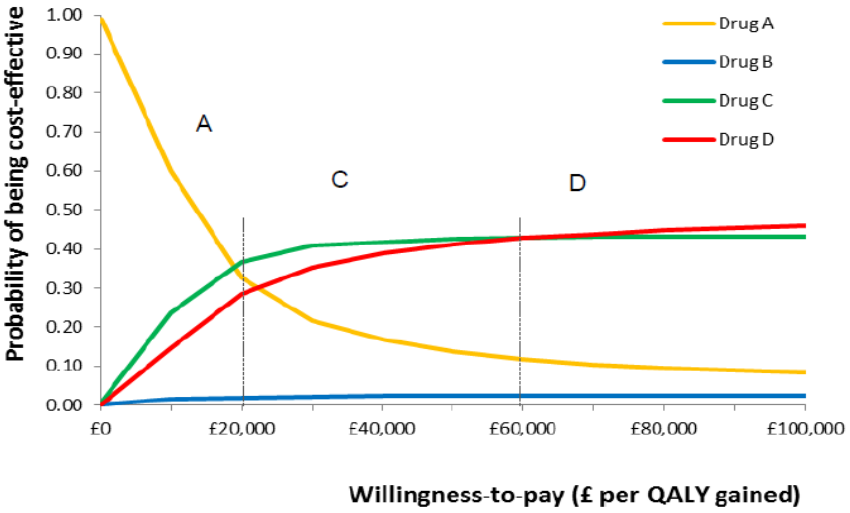

Figure 2.7. The graph represents a more complex scenario in which four different drugs are compared. In the range between £20,000/QALY and £60,000/QALY drug C is acceptable while for willingness to pay > £60,000/QALY drug D is preferable. Note that for every willingness to pay level the sum of drugs probability to be chosen is one, as the possibility to implement no drug is not considered.

2.2. Cost-effectiveness in cardiac surgery: the case of left ventricular assist devices (LVADs)

Cost-effectiveness analysis (CEA) in cardiac surgery continues to grow in relevance with increasing health care expenditures, a greater emphasis on value-based care, the continuing development of costly surgical and non-invasive technologies, advances in cardiac devices, and changes in eligibility criteria over the past two decades. Cardiac surgery interventions have high upfront costs and risks that may be compensated by long-term gains in survival, quality of life, and reduction in morbidity and health care resource utilization.

Furthermore, the usefulness of CEA is strictly related to the underlying data and assumptions, which may not be representative of the current practice, limiting generalizability of the findings. Due to the lack of robust long-term follow-up data on both clinical and economic outcomes and good cost estimation methodology, CEAs on the same topic may vary, even when perspective and setting are similar. For example, the time horizon of the study substantially impacts the results.

Although the rapidly evolving surgical technologies pose challenges to CEA methodologies, improvements in gathering and leveraging long-term economic and clinical data alongside trials and cardiac surgery registries represent future opportunities for the field.

A brief overview to better contextualize our analysis is herewith presented, based on the scientific literature concerning the evaluation of costs and outcomes of LVADs for end stage HF (Ferket *et al.*, 2018).

2.2.1. CEA for BTT and DT patients

Several countries (i.e., UK and other European countries, Australia, Canada, etc.) traditionally used CEAs for their healthcare policies in order to define the set of drugs and services within the publicly covered basic package of healthcare.

From the introduction in the market of the first-generation devices, LVADs' cost effectiveness had to be compared with optimal medical management that represented the only available therapy at the time. In terms of outcomes, LVAD therapy superiority with respect to optimal medical management for NHYA class IV HF patient was clear since REMATCH trial (2001)(Rose *et al.*, 2001). In terms of cost-effectiveness, CEAs had to prove LVADs to be cost-effective with

respect to medical management whether therapy was indicated as destination therapy (DT) or as bridge to transplant (BTT) (Sutcliffe *et al.*, 2013).

While for DT patients LVAD is permanent treatment that can last years, BTT indication refers to a "bridge period" on the device. Results of studies comparing BTT-LVADs and medical management are influenced by the average waiting time for transplant in the two groups. Longer time to transplant were associated to a drop in ICER values and larger gains in QALY for BTT-LVADs patient with respect to the MM group. These results suggested LVADs as a cost-effective opportunity for patients on long heart transplant waiting lists, which sets around one and half year in Italy due to the shortage of organs, common to almost all western countries (Ferket *et al.*, 2018; Varshney *et al.*, 2022).

In comparisons between LVAD DT therapy and medical management in heart transplant ineligible patients, all generations of LVADs were consistently more costly than medical management because of the high upfront implantation costs and re-hospitalization associated costs. DT patients are generally older than BTT ones. CEAs conducted for US health care system demonstrated a substantial improvement in the ICER over time, which can be mainly attributed to LVADs improved survival and quality-of-life (QoL), reduced implantation costs, improved patients' selection and reduced LVADs AEs with newer generation LVADs. Recent real-world analysis in the US context (CLEAR study) showed that HM3 LVAD improved survival and reduced adverse events led to reduction in costs by 17.4% to 26.1% compared to other LVADs. However, the lack of a common method to estimate costs, determined difficulties in comparing the results of CEAs studies (Ferket *et al.*, 2018; Pagani *et al.*, 2021).

Based on contemporary trials, in most European countries and also in the US (since 2020) the indication for the use of the device (BTT or DT) is not a limitation criterion of funding or reimbursement. In contrast, the UK is one of the few western regions where DT implants are still excluded due to lack of evidence of cost-effectiveness. As mentioned above, a considerable variability in cost effectiveness assessment exists both in the estimated ICER and in the willingness to pay threshold adopted in each country. Costs may vary substantially in different healthcare systems and parameters estimations for the analysis depend on the data available for the evaluation (Lim *et al.*, 2022).

To exemplify the concept and criticism highlighted above, the most recent analyses on the feasibility of LVADs as DT in UK is presented.

2.2.2. United Kingdom on LVADs as Destination therapy (DT)

In 2021, the National Institute for Health and Care Excellence England recommended LVADs treatment as destination therapy (DT) for end-stage heart failure patients ineligible for cardiac transplantation, but National Health Service (NHS) England did not fund DT at the time. Other Healthcare systems in countries such as the US and some European countries, had already started to use LVAD as DT. However, LVADs were used in the UK only for BTT patients mainly due to the lack of research over cost-effectiveness of LVADs for DT.

The aim of the work was to assess, for the first time, the cost-effectiveness of DT LVADs compared with medical management (MM) in the NHS England. Therefore, a cost-utility analysis was performed using the NHS payer perspective.

A Markov multiple-state economic model was developed using NHS cost data. LVAD survival and adverse event rates were derived from the ENDURANCE Supplemental Trial, while in the absence of contemporary clinical trials, MM survival was based on Seattle Heart Failure Model estimations.

Incremental cost-effectiveness ratios (ICERs) were calculated over a lifetime horizon, and a discount rate of 3.5% per year was applied to costs and benefits.

Table 2.4 shows the deterministic outcomes of the study.

	LVAD	MM	Δ
COSTS	£204 022	£77 790	£126 232
OUTCOMES	3.27 QALYs	0.54 QALYs	2,73 QALYs
ICER			46 207 £/QALY

Table 2.4. ICER of LVADs compared to Medical Management in NSS England. Data from (Schueler et al., 2021)

In conclusion, the implantation of the HeartWare™ HVAD™ System as DT in patients who are ineligible for cardiac transplantation resulted cost-effective in the NHS England healthcare system under the end-of-life willingness-to-pay threshold of £50 000/QALY, which is regarded as a cut-off point for interventions in “end of life” care in the UK healthcare system (Schueler *et al.*, 2021).

Figure 2.8 illustrates the results of the sensitivity analysis tests performed while Figure 2.9. represents the model utilized in the study.

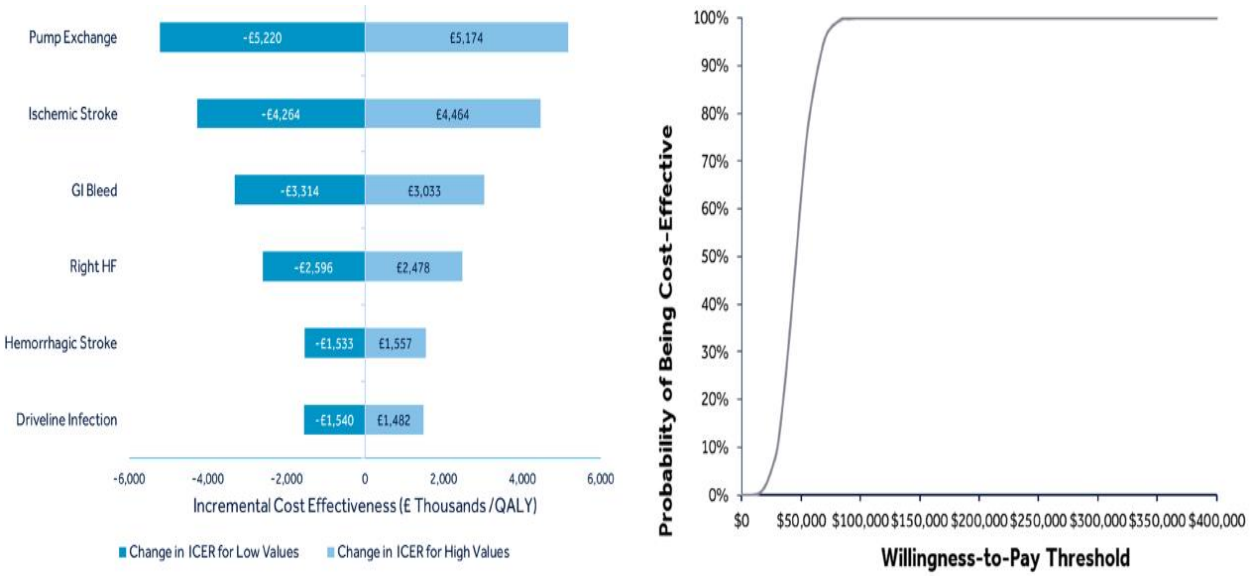

Figure 2.8. Tornado diagram and cost-effectiveness acceptability curve. Sensitivity analysis confirmed the robustness of the deterministic analysis. Image from (Schueler et al., 2021).

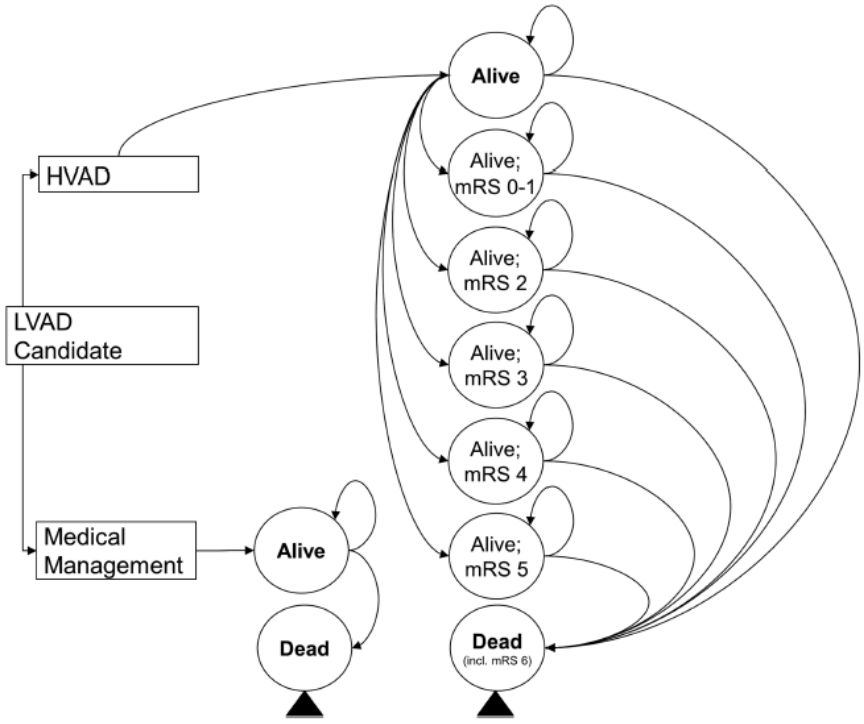

Figure 2.9. The model used for the analysis is a decision tree attached to a Markov model. mRS modified Rankin scale is an indicator of disability used as an outcome measure for stroke patients. Image from (Schueler et al., 2021).

In each cycle of the model used (1 month) alive patients were exposed to therapy related adverse event and death. The probabilities were derived from ENDURANCE and ENDURANCE Supplemental trails. Weibull statistical model was used to extrapolate survival data beyond

the available study follow-up period up to 10 years. AEs considered were GI bleeding, driveline infection, right HF and other requiring hospitalization. Stroke had additional health states to account for different level of stroke severity. Inpatient costs for VAD, including AEs and device from NHS national tariffs and reference costs. Monthly outpatient expenses were taken from a real-world UK database of BTT patients. MM inpatient and outpatient costs comprehensively were taken from the NHS BTT HTA study (2013). Utilities for the LVAD utility were calculated from ENDURANCE, ENDURANCE Supplemental and ADVANCE BTT+ CAP. MM utility based on pre-implant measurement of ENDURANCE and ENDURANCE Supplemental Trials (Rogers *et al.*, 2017; Milano *et al.*, 2018).

The study registered lower ICERs with respect to previous studies for DT population both in Europe and US and the results were in line with contemporary American publications using similar methods (MM survival using SHFM). The estimations for LVAD patients were based on individual patient data from contemporary devices' trials (Schueler *et al.*, 2021).

Limitations of the study were represented by (Faldu *et al.*, 2022):

i) the lack of a contemporary randomized clinical trial comparing LVADs with MM in patients non eligible for heart transplant in the DT indication led to the usage of the SHFM to simulate the comparator;
ii) the utility value for MM patients is considered constant through the years;
iii) the lack of UK DT LVAD data led to the usage of US clinical trials outcomes, which are not necessarily representative of UK common practice outcomes;
iv) the device considered for the analysis is currently recalled from the market.

The fresh debate over LVADs for DT in UK led to another study that developed an indirect comparison between HM3 LVADs and MM to consider the current gold standard device in the comparison. The study proceeded to perform an economic analysis comparing HM3 against HM2 LVADs (data of MOMENTUM3 trial) and a second one comparing MM with first- and second-generation HeartMate XVE and HM2 (based respectively on REMATCH and ROADMAP trials).

The two analyses were ultimately bridged in the form of a meta-analysis resulting in an indirect comparison between HM3 and MM patients over a 5-year horizon (Figure 2.10.).

Despite the limitations exhibited by the method adopted, the ICER was estimated to be £47.361 /QALY with a 97.1% probability of being under the end-of-life willingness to pay threshold of £50.000/QALY. However, ICER was found to vary significantly with the subgroup

of patients chosen: INTERMACS profile 1-3 inotropic dependent patients exhibited ICER of £45.6161/QALY while for INTERMACS profile 4-7 (less ill ambulatory HF) population the ICER was greatly above the average £64.051/QALY. (Lim *et al.*, 2022)

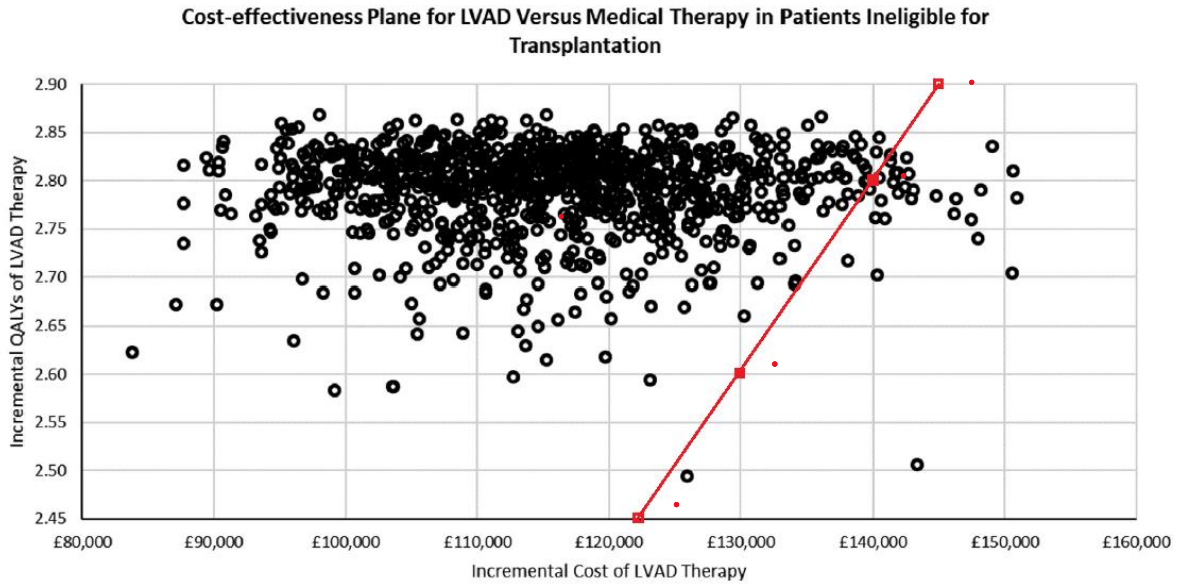

Figure 2.10. Cost-effectiveness plane for LVAD vs MM, time horizon 5 years. The red curve indicates the £50.000/QALY threshold. Image modified from (Lim et al., 2022)

2.2.3. The present and future of cost-effectiveness on LVAD

Traditionally, most CEAs have been designed to give answer for the "average" patient or population, leading to suboptimal outcomes in different patient subgroups. Yet, in an era of increasing individualization of care, there is a higher demand for CEAs that also provide results applicable to the individual patient. For example, when older age and higher comorbidity are associated with higher surgical risks and costs, less invasive treatments may become more attractive, especially when downstream benefits with surgery are foreseen to get minimized by the patient's limited life expectancy. Because CEAs aim at integrating all potential harms and benefits within the analysis, individualized CEAs are uniquely positioned to improve patient selection and guide personalized medical decision-making, further optimizing value of care (Ferket *et al.*, 2018).

Since LVAD cost-effectiveness based on the therapeutic indication (BTT or DT) is almost established, CEA will focus more and more on patient selection and on specific aspects of the treatment to better understand when LVAD therapy provide the most value care.

As observed in a previous study, the subpopulation of patients accessing LVAD therapy determines different cost and different gains in QALYs with respect to the alternative (MM). Fox example, ambulatory patients with advance HF, who are not dependent on intravenous inotropes, experience shorter hospitalizations and better survival on LVAD support than more severely ill patients, yet they still have to face risks due to device complications (Starling *et al.*, 2017). A 2017 CEA attempted to estimate the cost-effectiveness of LVADs for this category of patients in comparison with MM in the context of US Medicare patients. The ICER was determined to be $209.400/QALY as, with respect to MM, LVAD low-risk patients gained 1.74 QALY (0.61 years) at the additional cost of $364.400 over a lifetime ($597.400 per life-year gained). Even if the results of the study are obsolete, it is evident how LVAD costs and outcomes are highly influenced by re-hospitalizations rate, patient management, and severity of the illness at the time of implant (Figure 2.11.) (Baras Shreibati *et al.*, 2017).

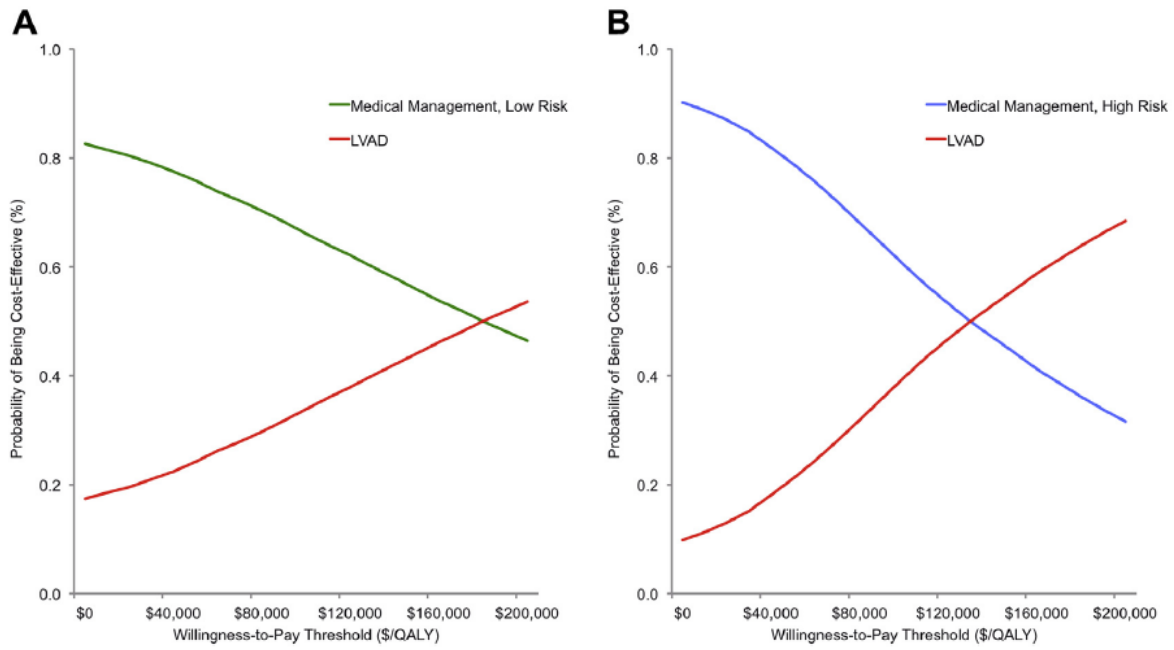

Figure 2.11. Probabilistic sensitivity analysis to estimate preferable therapy between LVAD and MM for low-risk (A) and high-risk (B) patients at each willingness to pay threshold. Image from (Baras Shreibati et al., 2017)

Because of the complexity and variety of cardiovascular diseases require increasingly specific treatment pathways, CEA will evolve to focus on the treatments rather than on the devices themselves. In patients with refractory cardiogenic shock, a recent study tried to estimate the cost-effectiveness of using extracorporeal membranous oxygenation (ECMO) as a bridge to transplant or LVAD implantation. The study unveiled ECMO not to be cost effective, when

used in this contest and, at the same time, suggested that patients undergoing shorter ECMO runs (3 days) paired with better ICERs and longer life expectancy on LVAD support or after transplant (Reza *et al.*, 2022).

These increasingly specific analyses will need to be supported by an abundance of detailed database and trials. One example is the yet to be publish SWEdish, a long missed randomized trial of a left ventricular assist device as DT versus guideline-directed medical therapy on Swedish university hospitals patients with advanced heart failure (Karason *et al.*, 2020).

2.2.4. ITAMACS – the Italian LVAD registry

In the Italian context, no explicit cost-effectiveness threshold exists yet to include therapies into the market, but AIFA decision making correlates with health economic evaluations. High values of ICERs>€40.000/QALY positively impact the outcome of pricing negotiation between AIFA and the manufacturers, especially in medicines for non-onco-immunological and non-rare diseases. New AIFA guidelines (2020) even modified the medicines price setting framework to include mandatory health economic evaluations for some specific therapies (Russo *et al.*, 2023).

The Italian national healthcare system already funds LVADs implantations regardless of BTT or DT indication even though there is no Italian CEA on LVAD therapy yet. LVADs implantation is a common practice in few specialized centres, such as the University-Hospital of Padua; the only data available on a national level reporting on LVADs and total artificial heart (TAH) is represented by ITAMACS retrospective registry, coordinated by CNT (Centro Nazionale Trapianti).

The study enrolled 289 adult patients recruited in 20 Italian centres. 280 patients were treated with LVADs (HeartAssist5,2%; CircuLite Synergy, 2%; INCOR, 8%; Jarvik2000, 24%; HeartMate II, 30%; HVAD, 34%;) and nine were implanted with TAH.

The majority of implants were indicated as BTT (n=142 patients, 50,7%) and the highest median age was registered in the DT group (66,5 years) (Table 2.5.).

	Number of patients [%]	Median age [years]
BTT	49 % (142)	55
DT	36 % (104)	66,5
Bridge to Candidacy	14 % (40)	58
Bridge to Decision	1 % (3)	64
INTERMACS 1	23%	
INTERMACS 2	31%	
INTERMACS 3	30%	
INTERMACS 4	16%	

Table 2.5. Results extrapolated from ITAMACS registry. Data from (Feltrin et al., 2015)

INTERMACS 1 and 2 were prevalent in younger patients (80% in patients aged less than 50y) and in BTT group (65%). INTERMACS 3 and 4 were prevalent in patients over 70y (63%) and in the DT group (59%).

30-day mortality was 10% while 1 year survival was 64.8%. In patients receiving commercially available LVADs (n=275) 1-years survival was correlated to the indication therapy and the INTERMACS profile. Only 43 patients (30% of BTT) obtained biological heart transplant at a mean interval of 345±230 days.

At the time, the number of implants were increasing, from 60 in 2010 to 91 in 2013 and the results were aligned to international data. Unfortunately, these results are not representative of current scenario, but an updated version of ITAMACS has yet to be published (Feltrin *et al.*, 2015).

3. Analysis of costs and effectiveness of LVAD in the Italian context: the case of the University Hospital of Padua

(Acknowledgements: We thank Prof. Gerosa G., Dott.ssa Mastro F. and the Cardiac Surgery Department of the University Hospital of Padua, for kindly providing us with access to the data required for present evaluations).

As anticipated in the previous chapter, the Italian National Healthcare System (NHS) funds LVADs as AHF treatment. However, no CEA on LVAD therapy was ever performed to actually assess the cost-effectiveness of these treatments using data coming from the Italian specialized centres performing these interventions. The data required to perform a complete CEA needs to be very detailed in order to take into account critical aspects of LVADs practice.

The only available data at national level are represented by the ITAMACS registry, which mainly considers clinical data of LVADs patients since its main focus in 2010-2013 was to compare the outcome data of Italian centres with international data (Feltrin *et al.*, 2015).

Nevertheless, data on LVAD recipients, such as rate of re-hospitalizations, reason of re-hospitalization and consequent treatments, length of stay, interventions HF-related pre and post implantation of the device, and measures of the quality of life (QoL) of patients, are essential to quantify costs and outcomes and to validate LVADs treatments and the way they are provided from Italian Hospitals.

Therefore, CEA on LVADs in the Italian context could transparently prove the actual sustainability of LVADs for the Italian-NHS but also it could be allow including patient selection strategies leading to better outcomes and to set different therapeutic prospectives for the device other than bridge-to-transplant (BTT) and end-of-life care (DT).

In the recent RESTAGE-HF prospective multicentre study, timing of referral and a relatively low mean age were decisive to achieve cardiac recovery in patients on LVAD support and subjected to pharmacological therapy to induce cardiac reverse modelling. A 52,3% rate of LVAD explants for myocardial recovery within 18 months and a 90% rate of survival free from the LVAD at 1year and 77% at 2 and 3 years testified the feasibility of LVADs as a Bridge-to-Recovery (BTR) treatment (Birks *et al.*, 2020).

As anticipated in paragraph 1.1.7., one of the main concerns associated with LVAD is the timing of referral to this therapy (McDonagh *et al.*, 2021; Morris *et al.*, 2021).

Over time, the phenotype of the LVAD recipient has changed. Compared with LVAD recipients from 2010-2014, patients implanted in the United States from 2015-2019 had more comorbidities and social obstacles to direct transplant candidacy. Contemporary VAD recipients increasingly require preoperative temporary MCS support (52% were in some degree of cardiogenic shock). These trends are mirrored in the global population of LVAD recipients. Although the increasing number of patients referred for LVAD therapy may be related to growing awareness of advanced HF, the increasing illness severity of these patients suggests that timing of referral to advanced HF centres may be too delayed. These late referrals can lead to LVADs implantations in patients too far advanced that progressive or irreversible end-organ damage has occurred, causing LVADs to be poorly beneficial and prevent improvements of myocardial function (Varshney *et al.*, 2022).

The estimation of the proper referral timing might be useful not only to provide the best value cure for the recipients but also to ensure for actual economic sustainability of this therapeutic pathway, especially for the Italian-NHS. Therefore, a CEA analysis comparing timely referred LVADs patients with respect to late referred ones would highlight the gap in costs and effectiveness between the two populations accessing the same treatment and spread awareness over the opportunity loss for these patients. Ultimately, CEA might be useful to suggest a timing for "cost-effective" implantation.

In the following, a preliminary study on the interventions carried out at the Cardiac Surgery Department of the Padua University Hospital is presented, paving the way for a complete cost-effectiveness analysis with a particular focus over the timing of referral.

3.1. Methods

3.1.1. Study Design

A retrospective nonrandomized single centre preliminary study is presented, considering 20 subjects enrolled from one of the Italian centres with the most experience in LVAD implantation: the University Hospital of Padua (Zucchetta *et al.*, 2014; Tarzia *et al.*, 2016, 2023; Loforte *et al.*, 2021).

Twenty patients with chronic advance heart failure (AHF) receiving Jarvik 2000 continuous axial flow LVAD, Heart Ware HVAD and Heat Mate III continuous centrifugal flow LADs were enrolled.

A key inclusion criterion of the study was to select patients who underwent LVAD implantation at the Cardiac Surgery department of the University-Hospital of Padua from April 2016 until March 2023, regardless of their LVAD indication, which was either BTT, Bridge to Candidacy (BTC) or DT.

3.1.2. Objectives of the Study

The main objective of the study was to provide a preliminary assessment of the effectiveness of LVAD implantation, considering the characteristics of the patients, their survival at 1, 6 and 12 months and their re-hospitalization rate.

A second objective was to develop a model to perform a cost-effectiveness analysis (CEA) of LVAD implantation comparing patients referred timely to LVAD therapy with late referred ones.

3.2. Preliminary results and Modelling for CEA

3.2.1. Baseline characteristics of patients

3.2.1.1. Pre-LVAD implantation

The study cohort consisted of twenty patients with a mean age at the time of the implantation of 59.85 years (max=75, min=12), accounting for two paediatric patients. Patients were prevalently male 18/20 (90%) and with a body mass index (BMI) = 23.87 ± 6.63.

Most of the patients (13) were diagnosed with post ischemic heart failure, while the remaining part was affected by primary dilated cardiomyopathy (4) or developed HF because of myocarditis (2). Note that all post ischemic heart failure diagnosed patients would be excluded from the RESTAGE-HF to achieve myocardial recovery (Birks *et al.*, 2020).

Left ventricular ejection fraction (LVEF) was reduced (<35%) in all patients. The most severe case reported LVEF= 8%, while mean LVEF= 23%. The majority of patients exhibited also a reduced right ventricle systolic function (13mm < TAPSE <20mm) and depressed FAC (area difference between RV end-diastolic and end-systolic < 30%), implying a right ventricle reduction in contractility. No patients experienced improvements in ejection fraction (EF).

During their history with HF prior to LVAD implantation, patients underwent other surgeries, such as percutaneous transluminal coronary angioplasty (PTCA) in combination with drug

eluting stent (DES) (11/20), single or multiple coronary artery bypass graft surgery (CABG) (3/20), mitralclips (1/20) and atrial-flow regulator (1/20).

Most patients (17/20) were treated with cardiac re-synchronization therapy (CRT-D) thanks to implantable cardioverter-defibrillator (ICD).

Eight patients required temporary mechanical circulatory support (t-MCS) prior to LVAD implantation: ECMO (4/20), intra-aortic balloon pump IABP (2/10), paracorporeal LVAD (2/20), RVAD levitronix (1/20), and apical left ventricular vent (1/20).

Frequent flyer for AHF were recorded for most of patients (17/20).

The average age at which patients developed HF was 49 years and the intercurrent time between HF diagnosis and LVAD implantation was 10.8 years on average.

At the time of implantation, the INTERMACS profiles of most patients were equally distributed in the INTERMACS 1-3 groups, while only 3 patients were registered as INTERMACS 4 profile.

INTERMACS 1	6/20
INTERMACS 2	5/20
INTERMACS 3	6/20
INTERMACS 4	3/20

Table 3.1. INTERMACS profiles reported in the pool.

3.2.1.2. After-LVAD implantation

All 20 patients of the cohort underwent LVAD implantation. Since surgeries were performed between April 2016 and March 2023, the device implanted was the one used at the University-Hospital of Padua in those years. As already said, LVADs devices utilized were: HM3 (16/20), Jarvik 2000 (2/20) and Heart Ware HVAD (2/20).

HM3	16/20
JARVIK2000	2/20
HVAD	2/20

Table 3.2. Types of devices implanted.

Patients were implanted with the therapeutic indications reported in *Table 3.3.* Destination therapy (DT) population had a mean age of 70,5 at the time of implantation, while BTT and BTC were reported to be 59,4 y.o. (or 50 including paediatric patients) and 63 respectively on average. These data testified that patients involved in the study were referred to LVAD therapy around 4 years later than the national average resulted from the ITAMACs registry for every indication (Feltrin *et al.*, 2015).

DT	8/20
BTT	9/20
BTC	3/20

Table 3.3 LVAD indication to therapy in the pool.

During the first year of LVAD support, a total of 26 re-hospitalizations were experienced just by 9 patients. The longest hospitalization experienced was 160 days, while the majority of the longest hospitalizations lasted around 25 days. The re-hospitalization causes and treatments required are reported in *Table 3.4*.

Right heart failure	5 patients
Infections/sepsis	2 patients
Exite infections	4 patients
arrhythmias	1 patient
Checklist/TCO (heart transplant)	5 patients
ICD substitution	1 patient
Others	
TREATMENTS	
Intubation IoT	5 patients
Inotropes	4 patients
CVVH (haemodialysis)	3 patients
Blood transfusion	4 patients

Table 3.4. Re-hospitalization causes and treatments required from LVAD patients in the pool.

Other interventions and adverse events recorded during LVAD support were: bleeding (3/20), ECMO support post TCO/LVAD (3/20), RVAD implantation (2/20), tracheotomy to address respiratory failure (1/20), hypoxic ischemic encephalopathy (coma)(1/20), removal of intestinal ischemia(1/20), LVAD thrombosis (1/20) and exit cable substitution(1/20).

3.2.2. Outcomes Analysis

3.2.2.1. Survival

The average time spent on LVAD support was of 1 year and 2 months in this pool, with two patients experiencing around five years survival after implantation.

Perioperative deaths, within 30 days from the implant, interested 3 patients who all were reported as INTERMACS 2 profile while none of them was indicated for LVAD as Bridge-to-Transplant (BTT) and their mean age was around 70 years.

At 6 months from the intervention, 8 patients had died on LVAD support and one exited the study as no more records were available.

At 12 months, 8 patients were still alive on LVAD support while two patients underwent heart transplant respectively at 7 and 9 months after LVAD implant. Therefore, ten out of nineteen (52,6%) patients were still alive at 12 months. ITAMACs survival at one year was 64.8% (Feltrin *et al.*, 2015). Figure 3.1 shows the survival curve for the considered pool of LVAD recipients.

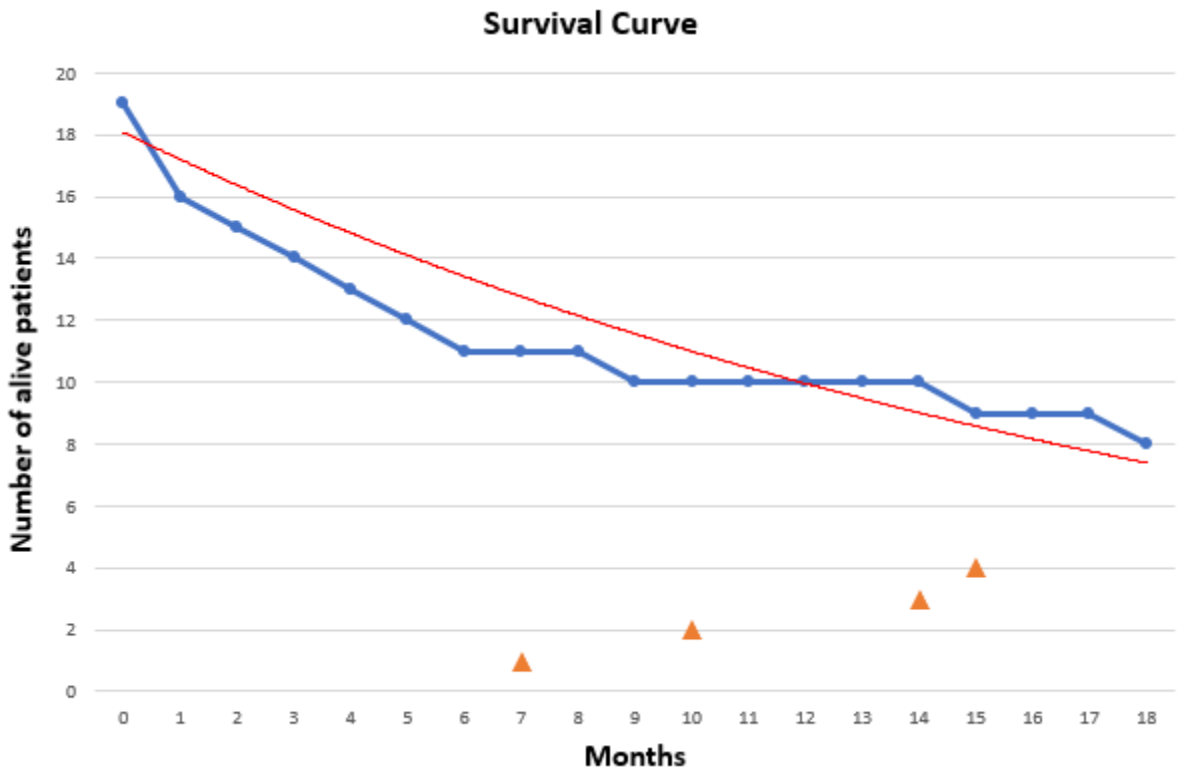

Figure 3.1 Survival curve derived from the pool (18 months). Occurrence of heart transplant is reported in orange triangles.

Among patients with BTT as LVAD indication, 4/9 (44%) received heart transplant and three died within 1 year on device support. One patient never achieved heart transplantation but was reported to be still alive after 3 years and 8 months on LVADs support (INTERMACS 4 profile at the time of the implant). One patient was excluded from the study since no more report was available after five months. These results are slightly more encouraging with respect to ITAMACs results (30% BTT transplanted) (Feltrin *et al.*, 2015).

Since a two or less years HF duration before LVAD implantation showed to increase the odds of device ex-plantation, the cohort was divided into two group (Varshney *et al.*, 2022).

One death and one transplant between the 6th and 12th month of LVAD support were recorded in the group of patients implanted within two years from the onset of HF (6/20). Two of the remaining patients were still alive at five years from implantation and one died one year after the heart transplant. The rate of LVAD ex-plantation was 33%.

In the group of patients implanted more than two years after LVAD implantation, from the onset of HF (14/20) the mortality was 21,4%, 61,5% and 69,2% at 1, 6 and 12 moths respectively. The rate of LVAD ex-plantation was 15,4% accounting for 2 LVAD ex-plantation in favour of heart transplantation.

The two years threshold was extended to 5 years, according to the recruitment criteria of RESTAGE-HF study to achieve myocardial recovery, to account for different rates related to the threshold change but no difference was recorded since no patient was implanted in the 3-5 years from HF diagnosis range (Birks *et al.*, 2020).

As highlighted above, most of the patients were treated with Heart Mate III (16/20) and the remaining part with Jarvik 2000 (2/20) and Heart Ware HVAD (2/20). Therefore, it is impossible to make a comparison of the outcomes with respect to the different models of device implanted, even though according to other real-world study, Heart Mate III achieved increased survival and reduced re-hospitalizations with respect all other LVADs on the market (Pagani *et al.*, 2021).

In this study, patients treated with Jarvik 2000 were both in their mid-seventies indicated to LVAD as DT and they had reached different outcomes (3 months vs 5 years survival on support). Patients treated with Heart Ware HVAD were in their mid-sixties, one of those achieving transplant after 7 months on support and the other one died at two months while waiting for candidacy to transplant.

3.2.2.2. Re-hospitalization rates

DT and older patients (since age is correlated with LVAD indication therapy) reported on average a lower rate of hospitalizations than BTT patients. The data available showed a rate of 0,88 for DT patients and of 2,1 for BTT ones over their time on LVAD support. These results might be conditioned by an average high mortality of DT patients in the first four months (5/8) on support, leading to less odds for re-hospitalization. It is worthy to notice that patients, who did not survive the perioperative thirty days, might have never left the hospital after implantation and therefore never experienced re-hospitalization.

Rate of hospitalization correlated with the timing of AHF referral reported an average re-hospitalization rate over LVAD support of 1,14 for “late referred” patients and 1,66 for those implanted with LVAD within two years from HF diagnosis. This difference between the two groups might be due to a longer average time on support experienced by the “timely referred” group (26,6 months vs 8,9 months), which led to greater opportunity of re-hospitalization with respect to the late referred group.

3.2.3. Analysis of Costs

The data available refers to patients’ history with HF pre and post LVAD implantation; hence, interventions and associated costs for each patient might show the differences in therapeutic pathway between late and timely referred patients.

In terms of costs, the comparison between these two populations could be performed considering either a limited set of costs strictly related to the LVAD implantation or the complete set of costs for health care services and drugs provided to LVAD recipients. The model proposed in the following could be adapted in both cases.

In the first case, each intervention and re-hospitalization should be assessed in terms of the corresponding DRG rate. For hospitalizations exceeding the maximum number of days for each specific single DRG (trim point) an extra daily tariff has to be applied to compensate for each day above the trim point.

Surgery for LVAD implantation alone is classified as DRG 103 “Heart transplant or cardiac assist system implantation” which value is 64.248,09 €, according to the updated DRG rates set by the Veneto Region (Regional Council Resolution dgr n. 426/2021). However, the DRG 103 value do not account for the cost of the device and periodical battery substitutions, which were estimated to be around 80.000 € and 11.000 €, respectively. Therefore, in 2014 the Veneto region decided an additional valorisation of 91.000 € for hospitalizations, which required durable LVAD implantation (dgr n. 2310/2014) and this value have been confirmed in 2021 (dgr n. 1026/2021). Therefore, the current valorisation for LVAD implantation sums up to 155.248,09 € (the trim point value associated to DRG 103 is 260 days).

In the second case, adopting a complete notion of costs would require the actual quantification of all the costs associated with the LVAD intervention, regardless of the value of the Drg tariff and this could be performed quantifying analytically the utilization of

healthcare resources for each single patient. This latter option is the most detailed one, but it is particularly challenging as it would require a long searching process of medical records with a high associated risk of missing information that might lead to underestimated costs.
Moreover, even in this case, the CEA would consider only the healthcare system perspective while a complete analysis should call for measuring also the indirect costs related to LVAD implantation (eg. productivity losses fro patients and their caregivers).
However, even limiting attention only to the costs directly incurred by the healthcare system, unfortunately the data available resulted from a preliminary search of patients' medical records are incomplete and some information are missing (e.g., the DRG associated to each intervention or the length of every re-hospitalization). Hence, a more detailed search is required to achieve more precise information about patients' re-hospitalizations and related lengths of stay, drugs administered and screening exams in order to access costs for each type of patients.
Moreover, the limited number of patients available for the current preliminary study would lead to unreliable estimations, when CEA is developed using a Markov model.

3.2.4. Modelling for CEA

In order to assess the cost-effectiveness of LVADs in patients undergoing implantation at the University Hospital of Padua with respect to their timing of referral, it is necessary to create a model that represents all the possibilities patients might encounter related to HF and LVAD.
Focusing on events occurring after LVAD implantation, the two populations do not differ for therapeutic pathway but just for the timing they are indicated to therapy. Furthermore, duration of hospitalizations and different patients' health conditions have to be taken into account. For these reasons, the Markov model was chosen to interpret both populations treatments.
Under this perspective, the Markov model does not need to differ in structure while dealing with these two populations, since the possible therapeutic pathway is the same. The only adjustments required is to set different probabilities to each health status transaction with respect to the population of choice.
In this context, the probabilities to move from one health status to another should be derived from the data available from University Hospital of Padua records.

However, since the current study does not have enough data to calculate reliable probabilities and costs, in the following three different possible models will be described, each one with different complexity, which might be used in future CEA evaluations, when more and more complete data would be retrieved.

3.2.4.1. First model: Multiple re-hospitalizations model

In this model, patients enter the simulation in the "Alive" compartment and at every iteration of the model they can either stay in that compartment, or move to first re-hospitalization compartment, heart transplant (THX) or Death compartment. The model would account for the length of stay of the hospitalizations, thanks to the possibility to stay in the hospitalization compartment for more than on cycle, and differentiates the probability for dying, undergoing THX and being re-hospitalize multiple times whether patients experienced previous re-hospitalization.

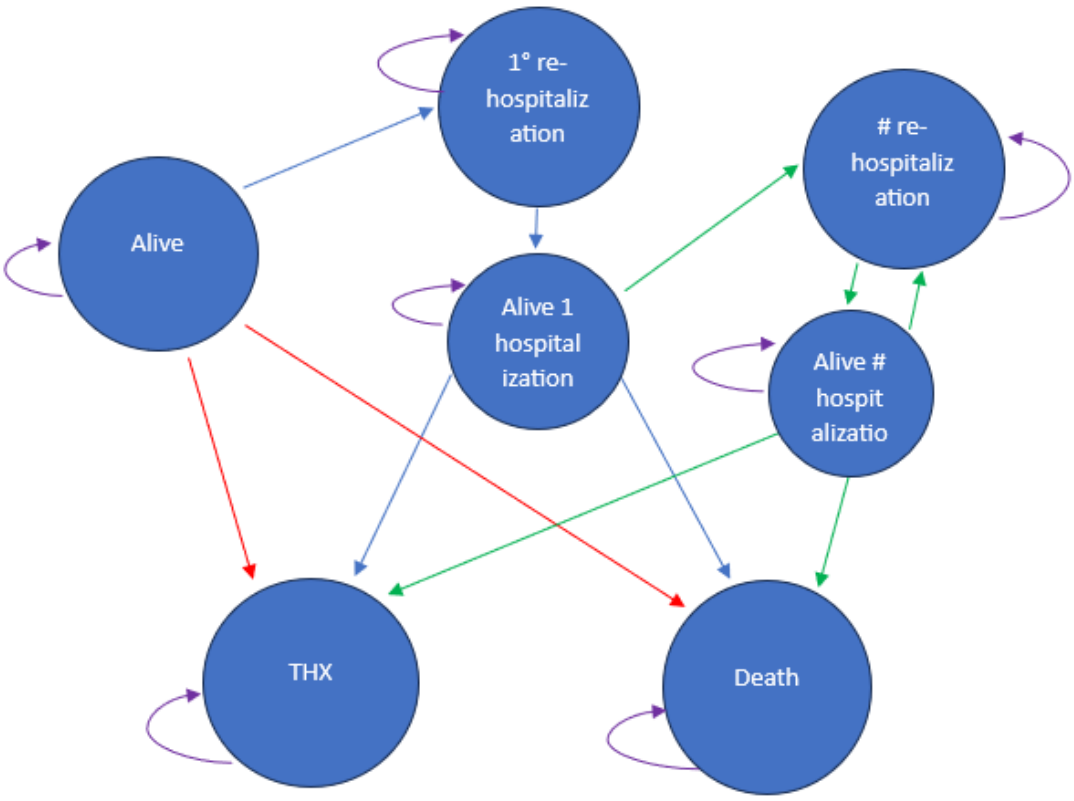

Figure 3.2. First Markov model proposal, including more than one hospitalization compartment.

This model design emphasizes the inclusion of subsequent re-hospitalization(s) and differentiating probabilities, but it does not account for the different impact of re-hospitalization types on transition probabilities. Furthermore, for each re-hospitalization compartment, a different re-hospitalization type might be sorted since it is not known a priori. The iteration value might be set with respect to the considered and prospective chosen.

This model is the more complex of the three and requires for a more precise characterization of patients as well as for a deeper analysis of medical records than the one available for the preliminary analysis.

3.2.4.2. Second Model: Simplified Multiple re-hospitalization model

The second model is a simplification of the previous one. It consists of four-compartments (Alive, Hospitalized, THX and Death) and it resumes the possibility of being re-hospitalized several times with the double arrows between the Alive and Hospitalized compartments. This simplification would lead to less precision in the estimates of costs and outcomes but accommodates to the possibility of missing information in the records. In particular, the results from this model would highlight whether macro-differences in cost effectiveness exits in the comparison between the two populations, but they also might be less stable when tested with sensitivity analyses.

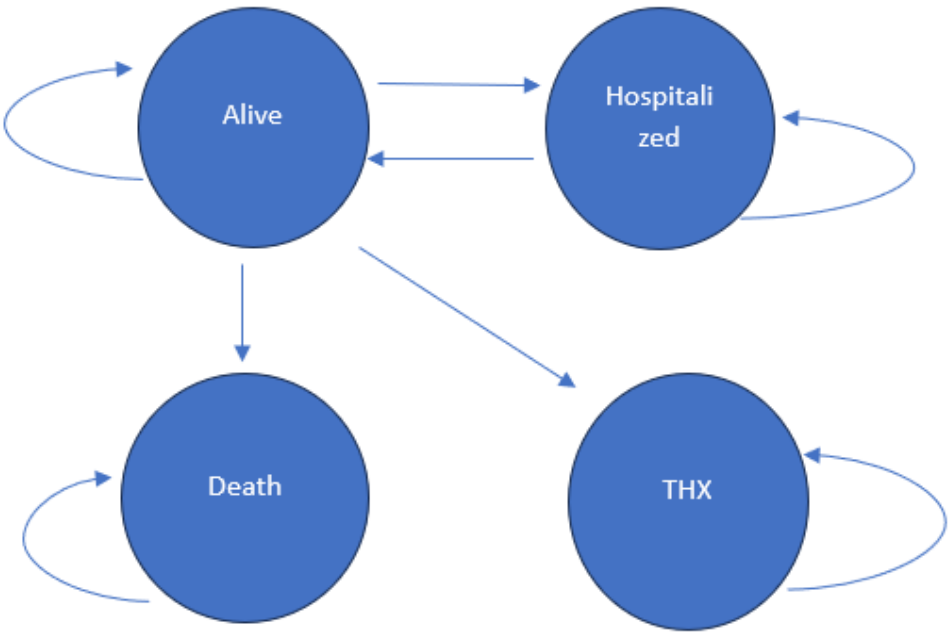

Figure 3.3. Second Markov model proposal, including only one hospitalization compartment.

3.2.4.3. Third Model: Department specific re-hospitalization model

This model differs from the previous two models as it focuses on the probability to be hospitalized in a specific department rather than on the probability to be re-hospitalized per se. This model is flexible, as it is straightforward and can overcome the lack of information in the records without loss in the integrity of the model. The information related to patient hospitalization department are always available, leading to precise estimation for the probability of being hospitalized in a given department.

For the sake of simplicity, Figure 3.4. just illustrates two of the re-hospitalization departments presented in the preliminary data. The complete set of departments considered would be: heart surgery department (CCH department), post-operative unit care of CCH department and others (T.I.P.O. intensive care), department of cardiology, general medicine department and general surgery department.

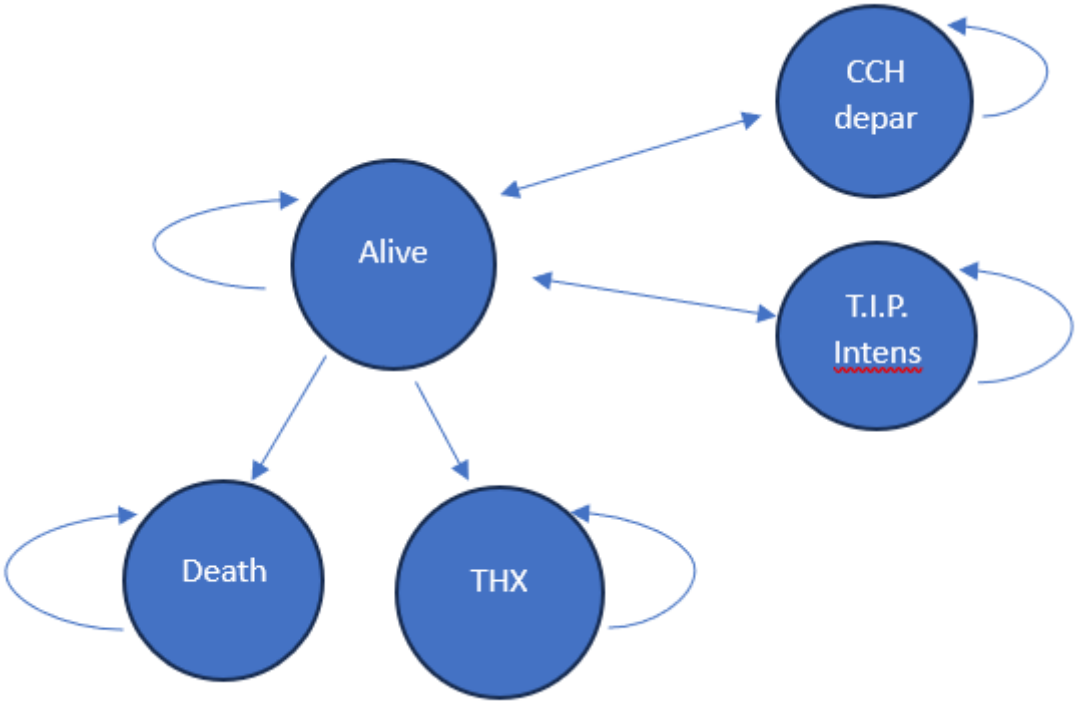

Figure 3.4. Third Markov model proposal, including specific probabilities for types of hospitalization.

3.2.4.4. Limitations in assigning probabilities and costs

For all the models presented above, the reason for each occurring readmission, treatments and, hence, the cost and outcomes associated with that specific readmission, have to be gambled with respect to the probability extrapolated from the dataset.

However, in the preliminary data there is no specific correspondence between how many days patients spent in a specific hospital department as well as the DRG they were assigned to. Furthermore, the amounts of certain treatments (e.g., inotropes) for each patient are not specified leading to the impossibility of estimating the costs involved.

4. Conclusions

Advanced heart failure (AHF) is an under studied stage of heart failure (HF), which is destined to afflict an increasing number of subjects due to the increasingly aging of population. The risk of mortality for this condition is really high and the costs for the more advanced therapeutic solutions available are high as well. Therefore, it is fundamental for the healthcare system to rely upon cost-effective care to deal with the burden of resources that these treatments are associated with. The shortage of heart donors, the long waiting lists, and the ineligibility of some patients for heart transplantation, led clinicians to rely on Left Ventricular Assist Devices (LVADs) implantation. However, the considerable amount of severe adverse events, suboptimal patients' management strategy, and late referral to these long-time used devices, are determinant for loss in effectiveness and increase in costs. Recently published cost effectiveness analysis (CEA) focused on whether LVAD therapy is cost-effective with respect to the indication therapy, i.e. BTT and DT. However, one of the greatest determinants of the success of these therapies, promoting in some cases myocardial recovery, is the device timing for implantation.

In the present work, a preliminary set of subjects was retrieved among the latest patients implanted with LVAD at the Cardiac Surgery Department of the Padua University Hospital.

The present study have analysed the baseline characteristics of the pool of patients before and after LVAD implantation and compared therapeutic outcomes with respect to the timing of referral, reporting better survival, more re-hospitalizations and a double rate of device explantation in patients timely referred. At the time of implantation, patients were found to be on average four years older with respect to the National average and reported poorer survival rate at 1-year from implantation.

In order to perform a complete CEA of LVADs comparing late and timely referred populations, three different Markov models were proposed to simulate the AHF related events which patients could face after LVAD implantation.

In conclusion, the differences between timely and late referred here reported should be further investigated on the basis of the framework proposed in the present study, increasing the number of patients enrolled and refining searching methodologies of medical records.

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