



**VILNIUS UNIVERSITY
FACULTY OF MEDICINE**

Medicine Study Program

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INTEGRATED STUDY MASTER'S THESIS

**A Comparison of Outcomes Among the Patients with Mechanical Circulatory Support
Devices and Heart Transplantation**

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Vilnius, 2026

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Summary

Heart failure is a major and growing global health burden, and a clinically important subgroup of patients progress to advanced heart failure despite guideline-directed medical therapy. At this stage, conventional treatment is often insufficient, and definitive therapies such as durable mechanical circulatory support, particularly left ventricular assist devices, and orthotopic heart transplantation must be considered. Heart transplantation has historically been regarded as the gold-standard therapy for eligible patients, but its use is limited by donor scarcity, strict candidacy criteria, and long-term complications related to immunosuppression. In parallel, left ventricular assist device therapy has evolved from an experimental bridge-to-transplant strategy into an established long-term treatment option, especially with contemporary third-generation devices such as the HeartMate 3.

The aim of this thesis was to critically evaluate contemporary evidence comparing durable mechanical circulatory support and orthotopic heart transplantation in patients with advanced heart failure. The objectives were to compare survival outcomes, complication profiles, quality of life and functional outcomes, healthcare utilization and costs, and to assess how patient selection and timing of therapy influence interpretation of these outcomes. This thesis was conducted as a structured literature review using contemporary adult studies identified through PubMed and Embase. Because of heterogeneity in study design, patient populations, device generations, outcome definitions, and follow-up duration, the evidence was synthesized qualitatively rather than by meta-analysis.

The reviewed evidence shows that survival after left ventricular assist device implantation has improved substantially across device generations. Contemporary HeartMate 3 therapy has narrowed the early and intermediate-term survival gap with heart transplantation, particularly compared with older devices. However, heart transplantation retains the most mature long-term survival evidence. Survival comparisons are therefore strongly dependent on follow-up duration, device generation, treatment indication, and patient selection. Heart transplant recipients are highly selected for transplant eligibility, operative fitness, pulmonary vascular status, end-organ function, psychosocial stability, and ability to adhere to lifelong immunosuppression. Left ventricular assist device cohorts are broader and include

bridge-to-transplant, bridge-to-candidacy, and destination-therapy patients with greater heterogeneity.

The complication profiles of the two therapies differ fundamentally. Left ventricular assist device morbidity is mainly driven by hemocompatibility-associated and device-related complications, including gastrointestinal bleeding, stroke, infection, right heart failure, arrhythmias, aortic regurgitation, and device malfunction. Although HeartMate 3 has markedly reduced pump thrombosis and stroke compared with earlier devices, gastrointestinal bleeding, driveline infection, and right heart failure remain clinically important. Heart transplantation complications are primarily related to primary graft dysfunction, rejection, cardiac allograft vasculopathy, lifelong immunosuppression, infection, malignancy, and renal dysfunction. Thus, the therapies expose patients to different long-term risks rather than simply differing in overall complication burden.

Both therapies improve quality of life and functional status in advanced heart failure. Contemporary left ventricular assist device therapy produces substantial early improvement in functional class, patient-reported health status, and exercise capacity, but recipients remain affected by device dependence, driveline care, battery management, infection anxiety, readmissions, and psychological stress. Heart transplantation avoids external device dependence and provides durable functional recovery among selected recipients, but long-term outcomes remain influenced by graft surveillance, immunosuppression, renal dysfunction, malignancy risk, and cardiac allograft vasculopathy. Healthcare utilization is substantial for both therapies, especially early after intervention. Contemporary data suggest that elective HeartMate 3 implantation and primary heart transplantation may have similar early cost trajectories, whereas urgent left ventricular assist device implantation is more resource-intensive because of greater critical-care and organ-support requirements.

Overall, this thesis concludes that durable mechanical circulatory support and heart transplantation should be viewed as complementary rather than strictly competing therapies. Heart transplantation remains preferred for eligible patients with suitable donor access and the strongest long-term evidence base. Contemporary HeartMate 3 left ventricular assist device therapy offers an increasingly effective alternative for patients awaiting transplantation,

temporarily ineligible for transplantation, or unsuitable for transplant. The most clinically meaningful comparison is therefore not simply left ventricular assist device versus heart transplantation, but timely and individualized allocation according to patient biology, reversibility of end-organ dysfunction, right ventricular reserve, transplant eligibility, organ availability, and treatment goals. Future research should prioritize longer-term HeartMate 3 outcomes, standardized definitions, improved risk prediction, and direct comparisons within the same healthcare systems.

Summary (in Lithuanian)

Širdies nepakankamumas yra ūmi ir vis auganti sveikatos priežiūros problema pasaulyje, o kliniškai reikšminga pacientų dalis progresuoja iki pažengusio širdies nepakankamumo, nepaisant gairėmis pagrįsto medikamentinio gydymo. Esant tokiai situacijai, įprastinis gydymas dažnai yra neveiksmingas, todėl yra būtina apsvarstyti radikalius gydymo metodus, tokius kaip ilgalaikis mechaninis kraujotakos palaikymas, ypač kairiojo skilvelio pagalbiniai prietaisai, ir ortotopinė širdies transplantacija. Širdies transplantacija istoriškai buvo laikoma auksiniu standartu tinkamiems pacientams, tačiau jos taikymą riboja donorų trūkumas, griežti kandidatų atrankos kriterijai ir ilgalaikės komplikacijos, susijusios su imunosupresija. Tuo tarpu kairiojo skilvelio pagalbinių prietaisų terapija iš eksperimentinės, tarpinės strategijos prieš transplantaciją, išsivystė į pripažintą ilgalaikio gydymo galimybę, ypač pasitelkiant šiuolaikinius trečiosios kartos prietaisus, tokius kaip „HeartMate 3“.

Šio baigiamojo darbo tikslas buvo kritiškai įvertinti dabartinius duomenis, lyginančius ilgalaikį mechaninį kraujotakos palaikymo ir ortotopinės širdies transplantacijos gydymo būdų tinkamumą pacientams, sergantiems pažengusio širdies nepakankamumo forma. Šio darbo uždaviniai buvo palyginti išgyvenamumo rodiklius, komplikacijų profilius, gyvenimo kokybės ir funkcinis rezultatus, sveikatos priežiūros sektoriaus išteklių naudojimą bei kaštus, taip pat įvertinti, kaip pacientų atranka ir gydymo laiko parinkimas daro įtaką šių rezultatų interpretacijai. Šis baigiamasis darbas atliktas vadovaujantis struktūrinės literatūros apžvalga, naudojant šiuolaikinius suaugusiųjų tyrimus, atrinktus iš „PubMed“ ir „Embase“ duomenų bazių. Dėl tyrimų dizaino heterogeniškumo, pacientų populiacijų, prietaisų kartų, radinių apibrėžčių ir pacientų sekimo trukmės, rezultatai buvo apibendrinti kokybiškai, o ne atliekant metaanalizę.

Apžvelgti tyrimai rodo, kad pacientų išgyvenamumo tikimybė po kairiojo skilvelio pagalbinio prietaiso implantacijos reikšmingai padidėjo keičiantis prietaisų kartoms. Šiuolaikinė „HeartMate 3“ terapija sumažino skirtumą tarp mažo ir vidutinės trukmės išgyvenamumo rodiklių, lyginant su širdies transplantacija, ypač lyginant su senesniais prietaisais. Vis dėlto, širdies transplantacija išlaiko patikimiausius ilgalaikio išgyvenamumo įrodymus. Būtent todėl išgyvenamumo rodiklių palyginimai labai priklauso nuo stebėjimo trukmės, prietaiso kartos, gydymo indikacijos ir pacientų atrankos. Širdies transplantacijai tinkami pacientai yra kruopščiai atrenkami pagal jų tinkamumą transplantacijai, operacinę riziką, plaučių kraujagyslių būklę, gyvybiškai svarbių organų funkciją, psichosocialinį stabilumą ir gebėjimą prisitaikyti prie visą gyvenimą trunkančios imunosupresijos režimo. Kairiojo skilvelio pagalbinių prietaisų kohortos yra platesnės ir apima pacientus, kuriems prietaisas taikomas kaip tarpinis gydymas iki transplantacijos, tarsi „tiltas“ iki tinkamumo transplantacijai arba kaip galutinis gydymo metodas, todėl jos pasižymi didesniu heterogeniškumu.

Šių dviejų gydymo metodų komplikacijų profiliai iš esmės skiriasi. Kairiojo skilvelio pagalbinių prietaisų sukeltą sergamumą daugiausia lemia su hemokompatibilumu ir prietaisu susijusios komplikacijos, įskaitant kraujavimą iš virškinamojo trakto, insultą, infekciją, dešiniojo širdies skilvelio nepakankamumą, aritmijas, aortos regurgitaciją ir prietaiso veikimo sutrikimas. Nors „HeartMate 3“ reikšmingai sumažino siurblio trombozę ir insultą, lyginant su ankstesniais prietaisais, virškinamojo trakto kraujavimas, ir dešiniojo širdies skilvelio nepakankamumas išlieka kliniškai reikšmingi. Širdies transplantacijos komplikacijos pirmiausia yra susijusios su pirminiu transplantato funkcijos sutrikimu, atmetimu, širdies alotransplantato vaskulopatija, visą gyvenimą trunkančia imunosupresija, infekcija, piktybiniais navikais ir inkstų funkcijos sutrikimu. Taigi, šie gydymo metodai pacientams kelia skirtingas ilgalaikes rizikas, o ne tiesiog skiriasi bendra komplikacijų našta.

Abu gydymo metodai gerina gyvenimo kokybę ir funkcinę būklę sergant pažengusiu širdies nepakankamumu. Šiuolaikinė kairiojo skilvelio pagalbinių prietaisų terapija lemia reikšmingą spartų funkcinės klasės, pacientų nurodomos sveikatos būklės ir fizinio krūvio tolerancijos pagerėjimą, tačiau pacientai išlieka priklausomi nuo prietaiso, išorinio kabelio priežiūros, baterijų valdymo, nerimo dėl infekcijos, pakartotinės hospitalizacijos ir psichologinio streso. Širdies transplantacija leidžia išvengti priklausomybės nuo išorinio prietaiso ir atrinktiems

pacientams užtikrina ilgalaikį funkcinį atsistatymą, tačiau ilgalaikiai rezultatai priklauso nuo transplantato stebėsenos, imunosupresijos, inkstų funkcijos sutrikimo, piktybinių navikų rizikos ir širdies alotransplantato vaskulopatijos. Sveikatos priežiūros išteklių naudojimas yra svarbus taikant abu gydymo metodus, ypač ankstyvuojų laikotarpiu po intervencijos. Šiuolaikiniai duomenys rodo, kad planinė „HeartMate 3“ implantacija ir pirminė širdies transplantacija gali turėti panašias pirminių kaštų tendencijas, tuo tarpu skubi kairiojo skilvelio pagalbinio prietaiso implantacija reikalauja daugiau resursų dėl didesnių intensyviosios terapijos ir organų funkcijų palaikymo poreikių.

Apibendrinant, šiame baigiamajame darbe daroma išvada, kad ilgalaikis mechaninis kraujotakos palaikymas ir širdies transplantacija turėtų būti vertinami kaip vienas kitą papildantys, o ne griežtai konkuruojantys gydymo metodai. Širdies transplantacija išlieka veiksmingiausiu pasirinkimu tinkamiems pacientams, turintiems prieigą prie tinkamo donoro, mat turi stipriausią ilgalaikių įrodymų pagrindą. Šiuolaikinė „HeartMate 3“ kairiojo skilvelio pagalbinio prietaiso terapija siūlo vis tobulėjančią alternatyvą pacientams, laukiantiems transplantacijos, laikinai netinkamiems transplantacijai ar transplantui. Turint tai omenyje, kliniškai reikšmingiausias palyginimas nėra tiesiog kairiojo skilvelio pagalbinis prietaisas prieš širdies transplantaciją, bet laiku atliktas ir individualizuotas gydymo paskyrimas, atsižvelgiant į paciento biologinius ypatumus, kritiškai svarbių organų funkcijos sutrikimo grįžtamumą, dešiniojo skilvelio rezervą, tinkamumą transplantacijai, organų prieinamumą ir gydymo tikslus. Būsiami tyrimai turėtų prioritezuoti ilgalaikius „HeartMate 3“ rezultatus, standartizuotas apibrėžtis, tikslesnę rizikos prognozę ir tiesioginius palyginimus tose pačiose sveikatos priežiūros sistemose.

Keywords

Advanced heart failure; durable mechanical circulatory support; left ventricular assist device; HeartMate 3; orthotopic heart transplantation; survival outcomes; complications; quality of life; functional outcomes; healthcare utilization; patient selection; bridge-to-transplant; destination therapy.

Introduction

Heart failure (HF) represents the terminal pathway of a wide spectrum of cardiovascular diseases and remains a major contributor to global morbidity and mortality, affecting an estimated 64 million individuals worldwide. (1) This persists despite significant advances in pharmacological and device-based therapies. Epidemiological projections from the United States suggest that the prevalence of HF may increase by nearly 46% between 2012 and 2030, reflecting both an aging population and improved survival from other cardiovascular conditions. (1) Collectively, these trends underscore the growing and sustained burden of HF as a chronic, global health challenge. (2) Failure to adequately recognize its prevalence, incidence, morbidity, and mortality has important implications not only for patient outcomes but also for escalating healthcare utilization and economic cost.

Advances in medical and technological management have enabled patients with HF to survive longer than ever before. However, this has also led to the emergence of a distinct and increasingly prevalent clinical entity: advanced heart failure (AHF). This subgroup of patients is characterized by persistent symptoms, recurrent decompensation, and poor prognosis despite optimal guideline-directed therapy, representing a critical stage at which conventional management strategies are no longer sufficient. (3)

The management of AHF poses a unique and evolving clinical challenge. As the disease progresses beyond the limits of medical therapy, advanced interventions become necessary to sustain life and improve functional capacity. Orthotopic heart transplantation has historically been regarded as the gold standard treatment for eligible patients, offering substantial survival benefit and improved quality of life. (3) However, its widespread applicability is fundamentally constrained by a critical shortage of donor organs, stringent selection criteria, and the long-term complications associated with immunosuppressive therapy. As has been succinctly noted in the literature, the number of patients awaiting transplantation far exceeds the availability of donor hearts. (3)

In parallel, the development of durable mechanical circulatory support (MCS) has transformed the therapeutic landscape of AHF. Continuous-flow left ventricular assist devices (LVADs), initially introduced as a bridge to transplantation, have evolved into an established long-term treatment modality, including destination therapy for patients who are not transplant candidates. (4) Ongoing technological advancements have improved device durability, reduced complication rates, and enhanced patient outcomes, contributing to their expanding role in contemporary clinical practice.

Consequently, the distinction between heart transplantation and mechanical circulatory support is becoming increasingly nuanced. The modern management of advanced heart failure requires individualized, patient-centered decision-making that carefully balances expected survival, quality of life, complication risk, and resource availability. This evolving therapeutic paradigm highlights the need for a critical and comprehensive evaluation of these treatment strategies within current clinical practice. Accordingly, this thesis aims to critically evaluate the current evidence comparing durable mechanical circulatory support and orthotopic heart transplantation in patients with advanced heart failure, with particular emphasis on survival outcomes, quality of life, treatment-associated complications and healthcare utilization.

1.1 Definition of Advanced Heart Failure and Diagnostic Criteria

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional cardiac abnormalities that impair ventricular filling and/or the ejection of blood. (1) Its etiology is heterogeneous, encompassing cardiovascular, metabolic, pulmonary, toxic, genetic, and autoimmune causes. Among these, the most common underlying conditions include ischemic heart disease, hypertensive heart disease, and diabetes mellitus, which frequently coexist and interact in affected patients. Given this etiological diversity, HF is similarly classified into multiple phenotypes that reflect underlying pathophysiological mechanisms and guide management. Classification based on left ventricular ejection fraction (LVEF) is most widely used, distinguishing heart failure with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF), and mildly reduced ejection fraction (HFmrEF), with additional recognition of

heart failure with improved ejection fraction (HFimpEF). Furthermore, HF may be categorized anatomically into left- and right-sided forms. (1) These classifications have evolved to facilitate tailored therapeutic strategies and prognostic assessment.

Despite advances in pharmacological, surgical, and device-based therapies, a subset of patients experience progressive clinical deterioration characterized by persistent symptoms, recurrent decompensation, and poor prognosis. This stage is defined as advanced heart failure (AHF). (3) According to the American College of Cardiology/American Heart Association (ACC/AHA), AHF corresponds to stage D disease, representing refractory HF requiring specialized interventions. At this stage, conventional therapies are insufficient to achieve symptom control, and advanced treatment options—including orthotopic heart transplantation, durable mechanical circulatory support, or palliative care—must be considered. (3)

Patients with AHF remain severely symptomatic despite optimal guideline-directed therapy, irrespective of LVEF. (5) However, precise definition of AHF remains challenging, and multiple classification systems have been developed to better characterize disease severity. Accurate identification of patients requiring advanced therapies is of critical clinical importance, as referral must occur within an optimal therapeutic window—neither prematurely nor after irreversible end-organ dysfunction has developed. The ACC/AHA and European Society of Cardiology (ESC) frameworks incorporate objective clinical, hemodynamic, and diagnostic criteria to define advanced disease. In contrast, the New York Heart Association (NYHA) classification primarily assesses functional limitation and symptom burden, contributing to risk stratification and prognostic evaluation. (5) However, symptom-based classification alone is insufficient to guide advanced therapeutic decision-making.

To address this limitation, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles were developed to provide a more granular assessment of clinical severity and hemodynamic status in patients with AHF. (5) These profiles are particularly relevant in the context of mechanical circulatory support, as they assist in patient selection, timing of intervention, and outcome prediction. Despite differences in structure, these classification systems share several common defining features of advanced disease, including severe and persistent symptoms, end-stage cardiac dysfunction, failure of conventional therapies,

recurrent hospitalizations, intolerance to guideline-directed medical therapy (including renin–angiotensin–aldosterone system inhibitors, β -blockers, and angiotensin receptor–neprilysin inhibitors), refractory congestion, poor functional capacity, electrical instability, cardiac cachexia, and progressive multiorgan dysfunction—particularly involving the kidneys and liver—as well as the presence of pulmonary hypertension. (5)

To facilitate earlier recognition of patients progressing toward advanced disease, the mnemonic “I NEED HELP” has been proposed as a practical clinical tool to prompt timely referral to advanced heart failure centers. (5) This framework incorporates key indicators such as declining functional status, severe reduction in LVEF, inotrope dependence, refractory congestion, hypotension, inability to tolerate or uptitrate guideline-directed therapies, recurrent hospitalizations, and electrical instability or persistently elevated natriuretic peptide levels. (5) The major classification systems for AHF are summarized and compared in the figure below, and the conceptual framework of this mnemonic is illustrated in the accompanying table:

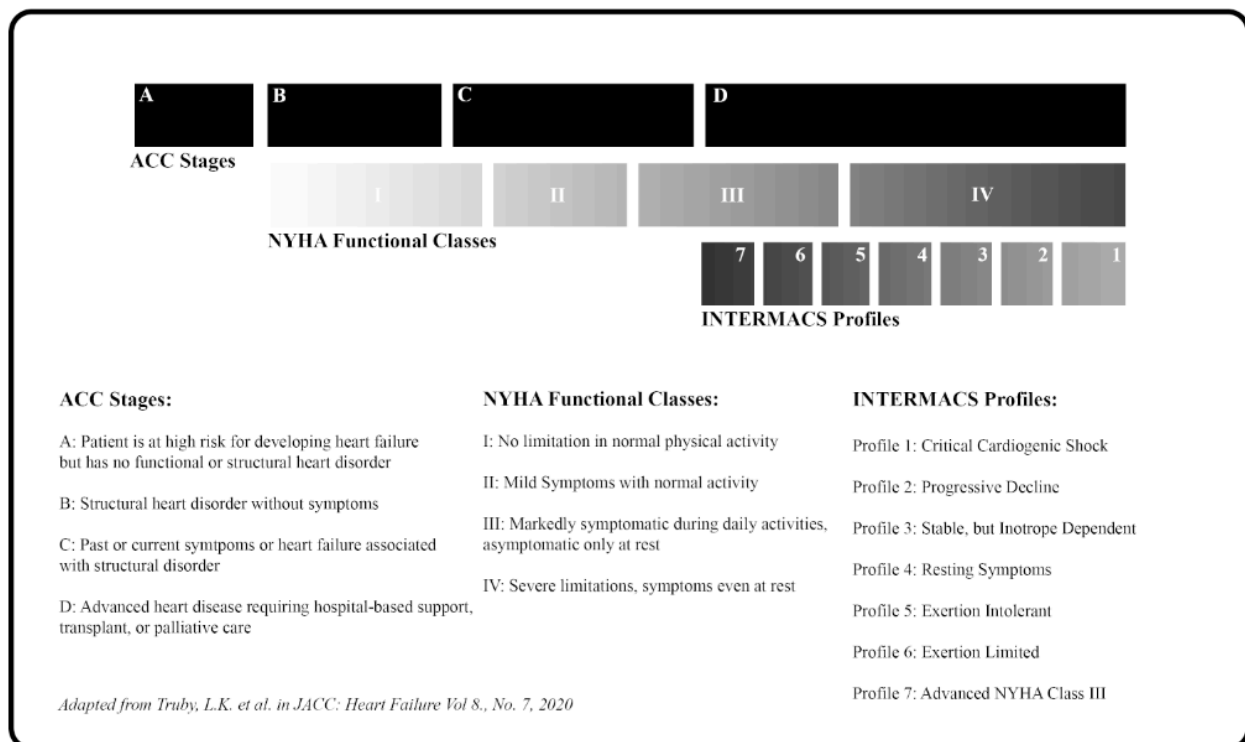


Figure 1. Heart failure stages are classified by either the American College of Cardiology (ACC), New York Heart Association (NYHA), or Interagency Registry for Mechanically Assisted Circulation (INTERMACS) profiles. Adapted from Truby, L.K. et al. (6)

"I NEED HELP" Mnemonic for AHF Referral		
I	Inotropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan
N	NYHA Class/Natriuretic Peptides	Persisting NYHA functional class III/IV and/or high BNP or NT-proBNP
E	End-organ Dysfunction	Worsening renal or liver dysfunction
E	Ejection Fraction	Very low ejection fraction (<25%)
D	Defibrillator Shocks	Recurrent appropriate defibrillator shocks
H	Hospitalizations	At least 1 hospitalization with HF in the past 12 months
E	Edema/Escalating Diuretic Agents	Persistent fluid overload and/or increased diuretic requirement
L	Low BP	Consistently low BP (systolic <90 to 100 mm Hg)
P	Prognostic Medications	Inability to up-titrate (or need to decrease/cease) ACE inhibitors, beta-blockers, ARNS, or MRAs

Table 1. Adapted table from Guglin et al., showing the “I NEED HELP” signs and symptoms that trigger AHF referral for more advanced treatment. Abbreviations: ACE: angiotensin-converting enzyme; ARNI: angiotensin-receptor neprilysin inhibitor, BNP: B-type natriuretic peptide, BP: blood pressure, MRA: mineralocorticoid receptor antagonist, NT-proBNP: N-terminal pro-B-type natriuretic peptide. (7)

1.2 Epidemiology of Advanced Heart Failure

From an epidemiological perspective, heart failure (HF) is widely recognized as a global health pandemic, affecting an estimated 64 million individuals worldwide, with prevalence continuing to rise. (1) Within this population, patients with advanced heart failure (AHF) represent a relatively small but clinically significant subgroup, accounting for approximately 1–10% of all HF cases. (3) Among patients receiving care in specialized referral centers, it has been estimated that approximately 4.5% progress to AHF annually. (5) The broad variability in these estimates reflects a key limitation in current epidemiological understanding, as the true prevalence of AHF remains difficult to define. Unlike HF as a whole, epidemiological studies rarely classify patients according to disease stage. Instead, most studies stratify patients based on functional status, such as the New York Heart Association (NYHA) classification, or left ventricular ejection fraction (LVEF). However, these parameters do not reliably identify advanced disease, as AHF is defined not only by symptom severity but also by refractoriness to guideline-directed therapy and progressive clinical deterioration. Consequently, standard epidemiological frameworks are insufficient to accurately capture this subgroup.

Much of the available data on AHF is therefore derived from highly selected populations, including patients enrolled in left ventricular assist device (LVAD) clinical trials or those referred to specialized advanced heart failure centers. These cohorts may not be representative of the broader HF population, as many patients with advanced disease are not referred for advanced therapies and remain managed in general cardiology or internal medicine settings. As a result, the true burden of AHF is likely underestimated, representing a significant limitation in current epidemiological data. (1,5)

Despite these limitations, the overall burden of HF continues to increase at both global and national levels. For example, in Lithuania, approximately 145,000 individuals are living with HF, with an estimated annual increase of 10,000 new cases, reflecting a substantial and growing public health challenge. (8) Importantly, rising HF prevalence is expected to translate into a parallel increase in the number of patients progressing to advanced stages of disease. This trend is partly driven by improvements in disease-modifying therapies, which prolong survival but also increase the likelihood of progression to refractory, end-stage HF. (3)

Available studies consistently demonstrate that AHF is associated with a markedly poor prognosis. Population-based data from Olmsted County, United States, suggest that fewer than 1% of patients with HF meet criteria for stage D disease, yet this subgroup experiences disproportionately high mortality. (5,6) In contrast, registry data from the Acute Decompensated Heart Failure National Registry (ADHERE) indicate a higher prevalence, approaching 5% among hospitalized patients, highlighting differences between community-based and hospitalized populations. In the same Olmsted County cohort, stage D HF was associated with a 5-year survival of approximately 20%. (3,5,6)

Prognosis is particularly poor among patients with severe hemodynamic compromise. Individuals requiring continuous inotropic support have been shown to have a 1-year survival as low as 6%, reflecting transition to end-of-life care. (3) Early randomized evidence from the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial further demonstrated the severity of advanced disease, with approximately

75% mortality at 1 year among medically treated patients and no survival at 2 years. Similarly, the Investigation of Non-Transplant-Eligible Patients Who Are Inotrope Dependent (INTREPID) trial reported survival rates of 22% at 6 months and 11% at 1 year in patients receiving inotropic therapy. Mortality risk in AHF increases with recurrent hospitalizations and the presence of hypotension, reflecting progressive hemodynamic instability. Although AHF may occur in patients with both preserved and reduced LVEF, severely reduced ejection fraction ($\leq 25\text{--}30\%$) is associated with worse outcomes. (3) These findings collectively underscore the severe prognosis associated with advanced disease.

Taken together, the growing prevalence of HF, coupled with the disproportionately poor outcomes associated with AHF, highlights an increasing need for advanced therapeutic strategies. In parallel with this rising burden, the use of advanced interventions continues to expand; in the United States alone, more than 3,000 patients annually undergo left ventricular assist device implantation and a similar number receive heart transplantation, while thousands more remain on transplant waiting lists. (6) These trends emphasize the critical importance of optimizing patient selection and treatment strategies in advanced heart failure.

1.3 Current Therapeutic Options for Advanced Heart Failure

Pharmacological therapy remains the cornerstone of management in AHF; however, its application is fundamentally constrained by the pathophysiological features that define the syndrome. (9) Although guideline-directed medical therapy (GDMT)--including β -blockers, renin-angiotensin-aldosterone system inhibitors or angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors--has demonstrated substantial benefits in patients with HFrEF, the tolerability of these agents is frequently limited in advanced disease due to hypotension, renal dysfunction, and electrolyte disturbances. (3,9) Consequently, treatment often necessitates cautious initiation and slow up-titration, with an emphasis on maintaining hemodynamic stability rather than achieving target doses. In parallel, diuretic therapy plays a central role in the management of chronic congestion, which is nearly universal in AHF, although escalating diuretic requirements may contribute to

neurohormonal activation and diuretic resistance. In patients with low-output states or refractory symptoms, intravenous inotropic agents may be required to preserve end-organ perfusion or alleviate symptoms, typically as a bridge to advanced therapies or as part of a palliative strategy. Thus, in AHF, pharmacological therapy is best understood not as definitive treatment, but as a dynamic and often limited component of care aimed at stabilization, symptom control, and facilitation of transition to device-based or surgical interventions. (3,9)

Device-based therapies such as cardiac resynchronization therapy (CRT) and cardiac contractility modulation (CCM) are useful as adjunctive, phenotype-specific therapies, rather than central definitive treatments. CRT, which uses a biventricular pacemaker, works by correcting electrical synchronous contractions, which makes it optimal for patients with electrical dyssynchrony, most commonly those with HFrEF and left bundle branch block (LBBB) and wide QRS complexes (>130 - 150 ms). (9,10) In these patients, the left ventricular fails to contract uniformly, leading to inefficient stroke volume, worsened mitral regurgitation and increased wall stress, all of which CRT can address through restoration of synchronous contraction. This means, however, that CRT works less effectively for patients with intrinsic myocardial failure with extensive fibrosis and restrictive physiology such as end-stage hypertrophic cardiomyopathy (HCM). (11)

CCM, meanwhile, works via delivery of high-voltage electrical signals during the absolute refractory period—meaning, rather than triggering a new heartbeat, they modify cellular signaling inside cardiomyocytes. (9) Over time, therefore, it has been postulated CCM can help improve calcium handling and improve myocardial energetics, leading to stronger contractions and improved functional capacity. This does not reverse structural disease and does not replace advanced therapies, therefore CCM is more useful as a bridge/adjunct for select non-transplant/non-LVAD candidates, and its survival benefit has not been strongly prospectively established in literature. This reinforces the idea that device-based therapies can provide important symptomatic and functional benefits, but only in a select subset of HF patients, and in AHF specifically, structural and hemodynamic derangements render these therapies insufficient, necessitating consideration of more definitive interventions. (9)

These definitive interventions, which are the primary focus of this thesis, take shape in the form of durable mechanical circulatory support (specifically LVADs) and heart transplantation. They represent the ultimate necessary therapeutic destination for AHF patients. LVADs as a therapy can be used either as a bridge to transplant or, as more studies seem to indicate, a viable destination therapy. (4) The evolution of durable LVAD therapy, addressed in the forthcoming section on evolution of MCS, has allowed it to occupy a central role in the management for not only transplant-ineligible patients with AHF, but also transplant-eligible patients. Orthotopic heart transplantation is frequently cited as a gold-standard therapy for select patients with AHF, but again, its population-level impact is constrained by donor-scarcity, waiting list dynamics, and candidacy restrictions.

It is worthwhile mentioning, lastly, that current therapeutic options in AHF are broader than simply drugs versus transplant/MCS. Structural heart intervention has been shown to modify symptoms and trajectory in select patients—in particular, secondary mitral and tricuspid regurgitation, which are common in AHF and worsen symptoms and prognosis. (12) While AHF patients broadly present with irreversible myocardial failure requiring LVAD or transplant, potentially reversible structural burden in specific patients might improve with targeted intervention. Functional mitral regurgitation, for example, represents a key driver of disease progression in many patients by promoting a cycle of volume overload, ventricular dilation, and worsening regurgitation. Transcatheter mitral valve repair techniques, such as edge-to-edge repair, can interrupt this cycle—clipping the anterior and posterior mitral leaflets through options like MitraClip create a double orifice that reduces regurgitant volume, decreases LV volume overload and pulmonary pressures, and increases forward cardiac output. (11,13,14) This can lead to improvements in symptoms and reductions in heart failure hospitalizations in appropriately selected patients.

Similarly, correction of aortic stenosis or relief of left ventricular outflow tract obstruction may significantly improve hemodynamics and functional capacity. (3) However, the benefits of structural interventions are highly dependent on patient phenotype and disease stage; in the presence of advanced myocardial remodeling and irreversible pump failure, these strategies are still often insufficient. In other words, structural heart intervention can be useful

when there is a dominant structural driver of HF and the myocardium is still functionally recruitable, but in AHF due to diffuse fibrosis, severe LV remodeling and multi-organ dysfunction, such corrections do not fix the disease. (3,11,13) Thus, while structural interventions can meaningfully alter the clinical trajectory in specific patients, they do not obviate the need for advanced therapies such as MCS or heart transplantation in those with end-stage disease.

1.4 Evolution of Mechanical Circulatory Support

The development of mechanical circulatory support (MCS) represents one of the most significant paradigm shifts in the management of AHF, evolving from experimental, short-term support systems into durable, long-term therapeutic modalities capable of fundamentally altering disease trajectory. This evolution has been driven not only by advances in biomedical engineering, but also by the persistent limitations of heart transplantation, including donor organ scarcity, waiting list mortality, and increasingly restrictive candidacy criteria.

From a conceptual standpoint, MCS devices can be broadly divided into two principal categories: ventricular assist devices (VADs) and other forms of mechanical support. (4,15) VADs are designed to augment cardiac output by assisting one or both ventricles and are classified according to the chamber supported into left ventricular assist devices (LVADs), right ventricular assist devices (RVADs), or biventricular assist devices (BiVADs). In contrast, other mechanical support modalities include the intra-aortic balloon pump (IABP), venoarterial extracorporeal membrane oxygenation (VA-ECMO), and the total artificial heart (TAH). These systems may be further categorized according to duration of support, with temporary devices—such as IABP, Impella systems, extracorporeal VADs, and VA-ECMO—primarily used in acute settings, and durable devices, including intracorporeal LVADs and TAH, intended for long-term circulatory support. (4,15)

The earliest iterations of mechanical support emerged in the mid-20th century with the advent of the cardiopulmonary bypass, first successfully utilized in 1953, followed by the

implantation of the first ventricular assist device in 1963 and the first total artificial heart in 1969. (16) These pioneering efforts established the conceptual feasibility of mechanical circulatory replacement; however, early devices were limited by large size, extracorporeal configurations, poor durability, and high complication rates, restricting their application to short-term support or experimental use.

The subsequent development of first-generation pulsatile-flow devices marked an important step toward long-term support. These systems were designed to replicate physiological cardiac cycles through volume-displacement mechanisms, incorporating multiple moving components such as pusher plates and biological valves. Their clinical utility was demonstrated in the REMATCH trial (2001), which showed a survival benefit of LVAD therapy over optimal medical therapy in patients ineligible for transplantation. However, these devices were associated with substantial limitations, including large device size, mechanical wear, and high rates of device failure, with failure rates approaching 35% at two years. (16) Consequently, although pulsatile devices validated the clinical potential of MCS, they were not suitable for widespread, long-term application.

A major technological inflection point occurred with the transition to continuous-flow devices. Second-generation axial-flow pumps, most notably the HeartMate II, received FDA approval for bridge-to-transplant use in 2008 and for destination therapy in 2010, marking a critical expansion in the clinical role of MCS. (12) These devices demonstrated substantial improvements in survival, including approximately 58% two-year survival compared with 24% for pulsatile devices. (16) Their smaller size, reduced mechanical complexity, and improved durability established continuous-flow support as the new standard of care. Within this framework, the left ventricular assist device (LVAD) has emerged as the dominant modality of durable MCS. LVADs are intracorporeal mechanical pumps designed to support systemic circulation by unloading the failing left ventricle and maintaining forward blood flow. Modern LVAD systems consist of several integrated components: an inflow cannula that directs blood from the ventricular apex into the pump, an internal rotary pump that generates continuous flow, and an outflow graft that returns blood to the ascending aorta. These internal components are

connected via a percutaneous driveline to an external controller and power source, which regulate device function and provide real-time monitoring. (16)

The hemodynamic performance of LVADs is governed by several key parameters displayed on the external controller. (4,16) Pump speed, measured in revolutions per minute, is the primary adjustable variable and determines the rate of blood propulsion. Power consumption reflects the energy required to maintain pump function and is influenced by both speed and flow dynamics. Estimated flow, expressed in liters per minute, serves as a surrogate for cardiac output and is dependent on both device settings and patient-specific factors such as preload and afterload. The pulsatility index provides an indirect measure of native ventricular contribution, reflecting the degree of residual cardiac function superimposed on continuous device flow. Collectively, these parameters illustrate a fundamental shift in cardiovascular physiology, in which circulation is partially or wholly maintained by a mechanical system rather than intrinsic myocardial function. (4,16)

Beyond their structural design, continuous-flow LVADs can be further categorized based on pump mechanics into axial-flow and centrifugal-flow devices. Axial-flow systems generate blood movement via a propeller mechanism within a tubular housing, whereas centrifugal devices utilize a rotating impeller within a chamber to create flow. These engineering differences have important physiological implications. Centrifugal pumps are more sensitive to preload and afterload conditions, resulting in greater flow pulsatility, whereas axial devices tend to produce relatively constant flow across varying pressure gradients, which may predispose to complications such as ventricular suction events in low-volume states. (15,17)

More recent advances have focused on third-generation centrifugal-flow devices with fully magnetically levitated rotors. The HeartMate 3, approved for clinical use in 2017 (bridge-to-transplant) and 2018 (destination therapy), represents a significant refinement in device design, incorporating magnetic levitation to minimize shear stress and reduce thrombosis. (12) Clinical trials, including MOMENTUM 3, demonstrated superiority over prior-generation devices with respect to survival free from disabling stroke or reoperation. (18,19) Importantly, the clinical role of MCS has evolved in parallel with these technological advances. Initially

conceived primarily as a bridge to transplantation, MCS is increasingly utilized as destination therapy in patients who are ineligible for transplant. This shift reflects both improvements in device performance and the persistent mismatch between the supply of donor organs and the growing population of patients with AHF. Indeed, contemporary registry data demonstrate a predominance of destination therapy over bridge-to-therapy strategies, underscoring the central role of durable MCS in modern heart failure management. (12) The total artificial heart (TAH), while representing the most complete form of mechanical circulatory replacement, has remained limited in application and is used primarily as a bridge to transplantation in select patients with biventricular failure, accounting for a small proportion of overall MCS use. (12,20)

Collectively, this trajectory reflects the transformation of mechanical circulatory support from an experimental rescue therapy to an established, life-prolonging treatment modality within AHF. However, this evolution has not eliminated the fundamental trade-offs inherent to device-based therapy. While modern LVADs offer substantial improvements in survival and quality of life, they introduce a distinct spectrum of device-related complications. These considerations are central to the comparative evaluation of MCS and heart transplantation, forming the basis for the analysis presented in this thesis.

1.5 Rationale and Aim of this Thesis

Despite substantial advances in the management of AHF, optimal selection between definitive treatment strategies remains inadequately defined in contemporary clinical practice. Orthotopic heart transplantation continues to represent the gold standard for eligible patients, offering superior long-term survival and quality of life. (21) However, its application is fundamentally constrained by donor organ scarcity, stringent selection criteria, and disparities in access. In parallel, durable mechanical circulatory support—particularly continuous-flow left ventricular assist devices (LVADs)—has evolved into a widely utilized and increasingly viable alternative, with expanding indications and progressively improving outcomes. Nevertheless, the comparative effectiveness of these therapies remains incompletely characterized and inconsistently reported across the literature. Differences in patient selection, rapid technological

evolution of mechanical circulatory support, and heterogeneity in study design contribute to persistent uncertainty regarding their relative benefits and risks. While transplantation is associated with superior long-term survival, LVAD therapy offers broader applicability but is accompanied by the potential burden of device-related complications, rehospitalization, and long-term management challenges.

Given the growing population of patients with advanced heart failure and the increasing reliance on both treatment modalities, a rigorous and critical evaluation of their outcomes is essential. This thesis therefore aims to systematically analyze and synthesize the available evidence comparing durable mechanical circulatory support and orthotopic heart transplantation, with particular emphasis on survival outcomes, complication profiles, quality of life, and healthcare utilization.

The objectives of this thesis are therefore:

1. To compare survival outcomes — specifically, to compare short and long-term survival between contemporary HeartMate 3 LVAD and heart transplantation cohorts across device generations and registries.
2. To compare complication profiles — specifically, to analyze and compare the incidence and clinical significance of complications associated with each therapy.
3. To compare quality of life and functional outcomes — specifically, to evaluate functional class, patient-reported health status, exercise capacity, psychological outcomes, and daily-life limitations using validated instruments.
4. To compare healthcare utilization and costs — specifically, to compare index hospitalization costs, readmission rates and cost drivers, and cost-effectiveness evidence across contemporary cohorts.

Methods

This thesis was conducted as a structured literature review aimed at evaluating and comparing clinical outcomes associated with durable mechanical circulatory support and orthotopic heart transplantation in patients with advanced heart failure. The methodology was designed to ensure a comprehensive and reproducible identification, selection, and synthesis of

relevant evidence. While a structured search strategy was employed, this study was not conducted as a formal systematic review and therefore did not include protocol registration or formal risk-of-bias assessment.

2.1 Data Sources and Search Strategy

A structured literature search was performed using the PubMed database as the primary source of biomedical literature, supplemented by additional searches in Embase. The search strategy was developed to capture studies evaluating outcomes of durable MCS—particularly LVADs—and orthotopic heart transplantation in the context of AHF. The search combined Medical Subject Headings (MeSH) terms and free-text keywords related to heart failure, mechanical circulatory support, heart transplantation, and clinical outcomes. The complete search strategy is presented below in Figure 2 to ensure reproducibility and transparency:

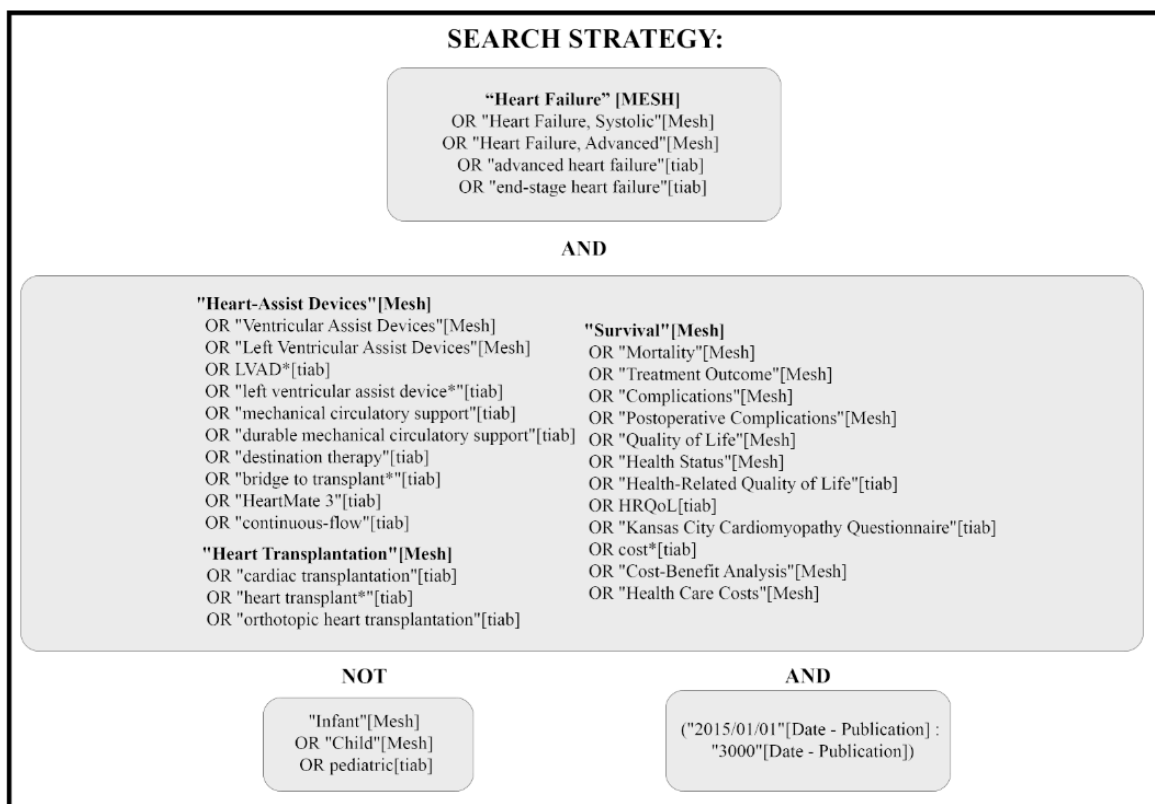


Figure 2. Complete search strategy used across PubMed; adapted to Embase for additional searches.

The search was limited to studies published between January 1, 2015 and the time of search execution to ensure inclusion of contemporary data reflecting current clinical practice and device technology. Pediatric populations were excluded to maintain focus on adult patients with AHF.

2.2 Study Selection Criteria

Studies were selected based on predefined inclusion and exclusion criteria aligned with the aim of this thesis. Eligible studies included those involving adult patients with AHF that evaluated outcomes associated with durable MCS and/or orthotopic heart transplantation. Studies were required to report at least one of the following outcome measures: survival, mortality, complication rates, quality of life, or healthcare utilization and costs. Only original research articles were included, encompassing randomized controlled trials, prospective and retrospective cohort studies, and large registry analyses. To ensure relevance to contemporary clinical practice, only studies published in English between 2015 and the time of the search were considered.

Studies were excluded if they focused on pediatric populations, case reports, editorials, or conference abstracts without sufficient outcome data. Additionally, studies addressing exclusively temporary mechanical circulatory support modalities were excluded, as the primary focus of this thesis is on durable therapies. Articles lacking relevant outcome measures or insufficient methodological detail were also excluded. Study selection was conducted through an initial screening of titles and abstracts, followed by full-text review of potentially eligible studies. Priority was given to high-quality evidence, including multicenter studies, large observational cohorts, and landmark clinical trials, in order to ensure a robust and clinically meaningful synthesis of the literature. A total number of 73 papers met the inclusion criteria and were included in the final qualitative analysis.

2.3 Data Extraction and Synthesis

Relevant data were extracted from included studies and organized according to the predefined outcome domains: survival, complications, quality of life, and healthcare utilization.

Data extraction focused on study characteristics, including study design, patient population, intervention type, and duration of follow-up, as well as reported clinical outcomes. Given the heterogeneity of study designs, patient populations, and outcome definitions, a quantitative meta-analysis was not performed. Instead, a structured qualitative synthesis of the literature was undertaken. Emphasis was placed on identifying consistent patterns, areas of agreement, and discrepancies across studies, as well as contextualizing findings within the evolution of mechanical circulatory support technology and transplantation practices. Where appropriate, outcomes were interpreted in relation to differences in patient selection and study methodology.

2.4 Methodological Considerations

The methodological approach of this review was guided by principles of structured literature analysis, including a predefined search strategy, explicit eligibility criteria, and systematic organization of extracted data. The restriction to contemporary literature reflects the rapid evolution of mechanical circulatory support, particularly the transition to continuous-flow and magnetically levitated devices, and ensures relevance to current clinical decision-making. The literature search, study selection, and data synthesis were conducted independently. Critical appraisal of included studies was performed with consideration of study design, sample size, potential sources of bias, and applicability to the target population of patients with AHF. Particular attention was given to differences in baseline patient characteristics and treatment indications, which may influence reported outcomes and limit direct comparability between MCS and HT.

Results

3.1 Survival Outcomes

Historically, survival outcomes following left ventricular assist device (LVAD) implantation were substantially lower than those observed following heart transplantation, limiting their use primarily to bridge-to-transplant strategies. (22) First-generation pulsatile-flow devices, such as the HeartMate XVE, were evaluated in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which

demonstrated a 48% reduction in mortality compared with guideline-directed medical therapy (GDMT). (20) Despite this relative benefit, absolute survival remained limited, with 2-year survival of approximately 23% in LVAD recipients compared with 8% in patients receiving medical therapy alone. These early devices were associated with significant limitations, including large size, mechanical wear, and high rates of infection, stroke, and device failure, with most systems requiring replacement within 18–24 months. (20)

The development of second-generation continuous-flow devices resulted in substantial improvements in survival. (20) The HeartMate II (HM-II), an axial-flow LVAD, received FDA approval for bridge-to-transplantation and destination therapy in 2008 and 2010, respectively. In a randomized trial published in the *New England Journal of Medicine* in 2009, 200 patients awaiting heart transplantation were assigned to receive either HM-II or the pulsatile-flow HeartMate XVE. The HM-II demonstrated superior 2-year survival free from disabling stroke or pump failure compared with HeartMate XVE (46% vs 11%; $p < 0.001$). (20) Additional adverse events, including infection, right heart failure, arrhythmia, and hospitalization, were also less frequent in the HM-II group. Not all second-generation devices demonstrated equivalent clinical performance, however. The HeartWare HVAD, a centrifugal continuous-flow pump, was evaluated in the ENDURANCE trial, which found no significant difference in 2-year survival free from disabling stroke or device replacement compared with HM-II (55.0% vs 57.4%; $p = 0.67$). However, stroke occurred more frequently in the HVAD group than in the HM-II group (29.7% vs 12.1%; $p < 0.001$). (20) Subsequent reports of higher mortality, neurological adverse events, pump restart delay, and heart failure events led to withdrawal of the HVAD from clinical use in 2021. (20)

Further advances with third-generation centrifugal-flow devices, particularly the magnetically levitated HeartMate 3 (HM3), have been associated with additional improvements in survival outcomes. (20) The MOMENTUM-3 trial enrolled 1,028 patients between 2014 and 2016 and compared HM3 with HM-II. At 2 years, HM3 demonstrated superior survival free from disabling stroke or reoperation for device malfunction compared with HM-II (76.9% vs 64.8%; $p < 0.001$). (20) Extended follow-up from the same trial showed higher 5-year overall survival with HM3 than with HM-II (58.4% vs 43.7%; $p = 0.003$). Survival free from disabling stroke or

device malfunction was also higher at 5 years in the HM3 group than in the HM-II group (54.0% vs 29.7%; $p < 0.001$). Conditional analyses further reported that among patients discharged after the index hospitalization, 5-year all-cause survival was approximately 62%. (20)

Registry-based analyses provide further insight into contemporary LVAD survival, while also demonstrating variability across populations. INTERMACS data report survival rates of 83.1%, 70.0%, and 60.8% at 1, 3, and 5 years, respectively. (20) In contrast, EUROMACS data report lower survival at equivalent time points, with 70.4%, 55.6%, and 44.5% survival at 1, 3, and 5 years. The Japanese J-MACS registry reports higher early survival, with 1-year survival of 92% and 2-year survival of 88%. The ELEVATE registry, a prospective predominantly European cohort of consecutive HM3 LVAD implants, reported 5-year survival of 63.3%. (21) Additional INTERMACS data showed HM3 5-year survival of 52% for bridge-to-transplantation and 42% for destination therapy, with 68% of patients achieving and sustaining significant symptomatic improvement, defined as NYHA functional class I–II. (20) These findings demonstrate consistent improvements in survival with contemporary LVADs, although variability persists between registries.

Survival outcomes following heart transplantation have been consistently reported across large international registries and are presented here alongside LVAD outcomes for direct comparison. According to ISHLT registry data, 1-year survival after heart transplantation exceeds 86%, 3-year survival ranges from 79% to 86%, and 5-year survival is approximately 72%. (21) Median survival following heart transplantation has been reported at approximately 12.1 years for patients transplanted between 2001 and 2009, with many contemporary recipients surviving 15 years or longer. Ten-year survival following heart transplantation has been reported at approximately 50–53%. (21) When considered by time interval, contemporary LVAD and heart transplantation cohorts demonstrate closely aligned survival at early follow-up. Reported 1-year survival ranges from approximately 80% to 87% in contemporary LVAD cohorts, compared with greater than 86% after heart transplantation. (18,21,23) At 3 years, HM3 LVAD survival has been reported at approximately 83%, compared with 79–86% following transplantation. (21) By 5 years, reported survival ranges from 58.4% in MOMENTUM-3 to

63.3% in the ELEVATE registry for HM3 LVAD recipients, compared with approximately 72% following heart transplantation. (20,21) This comparative data is summarized in Figure 3.

Direct comparative analyses further describe these patterns. In one propensity score–matched analysis of 3411 patients, patients wait-listed for heart transplantation, with or without bridge-to-transplant LVAD support, had significantly better 5-year survival than patients managed with destination-therapy LVAD alone, with a reported risk ratio of 0.42 (95% CI 0.38–0.46); put differently, the transplant wait-listing strategy was associated with an approximately 58% lower relative risk of death compared with destination-therapy LVAD alone. (22) In contrast, pooled estimates from a 2018 meta-analysis of eight studies including 7,957 patients showed no difference in 1-year mortality between heart transplantation and LVAD strategies. (7) Similarly, a UNOS analysis reported identical 1- and 2-year survival rates between LVAD-supported patients and recipients of marginal donor hearts, at 89% and 85%, respectively. (7) These findings should be interpreted alongside contemporary HM3 data, where 5-year survival ranges from 58.4% in MOMENTUM-3 to 63.3% in the ELEVATE registry; The Society of Thoracic Surgeons Intermacs National Database (STS Intermacs) reports similar survival achievements. (20,21,23)

Survival following LVAD implantation is not uniform and varies according to patient characteristics and post-implant clinical trajectories. In an INTERMACS-based analysis of 4,615 LVAD recipients, renal function trajectories were associated with differential survival outcomes. (24) Patients with persistent renal dysfunction or highly variable renal trajectories demonstrated lower 1-year survival, approximately 61.8% and 65.8%, respectively, compared with other renal trajectory groups. (24) These findings indicate substantial heterogeneity within LVAD-supported populations and suggest that survival estimates are influenced not only by device generation, but also by baseline patient characteristics and post-implant organ function.

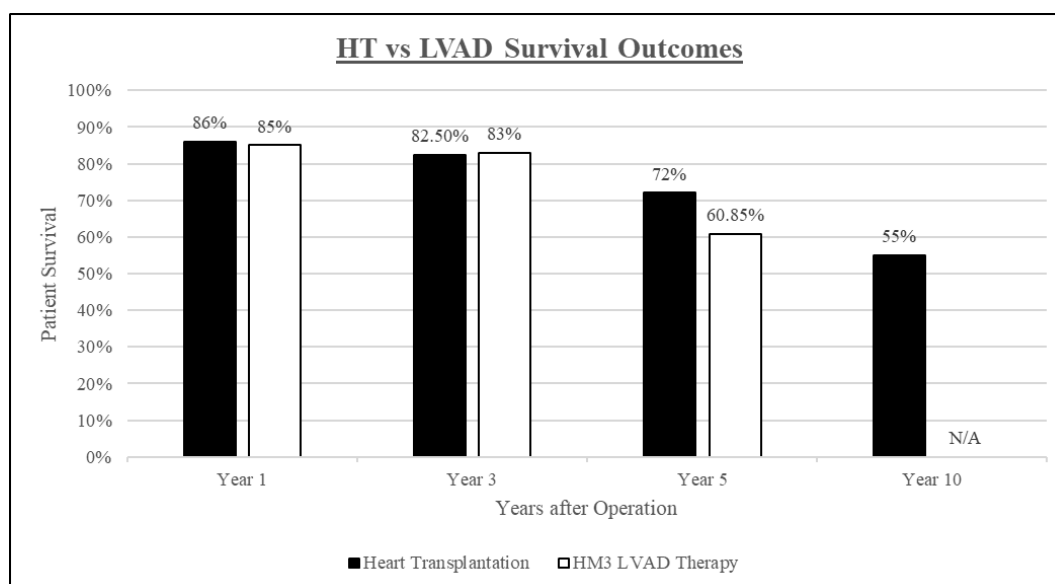


Figure 3. Long-term survival outcomes of HeartMate 3 LVAD vs heart transplantation (HT). Year 3 of HT is taken as an average of survival data ranging from 79-86%. Year 5 of LVAD therapy is taken as an average of 58.4-63.3% survival ranges from different registries. As no 10 year data is available for HM3 patients, “N/A” is used as a placeholder. Data sourced from Kakoudaki et. al., as well as MOMENTUM-3 and ELEVATE registries.

3.2 Complications

3.2.1 LVAD Complications

Despite the technological improvements addressed previously in the evolution of the HM3, particularly improvements in hemocompatibility and shear stress reduction, bleeding remains one of the most significant complications affecting long-term LVAD support. (20) Following the perioperative period, the gastrointestinal (GI) tract is the primary site of bleeding in LVAD patients, and in approximately 50% of these cases, bleeding has been linked to gastrointestinal angiodysplasias. (20) GI angiodysplasias, or arteriovenous malformations (AVMs), are small vascular malformations composed of abnormal, fragile, dilated blood vessels that can cause recurrent GI bleeding. Their development in LVAD recipients has been attributed to two mechanisms related to continuous-flow support. First, continuous-flow physiology reduces normal pulsatility, resulting in lower pulse pressure and altered microcirculatory flow, which may promote AVM formation in an inflammatory-state environment. Second, continuous-flow LVADs expose blood to shear stress, which can break down

high-molecular-weight multimers of von Willebrand factor, producing an acquired von Willebrand syndrome that reduces platelet adhesion and increases the likelihood of bleeding from these fragile vascular lesions. (20) The 5-year MOMENTUM-3 analysis reported a 44% relative reduction in bleeding risk with HM3 compared with HM-II and a 40% reduction in GI bleeding specifically; however, 27.8% of patients still developed GI bleeding within the first 5 years after HM3 implantation, making it a persistent major adverse event in clinical practice. (20,21,25)

Neurologic events, including ischemic and hemorrhagic stroke, have decreased with HM3 but continue to represent a significant clinical challenge, particularly within the first month after LVAD implantation. (20) MOMENTUM-3 subanalysis showed that stroke occurrence was significantly lower with HM3 than with HM-II; in the long-term period beyond 6 months, HM3 was associated with a 3.3-fold lower stroke rate than HM-II. (20) However, post-implant stroke significantly reduced 2-year survival regardless of stroke subtype or initial neurological severity compared with patients without stroke, with reported survival of $43 \pm 12\%$ after hemorrhagic stroke and $57 \pm 9\%$ after ischemic stroke. The most recent 5-year MOMENTUM-3 follow-up showed that stroke rates remained lower with HM3 than with HM-II, at 0.05 versus 0.136 events per patient-year, corresponding to a rate ratio of 0.37 (95% CI 0.27–0.50; $p < 0.001$). Despite these improvements, stroke remained a complication in 10.7% of patients within the first 5 years after implantation. Ischemic stroke remains particularly clinically important in LVAD recipients given the multifactorial thromboembolic risk in this population and the frequent coexistence of atrial fibrillation. (20,25)

Infections represent one of the most frequent and persistent complications among LVAD patients. After the first 3 months post-implantation, infections are the most commonly reported adverse event, occurring in more than 50% of patients supported with an LVAD for 5 years. (20) Whereas technological advances across LVAD generations have decreased the incidence of several other complications, infection incidence remains high across device generations and accounts for approximately 7% of LVAD-related deaths within the first year after implantation and 15% thereafter. LVAD infections affect more than mortality alone; they are associated with increased risks of thrombosis, bleeding complications, longer hospital stays, need for LVAD exchange, and progression from heart failure to heart transplantation. (20,25)

LVAD-specific infections are those that directly involve any component of the device, including the driveline, pump, pump pocket, or inflow/outflow cannulae. (20) These infections can be categorized as early onset, occurring within 1 month after implantation, or late onset, occurring thereafter. Pneumonia and surgical site infections tend to predominate among early-onset infections, whereas the driveline is more likely to be the source of late-onset infections. LVAD-related infections are also important and include infections that occur as complications of implantation or device-specific infection, such as infective endocarditis, mediastinitis, and intravascular catheter-related bloodstream infections. MOMENTUM-3 data showed that local infections unrelated to pump components were the most prevalent infectious events, accounting for 56%, followed by driveline infections at 27%, sepsis at 16%, and infections involving the pump or pump components at less than 1%. (20) Bacterial pathogens were responsible for 66% of infectious events, and nearly half of all patients with infection experienced recurrent infection. Important correlates of infection included sex, pre-implant IABP use, obesity (BMI ≥ 30 kg/m²), and history of cardiac surgery. (20)

LVAD-related infections occur in at least one-third of LVAD patients within the first year after implantation, with driveline infections being the most common LVAD-specific infection. (20) INTERMACS, EUROMACS, and IMACS registries report an incidence of driveline infection of 9–11.2% per patient-year, with prevalence reaching up to 30%. (20) Because the LVAD requires a percutaneous cable to pass through the skin, the driveline creates a persistent route for microbial entry and substantially increases susceptibility to microbial contamination and infection. Although these infections often begin at the driveline exit site, they can extend along the driveline tunnel to deeper pump components and may disseminate via the bloodstream to distant sites. Driveline infection is more prevalent in patients with higher BMI, a history of trauma at the driveline site, younger age, and longer duration of LVAD support. Diabetes, chronic kidney disease, nutritional status, and sex have not been consistently associated with driveline infection rates. (20,24,25)

Device type may also be relevant, as retrospective studies suggest that HM3 patients are less likely to develop driveline infections or other LVAD-specific infections than patients supported with HVAD. (20) Older devices also show greater risk of pump pocket infections, which occur in approximately 2–10% of patients. MOMENTUM-3 trial data showed no

significant difference in 2-year survival between patients with and without driveline infections (83.7% vs 84.8%; $p = 0.64$; HR 0.89, 95% CI 0.53–1.48). (20) Although infection may negatively affect post-implant survival, adverse outcomes are primarily driven by localized or systemic infections not related to the device, and the majority of deaths are attributable to non-infectious factors.

Another significant complication related to LVAD therapy is right heart failure (RHF), which affects 29.9% of HM3 patients within 5 years after implantation and continues to contribute substantially to morbidity and mortality. (20) MOMENTUM-3 data show that HM3 technology did not significantly reduce RHF burden compared with previous LVAD generations. RHF is an inherent concern in LVAD therapy because LVADs directly support only the left ventricle. Although LVADs unload the LV and pump blood into the systemic circulation, the right ventricle must still deliver blood through the pulmonary circulation to fill the LVAD-supported left side; if the RV fails, LVAD preload falls, systemic flow becomes inadequate, and venous congestion develops. While the detailed pathophysiology of RHF is outside the scope of this review, the lack of standardized definitions in the literature makes incidence rates difficult to compare. Reported estimates vary from approximately 5% when RHF is defined as the need for postoperative right ventricular assist device support to as high as 40% when definitions include the need for prolonged inotropes. (20,26) There is also increasing recognition of late RHF, with some definitions describing it as the need for inotropic support more than 30 days after LVAD implantation, while others define it as rehospitalization for heart failure after the index hospitalization requiring medical or device therapy. RHF is significant in its association with worse outcomes after LVAD implantation; among BTT patients, late RHF was associated with markedly lower 5-year survival, reported as 26% compared with 87% in those without late RHF. (20)

Cardiac arrhythmias are another common and potentially critical complication of LVAD support. Broadly, arrhythmias affect 31.8% of HM3 patients within the first 5 years after implantation. (20) Ventricular arrhythmias specifically occur in approximately 20–50% of patients, particularly during the first month following implantation, with early ventricular arrhythmias associated with worse short-term outcomes and increased mortality. One multicenter study identified early ventricular arrhythmias with electrical storm as the strongest predictor of

30-day mortality, conferring a seven-fold increase in risk. (20) Late ventricular arrhythmias, by contrast, have not been consistently associated with worse long-term survival, but have been linked to RHF; recurrent ventricular tachycardia can impair RV filling and contraction, worsen RV output, and reduce LVAD preload. Although ventricular arrhythmias may initially be tolerated in LVAD-supported patients, persistent or late ventricular arrhythmias can lead to RV dysfunction, impairment of LVAD flow, and thrombus formation. Atrial arrhythmias are also frequent, with 42% of MOMENTUM-3 patients having a preoperative history of atrial fibrillation. However, atrial arrhythmias have not been clearly associated with increased mortality, thromboembolism, or stroke in LVAD-supported patients. (20)

Other potential complications associated with LVADs include pump thrombosis, aortic regurgitation, suction events, hypotension and shock, and cardiac arrest. (20) While pump thrombosis has historically been a potentially fatal LVAD complication, MOMENTUM-3 data show that pump thrombosis is almost non-existent with contemporary HM3 technology, occurring at only 0.01 events per patient-year compared with 0.25 events per patient-year with HM-II. (20,25) This reduction is clinically important given the high morbidity and mortality associated with pump thrombosis in earlier LVAD generations.

Aortic regurgitation is a more common complication of continuous-flow LVAD support, with de novo aortic regurgitation developing in up to 25% of patients within the first year and increasing with longer duration of support. (20,25) Aortic regurgitation may develop as a result of persistent aortic valve closure, increased transvalvular gradients, altered aortic root flow, leaflet fusion, and aortic remodeling. Clinically significant aortic regurgitation can create a closed-loop circulation between the LVAD, aortic root, and left ventricle, reducing effective forward flow and limiting LV unloading. In MOMENTUM-3, moderate-to-severe de novo aortic regurgitation occurred less frequently with HM3 than with HM-II (5.6% vs 11.5%; $p < 0.01$). (20) However, management remains challenging because increasing LVAD speed may worsen aortic valve closure and progression of aortic regurgitation; in one analysis, 78% of patients developed worsening aortic regurgitation after pump speed increase. Surgical and transcatheter interventions carry substantial procedural risk. (20,25) Figure 4 below summarizes all of the major HM3 LVAD complications described within this section:

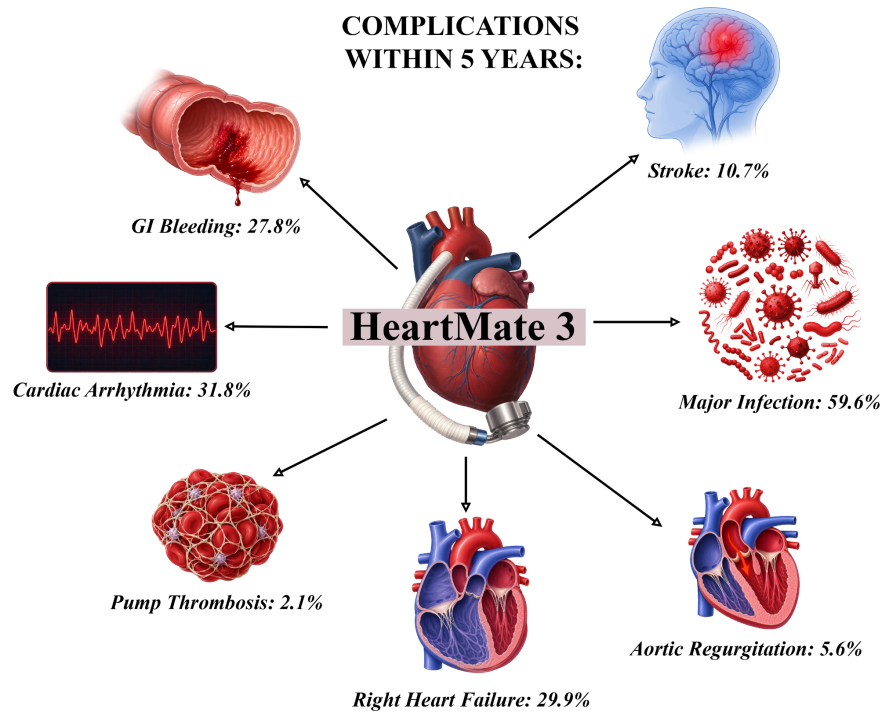


Figure 4. Major complication incidence of HM3 LVADs within 5 years; adapted from Moeller et. al. (20)

3.2.2 Heart Transplant Complications

Heart transplantation is associated with a distinct spectrum of complications that differ substantially from those observed after LVAD implantation. Whereas LVAD-related morbidity is frequently driven by device-related, hemocompatibility, infectious, and hemodynamic complications, post-transplant morbidity is largely related to early graft dysfunction, alloimmune injury, immunosuppression, and progressive graft vasculopathy. (21) The major complications reported after heart transplantation include primary graft dysfunction, acute rejection, cardiac allograft vasculopathy, infection, malignancy, renal dysfunction, arrhythmias, coagulopathy, tricuspid regurgitation, and respiratory complications. (21,27)

Early post-transplant complications are dominated by graft dysfunction and hemodynamic instability. Primary graft dysfunction is a major early complication, occurring within the first 24–72 hours after surgery and involving severe impairment of donor-heart function affecting the left ventricle, right ventricle, or both. (21) It has been reported in 13.9% of patients within 24–72 hours. Severe early graft dysfunction may present with low cardiac index,

hypotension, and cardiogenic shock physiology, often requiring aggressive support with inotropes and, in severe cases, mechanical circulatory support. (21,26)

Right ventricular failure represents an important manifestation of early graft dysfunction. (27) It may be related to elevated pulmonary vascular resistance in the recipient and may present with elevated central venous pressure, hypotension, systemic venous congestion, and peripheral edema. Left ventricular failure may also occur, although it is described less frequently than right ventricular failure, and may present with reduced ejection fraction, pulmonary edema, and elevated filling pressures. Cardiac arrhythmias are also frequent in the early post-operative period, occurring in more than 60% of recipients. Sinus node dysfunction is particularly common, occurring in up to 50% of patients, while atrial fibrillation and atrial flutter are also observed. Ventricular arrhythmias are less common but remain clinically important when present. (21,27)

Alloimmune complications remain central to the post-transplant complication profile. Acute allograft rejection may occur as hyperacute rejection, acute cellular rejection (ACR), or antibody-mediated rejection (AMR). (21) ACR is the most common form and is primarily T-cell mediated, whereas AMR involves donor-specific antibodies directed against antigens expressed on donor tissue. Hyperacute rejection, historically associated with ABO incompatibility, is now rare in contemporary practice. Despite advances in immunosuppressive therapy, rejection remains particularly relevant within the first post-transplant year, with acute rejection reported in 32.9% of recipients at 1 year. Clinical presentation varies from asymptomatic rejection detected on surveillance endomyocardial biopsy to severe graft dysfunction with cardiogenic shock. (21)

Over longer follow-up, cardiac allograft vasculopathy (CAV) becomes one of the major graft-related complications. (21) It represents a progressive form of accelerated coronary artery disease involving both immune and non-immune mechanisms. Because the transplanted heart is denervated, angina is often absent, meaning the condition may progress without typical ischemic symptoms. The incidence increases with time after transplantation, with approximately one-third (33%) of recipients affected within 5 years and approximately half affected by 10 years. (21)

The need for lifelong immunosuppression produces a separate group of post-transplant complications. (21,27) Infectious complications are particularly frequent in the early

post-operative period, when immunosuppressive intensity is highest. Opportunistic infections, including cytomegalovirus, fungal infections, and bacterial infections, are common, while other reported infectious complications include surgical site infection, pneumonia, and line-related infections. Infection risk is highest early after transplantation and generally decreases after the first year as immunosuppressive dosing is reduced. (21,27)

Long-term immunosuppression also contributes to malignancy risk through reduced host immunosurveillance and increased susceptibility to oncogenic viral effects. Epstein–Barr virus (EBV), human herpesvirus 8, human papillomavirus (HPV), and hepatitis B and C have been implicated in post-transplant malignancy. Skin cancers, particularly basal cell carcinoma and cutaneous squamous cell carcinoma, are common, and post-transplant lymphoproliferative disorders are also recognized. Reported risk factors include male sex, older age, prior malignancy and re-transplantation. Malignancy accounted for approximately 22% of deaths annually 5 years following transplantation. (21)

Renal dysfunction is another major immunosuppression-related complication and source of post-transplant morbidity. (21) Calcineurin inhibitors, including tacrolimus and cyclosporine, are nephrotoxic and may contribute to chronic renal failure. Renal dysfunction was reported in 45% of recipients at 1 year. (21) In severe cases, renal dysfunction may progress to the need for hemodialysis or kidney transplantation. Renal complications may also be influenced by pre-existing kidney disease, intraoperative factors, and post-operative hemodynamic instability. (21,24,27)

Additional perioperative and early post-operative complications include coagulopathy, bleeding, thromboembolism, tricuspid regurgitation, and respiratory complications. (27,28) Post-operative bleeding is common, whereas thromboembolism appears less frequent early after transplantation. Tricuspid regurgitation is also frequently observed, usually mild and asymptomatic, although it may become clinically significant in some recipients. Respiratory complications include prolonged ventilation and pulmonary dysfunction, particularly in patients with hemodynamic instability or right ventricular impairment. (21,27)

3.4 Quality of Life and Functional Outcomes

Quality of life and functional outcomes were evaluated across the reviewed studies using physician-assessed functional class, objective exercise measures, patient-reported quality-of-life scores, psychological outcomes, and measures of daily activity or disability. The most frequently reported functional measure was New York Heart Association (NYHA) functional class, which categorizes HF symptoms from class I (no limitation of ordinary activity) to class IV (symptoms at rest.) Objective functional outcomes included six-minute walk distance (6MWD) and peak oxygen uptake (peak VO_2), while patient-reported outcomes included the Kansas City Cardiomyopathy Questionnaire (KCCQ), the EuroQol-5 Dimension questionnaire (EQ-5D), the EuroQol visual analogue scale (EQ-VAS), the 36-Item Short Form Health Survey (SF-36), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). In these instruments, higher KCCQ, EQ-VAS, EQ-5D index, and SF-36 scores indicate better health status, whereas lower MLHFQ scores indicate better heart-failure-related quality of life. (29–31)

3.4.1 Functional Class

Contemporary third-generation LVAD data demonstrate substantial improvement in NYHA functional class after implantation, particularly with HM3. In the ELEVATE registry, NYHA functional class improved from 53% class IV at baseline to 82% class I-II at 6 months. (32) In the MOMENTUM-3 quality-of-life analysis, baseline functional limitation was even more severe, with 95% of patients in NYHA class IV before implantation; by 6 months, 77% had improved to NYHA class I-II. These results show a shift from symptoms at rest or severe limitation with minimal activity to absent or mild symptoms during ordinary activity in most contemporary HM3 recipients with available follow-up data. (32)

Older magnetically levitated LVAD recipients showed a similar direction of functional improvement. In the Society of Thoracic Surgeons Interagency Registry for Mechanically Assisted Circulatory Support (STS-Intermacs) 2025 Annual Report, among patients aged 65

years or older receiving magnetically levitated LVADS, 83% were NYHA class IV and 14.2% were NYHA Class III before implantation. (33) At 6 months, 9.5% were NYHA Class I, 47.5% were class II, 25.8% remained class III, and 7.35% remained NYHA class IV. Therefore, even with older LVAD technology, approximately 57.0% of older recipients were NYHA class I-II at 6 months, while approximately one-third remained class III-IV. (33)

Longer-term LVAD functional-class data are available from BTT cohorts, although some involve earlier continuous-flow devices rather than HM3. In a Japanese nationwide bridge-to-transplant LVAD registry of 442 patients supported with HMII, 77.6% were NYHA class IV before implantation. (29) By 3 months after implantation, 86% had improved to NYHA class I-II, and more than 80% remained in NYHA class I-II through 60 months of follow-up. Although this was not an HM3 cohort, it provides long-term evidence that durable LVAD support can sustain improvement in functional class among BTT patients. (29,31)

Heart transplantation also demonstrated strong functional recovery, particularly among selected long-term survivors. In a cohort of 75 HT recipients assessed 20-31 years after transplantation, 95.7% were NYHA class I-II, including 87% in class I and 8.7% in class II; 4.3% were class III and 0% were class IV. (31) Only 15.2% had reduced left ventricular ejection fraction (LVEF), defined as less than 55%. Thus, very long-term HT survivors in this cohort generally retained favorable clinical functional class and preserved systolic graft function. (31)

3.4.2 Patient-Reported Quality of Life

Third-generation LVAD studies report large early gains in patient-related health status. In a scoping review and meta-analysis of 11 third-generation LVAD studies, pooled data from 4 studies and 332 patients showed a mean 28.92-point increase in EQ-VAS at months compared with baseline, with a 95% confidence interval of 26.71-31.14 and low heterogeneity ($I^2=15\%$). (32) Since EQ-VAS asks patients to rate their overall health from 0 to 100, this represents a large improvement in patient-related overall health after third-generation LVAD implantation. HM-3 specific data show similar improvement. In the ELEVATE registry, EQ-VAS increased from 36

at baseline to 67 at 6 months post-implantation. (34) In MOMENTUM-3, KCCQ increased by 28 points at 6 months. Because KCCQ is scored from 0 to 100 and measures HF symptoms, physical and social limitation, and quality of life, a 28-point increase indicates a large improvement in disease-specific health status. (32)

Contemporary magnetically levitated LVAD data in older patients also show improved patient-reported outcomes. In the STS-Intermacs 2025 Annual Report, among patients aged 65 years or older, mean KCCQ increased from 38.6 before implantation to 65.4 at 6 months, while EQ-VAS increased from 52 to 74. (33) A KCCQ score in the high 30s reflects poor-to-fair health status with substantial HF limitation, whereas a score in the mid-60s reflects fair-to-good health status. (33) Broader continuous flow-LVAD registry data, meanwhile, show that patient reported improvements may persist beyond early follow-up among patients with available data, although these cohorts included multiple device types rather than HM3 alone. In an STS-Intermacs analysis of 22,230 continuous-flow LVAD recipients, EQ-VAS improved from 38.2 ± 28.3 before implantation to 70.7 ± 22.9 at 6 months. (30) Among patients with 3-year data, EQ-VAS improved from 40.1 ± 27.8 at baseline to 70.3 ± 23.1 at 3 years. KCCQ improved from 28.2 ± 23.9 to 64.3 ± 23.2 at 6 months and from 29.8 ± 23.7 to 63.0 ± 23.7 at 3 years. These changes represent improvement from severe HF-related limitations to a substantially better patient-reported health state. (30)

HT was also associated with improved health-related quality of life. In a systematic review of 22 adult HT studies, including 14 cross-sectional studies, 6 prospective studies, and 2 mixed-methods studies, post-transplant health-related quality of life was generally stable up to 10 years after transplantation. (35) In one prospective comparative study summarized in the review, MLHFQ scores improved from 72 to 29 after transplantation and were better at 3, 6 and 12 months compared with LVAD-supported patients. Since lower MLHFQ scores indicate fewer HF-related symptoms and limitations, this reflects substantial disease-specific quality-of-life improvement after HT. (35) Very long-term HT survivors maintained preserved quality-of-life scores but had lower physical quality-of-life scores than matched controls. In recipients assessed 20-31 years after HT, SF-36 (which surveys general physical and mental health, including physical function, social function, pain, vitality and emotional well-being) physical $58.19 \pm$

30.49 versus 84.74 ± 18.76 in controls, physical role functioning was 51.64 ± 44.22 versus 80.17 ± 32.70 , and general health perception was 47.9 ± 24.37 versus 64.29 ± 18.17 . (31) The SF-36 physical component summary was 40.77 ± 14.54 versus 50.88 ± 9.82 . By contrast, SF-36 mental component summary scores were similar between HT recipients and controls— 47.15 ± 15.06 versus 48.89 ± 10.16 —and Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores did not differ significantly. (31)

3.4.3 Exercise Capacity and Physical Performance

Objective exercise capacity after LVAD implantation improved in several studies, although long-term exercise data often come from earlier continuous-flow devices. In a Japanese BTT registry of 422 HM-II-supported patients, 6MWD increased from 331 ± 105 m at baseline to 447 ± 101 m at 3 months ($p=0.004$). (29) Peak VO_2 increased from 11.9 ± 3.4 mL/kg/min to 13.3 ± 4.3 mL/kg/min at 3 months ($p=0.002$). Both improvements were maintained during follow-up to 60 months. In the same cohort, the EQ-5D index (which surveys general health across mobility, self-care and daily activities) increased from 0.64 to 0.79, and EQ-VAS increased from 50 to 80 at 3 months. (29) Rehabilitation data further support functional improvement after LVAD implantation. One systematic review and meta-analysis reported an additional 60.06 m improvement in 6MWD for LVAD patients who participated in exercise-based cardiac rehabilitation (EBCR) compared with standard therapy. (36) EBCR was also associated with a 1.64 mL/kg/min improvement in peak VO_2 . However, peak VO_2 and exercise capacity often remained below age-adjusted normal values after LVAD implantation. (36) STS Intermacs also reported a nearly 180 meter improvement in 6MWD post implant. (23)

Comparative longitudinal data suggest that physical quality of life may increase further after HT following BTT LVAD support. In a cohort of 19 patients followed from pre-LVAD status through LVAD support and then HT, SF-36 physical component summary improved from 22.9 ± 10.4 before LVAD implantation to 40.1 ± 7.1 during support and increased further to 46.3 ± 7.9 after HT. (37) SF-36 mental component summary remained stable, from 49.1 ± 15.0 before implantation to 52.4 ± 6.3 during support and 53.3 ± 5.8 after HT. (37) Additionally, in a

prospective cohort of 45 heart transplant recipients followed for 1 year after transplantation, functional exercise capacity improved substantially, with 6-minute walking distance increasing by approximately 175 ± 16 m from hospital discharge to 12 months post-HT. However, despite this recovery, 6MWD remained below age- and sex-matched predicted values at 1 year. (38)

3.4.4 Daily Activities, Disability, and Lifestyle Limitations

LVAD therapy improved symptoms and perceived health status, but daily activity and social participation did not always improve to the same degree. In one Japanese cohort of 32 LVAD recipients, EQ-VAS improved from 45.0 to 76.5 ($p=0.001$), EQ-5D-5L index improved from 0.59 to 0.77 ($p=0.008$), SF-12 physical component summary improved from 22.8 to 37.7 ($p=0.017$), and SF-12 mental component summary improved from 48.6 to 56.9 ($p=0.001$). (39) MLHFQ score improved from 73.5 to 41.5 ($p=0.003$). However, SF-12 role/social component did not significantly improve, changing from 38.7 to 29.4 ($p=0.395$), and the Frenchay Activities Index, which measures domestic, leisure, and outdoor activity, changed from 11.0 to 14.5 without statistical significance ($p = 0.108$). (39) Post-discharge disability data show that a substantial minority of LVAD recipients continue to have broad functional limitations. In a two-center study of 121 discharged LVAD patients living at home, 65.3% had no disability by WHODAS 2.0, while 34.7% had disability, including 25.6% with moderate disability and 9.1% with severe disability. (40) Moderate-to-extreme EQ-5D problems were reported by 24–35% of patients across mobility, self-care, usual activities, pain or discomfort, and anxiety or depression domains. EQ-VAS was ≥ 80 in approximately one-third of patients, but ≤ 40 in approximately 10%, meaning that a minority of discharged LVAD patients continued to rate their overall health poorly despite living at home with device support. (40)

Device-related lifestyle limitations were specific to LVAD therapy. In a mixed-methods study developing an LVAD-specific quality-of-life measure, patient-reported domains included general health, life with the LVAD, equipment and clothing, and emotional impact. (41) Patients reported limitations related to: battery management, equipment weight, driveline care, dressing changes, clothing restrictions, sleep disturbance, travel, social participation, infection anxiety,

family dependence, and emotional adjustment. (41) These device-specific burdens are not directly captured by NYHA class, 6MWD, KCCQ, EQ-5D or other previous metrics.

HT removes the need for external device hardware and driveline management, but long-term daily function remains influenced by chronic post-transplant morbidity. Among recipients 20–31 years after HT, cardiac allograft vasculopathy was present in 87%, compensated renal insufficiency in 52.2%, hemodialysis in 19.5%, renal transplantation in 8.7%, malignant skin cancer in 29.5%, and post-transplant lymphoproliferative disorder in 15.2%. (31) These chronic conditions coexisted with favorable NYHA class and preserved mental health scores. (31)

3.4.5 Psychological Outcomes

Psychological outcomes differed between LVAD and HT populations. In a two-center study of discharged LVAD patients, 14.9% had moderate-to-severe depression by Patient Health Questionnaire-9 (PHQ-9), 11.7% reported suicidal ideation, 17.5% had moderate-to-severe anxiety by Generalized Anxiety Disorder-7 (GAD-7), and 23.5% screened positive for possible post-traumatic stress disorder using the Impact of Event Scale-Revised (IES-R). (40) At the end of the interview, 15% requested referral to mental health services. Hospital readmission was associated with worse psychological outcomes: 18 of 21 patients with moderate-to-severe anxiety and 23 of 28 patients with a positive post-traumatic stress screen had at least one readmission. (40) It is also worth mentioning that LVAD patients often have to balance the physical and psychological aspects of living with a physical, external device, including the need to be connected to a power supply and inability for certain physical activities like swimming, saunas, or other forms of sport and relaxation. (21)

HT recipients showed more stable psychological outcomes in long-term survivor cohorts. At 20–31 years after HT, SF-36 mental component summary scores did not differ significantly from matched controls, and HADS anxiety and depression scores were also similar. (31,35) However, patient-reported functioning was associated with social support. Cluster analysis identified lower and higher functioning HT recipient groups, and the lower-functioning group had lower perceived social support scores than the higher-functioning group, 54.89 ± 8.3 versus

62.87 ± 5.63. A systematic review of HT quality of life similarly found that depression, demoralization, pain, gastrointestinal symptoms, sexual dysfunction, and poor oral health were associated with worse quality of life, while social and family support were associated with better quality of life. (31,35)

3.4.6 LVAD vs HT Comparative Quality of Life

Direct comparative quality of life evidence is certainly limited across literature, but some studies show different trajectories between LVAD support and HT. In the aforementioned 19-patient BTT cohort, physical quality of life improved after LVAD implantation and improved further after HT: SF-36 physical component summary increased from 22.9 ± 10.4 before implantation to 40.1 ± 7.1 during LVAD support and 46.3 ± 7.9 after HT. (37) SF-36 mental component summary remained relatively stable across all phases. (37) The same cohort also showed the treatment burden associated with prolonged BTT LVAD support. Mean LVAD support duration was 64.1 ± 14.7 months, 16 of 19 patients (84.2%) required at least one readmission while awaiting HT, and 7 of 19 patients (36.8%) underwent pump exchange because of complications such as pump thrombosis or mechanical failure. (37) Lastly, in a separate HT systematic review, one prospective comparative study reported better MLHFQ scores after HT than during LVAD support at 3, 6, and 12 months, with the score decreasing from 72 to 29 after HT. Physical function also improved significantly in HT recipients compared with LVAD patients at 12 months. (35)

3.5 Healthcare Utilization and Costs

3.5.1 Contemporary HT vs HM3 LVAD Costs

The strongest contemporary comparative evidence comes from a Finnish real-world study of 78 AHF patients treated at Helsinki University Hospital between 2022 and 2025, after the center adopted exclusive use of the HM3 for LVAD implantation. (42) Patients were categorized as primary HT, HT after prior LVAD, elective LVAD and urgent LVAD; urgent LVAD was defined by pre-procedure ECMO, reflecting greater acuity. The results of the study show costs were concentrated early after intervention. At 3 months, median cost per patient was €177,380

for primary HT, €207,826 for HT after prior LVAD, €187,558 for elective LVAD, and €293,355 for urgent LVAD. At 6 months, median costs were €190,229, €221,266, €199,867, and €316,139, respectively. Urgent LVAD was significantly more expensive than both primary HT and elective LVAD at 3 and 6 months; at 3 months, the comparisons were $p=0.004$ versus primary HT and $p=0.003$ versus elective LVAD. (42)

By 12 months, median costs were €186,561 for primary HT, €231,638 for HT after prior LVAD, €209,660 for elective LVAD, and €303,407 for urgent LVAD. (42) At 24 months, they were €175,692, €231,782, €235,884, and €314,548, respectively. (42) These costs are visualized in Figure 5 below. Differences were no longer statistically significant at these later time points, largely because of wider variation and smaller follow-up samples. All groups had a sharp cost peak in the first 3 months, followed by marked decline thereafter. In primary HT, early costs were primarily tied to the surgery and intensive care, whereas in elective LVAD, device/equipment costs were the most substantial, and in urgent LVAD, both device costs and emergency care contributed. The data indicates that the main driver of excess cost in urgent LVAD was critical-care utilization rather than the equipment or procedure itself. Compared with elective LVADs, urgent LVADs required longer intensive care unit stays (20.5 vs 5 days), longer ventilator time (13 vs 2 days), longer total hospital stay (55.5 vs 21 days), higher dialysis use (50% vs 6.7%) and more frequent RVAD support (30% vs 3.3%). These results suggest that cost differences are strongly shaped by timing and acuity of LVAD implantation rather than by the LVAD therapy alone. (42)

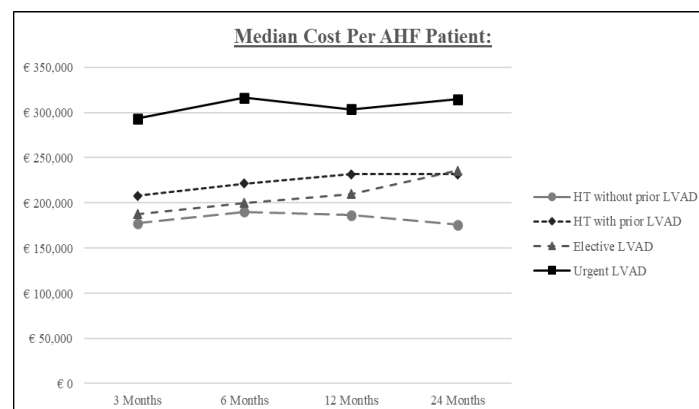


Figure 5. Median costs per advanced heart failure patient treated in Helsinki University Hospital across a 24-month period. Data extracted from Kandolin et al. (42)

3.5.2 National Index Hospitalization Costs

Older United States national inpatient data provide a broader context for the system-level utilization of both LVADs and HT. From 2009 to 2014, the National Inpatient Sample identified 28,765 total index hospitalizations for either HT or LVAD implantation: 11,435 of those were for HT, and 17,330 for LVAD. (43) Annual HT hospitalizations increased from 1,795 to 2,140 during this timeframe, while LVAD hospitalizations increased more dramatically from 2,205 to 3,645. According to this data, LVAD implantation had a greater index hospitalization burden than HT. The median length of stay for LVADs was 28 days versus 21 days for HT, and the mean index hospitalization cost was \$224,684 vs \$181,497. LVAD recipients also had a greater baseline comorbidity burden, with 55.4% having a Charlson Comorbidity Index of at least 3 compared with 45.7% of HT recipients. (43)

Annual expenditure increased substantially for both procedures. HT annual expenditure rose from approximately \$288 million to \$451 between 2009 and 2014, while LVAD expenditure nearly doubled from \$400 million to \$800 million. (43) Combined annual expenditure increased from approximately \$688 million to \$1.25 billion. Medicare and Medicaid together accounted for more than approximately half of index hospitalization costs, with Medicare spending approximately \$770 million on HT and \$1.8 billion on LVAD implantation during the study period. HT after LVAD support also carried a higher index transplant cost. Mean cost of HT hospitalization with concurrent LVAD explantation was \$201,848 compared with \$174,793 without LVAD explantation, indicating additional procedural costs associated with BTT pathways. (43)

3.5.3 LVAD and HT Readmissions and Cost Drivers

Post-implant healthcare utilization after LVAD therapy seems primarily tied to readmissions and complication management. In a large STS-Intermacs analysis of 22,250 continuous-flow LVAD recipients, rehospitalization occurred in 53.3% by 6 months and 80.4% by 3 years. (30) Early adverse events include many of the aforementioned complications intrinsic to LVAD therapy, such as infection and bleeding. A single-center LVAD cost analysis of 87

patients surviving at least 12 months showed that LVAD costs were strongly front-loaded. (44) Median Medicare reimbursement for the initial LVAD hospitalization was \$230,509 with the median postoperative length of stay of 22 days. However, the median total inpatient cost for the first year was \$247,208, while median readmission cost per patient was \$21,851, or approximately 9.5% of the initial implantation cost. (44) Thus, in other words, more than 90% of first-year inpatient cost occurred during the index hospitalization, which corroborates the data from Helsinki University suggesting that initial upfront costs dominate financial burden. (30,42)

Readmissions remained common despite being proportionally less costly than implantation. In the first year after LVAD implantation, 70% of patients had at least one readmission; 50% of readmitted patients had their first readmission within 38 days of discharge, and 75% within 4 months. (44) The most common readmission causes include some of the complications mentioned previously, with GI bleeding affecting 25.3% of patients and infections affecting 16.1%. The most expensive complication took form in the shape of device malfunction requiring exchange—although less common (8.0%), median reimbursement was \$230,509 and median length of stay was 27.5 days, essentially equivalent to the original LVAD implantation admission. (44) Revenue data from a larger single-center cohort of 163 second- or third-generation LVAD recipients similarly identified recurrent heart failure and infection as major post-LVAD cost drivers. (45) The mean primary LVAD hospitalization lasted 59 ± 50 days, including 29 ± 36 intensive care unit days. During follow-up, patients generated 588 analyzed readmissions, with mean additional inpatient time of 70 ± 87 days per patient. Recurrent heart failure accounted for 16.84% of readmissions and 25.82% of readmission revenue, while infection accounted for 14.97% of readmissions and 25.37% of readmission revenue. (45)

In a National Readmissions Database analysis in the USA of 12,111 patients treated from 2010 to 2014, 5,440 underwent HT and 6,671 underwent LVAD implantation. (46) The analysis demonstrated that although readmissions occurred frequently after both therapies, they were higher after LVADs, with 29% vs 24% at 30 days and 62% vs 46% at 6 months. (46) Readmission costs were also higher after LVAD implantation at both 30 days (\$29,115 vs \$21,586) and 6 months (\$34,878 vs \$20,144), in addition to the fact that readmission length of stay was longer after LVAD at both time points: 10.1 vs 6.81 days at 30 days and 10.4 vs 6.28

days at 6 months. (46) However, after adjusting for demographics, comorbidities, and disease severity, LVAD was not associated with significantly different odds of 30-day readmission compared to HT, though it did seem to have greater probability of 6 month readmission. This seems to suggest that the post-discharge utilization gap may be more pronounced over longer follow-up than during the immediate 30-day period. Additionally, readmission causes differed between the therapies in this study. The most common readmission diagnosis after HT involved complications of the transplanted heart itself, accounting for 31.0% of 30-day readmissions and 23.5% of 6 month-readmissions. Leading 6 month readmission causes for LVADs, meanwhile, included mechanical device complications (7.9%) and device infection (7.8%). (46)

3.5.4 Cost-Effectiveness of HM3 LVAD

HM3 cost-effectiveness models consistently show higher total costs than GDMT alone, but also substantially greater quality-adjusted survival. In a United Kingdom model of transplant-ineligible AHF patients, HM3 generated 2.8307 quality-of-life-years (QALYs) at a modeled cost of £141,598, compared with 0.4331 QALYs and £28,047 for medical therapy. (47) The incremental cost was £113,551, the incremental QALY gain was 2.3976, and the incremental cost-effective ratio (ICER; refers to the additional cost required to gain one additional life-year or QALY) was £47,361 per QALY gained. Cost-effectiveness was more favorable in inotrope-dependent patients, with an ICER of £45,616 per QALY, compared with £64,051 per QALY in less ill (INTERMACS 4-7) ambulatory patients. (47)

A Singapore model similarly found that HeartMate 3 increased both cost and QALYs. LVAD therapy produced 5.95 life-years and 4.15 QALYs at SGD 496,969, compared with 1.29 life-years, 0.71 QALYs, and SGD 92,292 for medical management. The ICER was SGD 117,370 per QALY gained, or approximately US \$87,590. Again, results were more favorable in inotrope-dependent patients (SGD 106,458 per QALY) than in inotrope-independent patients (SGD 174,798 per QALY). (48)

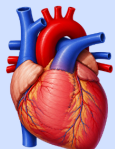
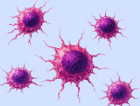
CONTEMPORARY OUTCOMES FOR HM3 LVADs			
1 Year Survival: ~86% 5 Year Survival: ~58.4-63.3% 	Complications: - Major infection - Cardiac Arrhythmia - Right Heart Failure - GI Bleeding - Stroke 	Significant and Sustained Functional Capacity Improvement: - ~80% Improvement to NYHA Class I and II - ~180 m improvement in 6-minute walk test distance 	Healthcare Costs: Elective LVAD at 24 months: € 235,884 Urgent LVAD at 24 months: € 314,548 
HEART TRANSPLANTATION OUTCOMES			
1 Year Survival: ~85% 5 Year Survival: ~72% 	Complications: - PGD - Acute rejection - CAV - Malignancy - Renal Dysfunction - Infections 	Significant and Sustained Functional Capacity Improvement: - ~96% Improvement to NYHA Class I and II - ~175 ± 16 m improvement in 6-minute walk test distance after 1 year	Healthcare Costs: HT without prior LVAD: € 175,692 HT with prior LVAD: € 231,782

Figure 6. A visual summary of the key contemporary outcomes after durable left ventricular assist implantation and orthotopic heart transplantation. Primary graft dysfunction here has been abbreviated as PGD, and cardiac allograft vasculopathy as CAV. Partially adapted from illustration by Tedford et al. (23)

Discussion

4.1 Analysis of Key Findings

4.1.1 Survival Outcomes

The findings of this review indicate that the comparison between durable LVAD therapy and HT cannot be reduced to a single hierarchy of outcomes. Instead, the relative performance of each therapy depends on a constellation of factors, including the outcome domain being assessed, the time horizon of follow-up, the generation of LVAD technology studied, the indication for implantation, and importantly, the baseline clinical condition of the patient receiving either therapy. Across the reviewed literature, HT remains associated with the most

established long-term survival profile, but contemporary data overwhelmingly suggests that third-generation LVAD therapy, particularly the HM3, has substantially narrowed the early and intermediate-term survival gap and meaningfully expanded treatment access for patients who are not transplant candidates or who require BTT support. (20,49)

Survival outcomes of each therapy, either LVAD or HT, provide simple metrics by which to assess their long-term success, but the collective data assessed within this review suggests that survival alone does not tell the full story. The survival data show clear historical progression in LVAD outcomes, and even the earliest REMATCH trial data showed first-generation LVAD therapy provided survival benefit at 2 years compared with GDMT (23% vs 8%), showing that despite the clear superiority of contemporary HM3 technology, any generation of LVAD therapy provides AHF patients better outcomes than GDMT therapy alone. (20) The HM3 era demonstrates superiority over previous LVADs like the HM-II in most meaningful ways—the MOMENTUM-3 trial data shows its improved 2- and 5- year survival free from disabling stroke or device malfunction (76.9% vs 64.8% with HM-II at 2 years, 58.4% vs 43.7% at 5 years) and higher overall 5-year survival (58.4% vs 43.7%). Conditional 5-year survival among patients discharged after index hospitalization was even greater at 62%, highlighting critically the importance of early post-implant survival and recovery. (20)

The comparison of LVAD survival to HT survival reveals that the survival gap has been shrinking generationally, and that at present, early follow-up within 1- and 2- year intervals is similar between the two therapies. HT registry data reports 86% survival at 1 year compared with 80 to 87% in LVAD cohorts, 79-86% survival compared to 83% at 2 years, and by 5 years, 72% HT survival compared with 58.4% to 63.3% survival for HM3 VLAD recipients in MOMENTUM-3 and ELEVATE registries. (20–22,34) Therefore, LVAD and HT survival outcomes appear similar in the selected cohorts up until 5 years, at which point HT retains better long-term survival. However, direct survival comparisons are critically limited by selection bias. (50) HT recipients are highly selected for transplant eligibility, whereas LVAD cohorts include both BTT and DT patients who often present with greater comorbidity, older age, renal dysfunction, or other contraindications to transplant. (7,18,20,21) In other words, HT survival outcomes benefit from the fact that patients are in comparatively better overall baseline health.

(18) Even propensity-matched evidence referenced here, which showed lower 5-year mortality among transplant waitlisted patients compared with DT LVAD patients, cannot be interpreted as a pure treatment effect alone—it also reflects differences in candidacy, reversibility of end-organ dysfunction, and baseline clinical risk. This distinction is especially critical for any discussion on LVADs and HT and will be expanded upon further in a forthcoming section on patient selection and timing of therapy, because the main survival finding is not simply that one therapy is superior, but that survival comparisons are heavily mediated by patient selection and treatment indication.

4.1.2 Complication Profiles

The complication data show that LVAD therapy and HT expose patients to fundamentally different morbidity profiles. LVAD complications are dominated by hemocompatibility-related events, infection, neurological events, RHF, arrhythmias, aortic regurgitation, and inherently, device-related complications. (20,21) While HM3 has reduced several historically important LVAD complications, particularly pump thrombosis and stroke, it has not eliminated the broader morbidities associated with long-term mechanical support. For example, the 5-year MOMENTUM-3 follow-up showed a lower stroke rate with HM3 compared with HM-II (0.05 vs 0.136 events per patient year), yet stroke still occurred in 10.7% of patients within 5 years and remained strongly associated with reduced post-implant survival. (20) This trend continues with other LVAD complications, too, where improvements do not translate to total eliminations. Bleeding and infection remain persistent limitations for LVAD therapy, for example, as despite a 44% reduction in overall bleeding risk and a 40% reduction in GI bleeding with HM3 over HM-II, GI bleeding still occurred in 27.8% of HM3 patients within 5 years. (20,22) Infections also remained frequent with more than half of patients experiencing infection over long-term support and driveline infections representing a uniquely device-related vulnerability. In other words, HM3 has improved the hemocompatibility profile of LVAD support but not removed the consequences of continuous-flow physiology, acquired von Willebrand syndrome, anticoagulation, external hardware, and a percutaneous driveline. (20,21,30)

RHF is another particularly important complication because it has not been substantially reduced by HM3 technology unlike those mentioned previously. Although LVADs unload the left ventricle, they do not directly support the right ventricle, which must continue delivering blood through the pulmonary circulation to fill the LVAD-supported left side. RHF affected 29.9% of HM3 patients within 5 years and remains strongly associated with morbidity and mortality. (20) The reported incidence varies widely depending on definition, ranging from approximately 5% when defined by postoperative RVAD requirement to as high as 40% when prolonged inotropic use is included. (20) This variability highlights both the clinical importance of right ventricular reserve and the methodological problem of inconsistent complication definitions.

HT complications, in contrast, are centered on graft function, alloimmune injury, immunosuppression, and late graft vasculopathy. Early post-transplant risk includes primary graft dysfunction, reported at 13.9% within 24–72 hours, while acute rejection occurs in approximately 32.9% of recipients within the first year. (21,27) Over longer follow-up, cardiac allograft vasculopathy becomes a major limitation, affecting approximately one-third of recipients by 5 years and around half by 10 years. Immunosuppression also produces a distinct long-term burden, including infection, malignancy, and renal dysfunction. Renal dysfunction has been reported in 45% at 1 year, and malignancy accounts for approximately 22% of deaths annually beyond 5 years post-transplant in the cited literature. (21,27)

Therefore, the major complication finding is not that LVADs simply have “more” complications than HT, but that the complications are mechanistically different. LVAD morbidity arises from the presence of a mechanical device, altered flow physiology, anticoagulation, driveline exposure, and right ventricular dependence. (21,27) HT morbidity arises from donor-organ injury, rejection, lifelong immunosuppression, vasculopathy, renal toxicity, and malignancy. (27) This distinction matters clinically because the two therapies require different surveillance strategies, different patient counseling, and different long-term management priorities.

4.1.3 Quality of Life and Functional Outcomes

Both LVAD therapy and HT were associated with substantial improvement in functional status and health-related quality of life, but the pattern of recovery differed. Contemporary third-generation LVAD data show large early gains from a severely impaired pre-implant state, with HM3 datasets showing patients overwhelmingly shifted from NYHA class III-IV to class I-II by 6 months—53% class IV at baseline to 82% class I-II at 6 months according to the ELEVATE registry, and 95% at class IV before implantation transitioning to 77% at class I-II in MOMENTUM-3 post-implant. (32,34) Patient-reported outcomes improved in parallel, with almost every self-reported patient metric showing meaningful gains, including a 28-point KCCQ increase in MOMENTUM-3 and a EQ-VAS improvement from 36 to 67 in ELEVATE. (33,40,41) These improvements are clinically meaningful because they represent a transition from severe, often resting symptoms to a level of function compatible with ordinary activity in many patients.

HT also produces strong functional recovery, particularly among long-term survivors. In a cohort of recipients assessed 20-31 years after transplantation, 95.7% were NYHA class I-II and none were class IV. (29,32,33) Mental health outcomes were also relatively preserved, with SF-36 mental component scores similar to matched controls. However, physical quality of life remained lower than in controls in these reports, including lower physical functioning, general health perception, and overall physical component summary scores. (39,40) These findings suggest that HT can certainly provide durable functional status and psychological stability among selected survivors, but not complete normalization of physical health.

The quality-of-life comparison therefore depends on which domain is being measured. LVAD therapy produces large early improvements in symptoms, perceived health, and walking capacity, but residual limitations critically include device management, battery dependence, driveline care, clothing restriction, caregiver dependence, infection anxiety and readmissions. (39,40,51) HT avoids external device burden but is associated with its own set of potential chronic complications ranging from cardiac allograft vasculopathy, renal dysfunction, malignancy and immunosuppression. (31) Thus, the key quality-of-life finding is that both

therapies improve the AHF state, but neither restores patients to a completely uncomplicated normal health state on their own. While broadly it can be stated that HT recipients generally experience superior long-term quality of life compared to LVAD patients and have potentially better outcomes, these advantages are tied to the fact that HT is free from an external device and allows patients to participate in most physical activities without burden. (21,52) LVAD recovery is often rapid but device-dependent in comparison; HT recovery is more physiologic but complicated by draft and immunosuppression-related morbidity. (27,53,54) This supports the need to evaluate functional class, exercise capacity, patient-reported outcomes, psychological status and daily-life restrictions are separate but deeply related outcomes.

4.1.4 Healthcare Utilization and Costs

The cost and utilization findings show that both LVAD therapy and HT are resource-intensive, especially early after intervention. The most relevant contemporary comparative evidence used in this review comes from the Finnish HM3-era cohort from Helsinki University, which showed primary HT and elective HM3 LVAD had broadly similar early cost trajectories, while urgent LVAD was substantially more expensive—at 3 months, median costs were €177,380 for primary HT, €207,826 for HT after prior LVAD, €187,558 for elective LVAD, and €293,355 for urgent LVAD. (42) At 6 months, costs were €190,229, €221,266, €199,867, and €316,139, respectively. Urgent LVAD was significantly more expensive than both primary HT and elective LVAD at 3 and 6 months. (42) The Finnish study is particularly important because it demonstrates that cost is strongly influenced by urgency and acuity rather than device therapy alone. Compared with elective LVAD, urgent LVAD required longer intensive care unit stay (20.5 vs 5 days), longer ventilator time (13 vs 2 days), longer total hospital stay (55.5 vs 21 days), higher dialysis use (50% vs 6.7%), and more frequent right ventricular assist device support (30% vs 3.3%). (42) This directly links timing of referral and implantation to healthcare utilization. In other words, delayed intervention after deterioration to extracorporeal membrane oxygenation-level acuity appears to convert LVAD therapy into a much more resource-intensive pathway.

Historical U.S. national data also provide broader system-level context. Between 2009 and 2014, LVAD implantation had higher mean index hospitalization cost than HT (\$224,684 vs \$181,497) and longer median length of stay (28 vs 21 days). (43) Annual LVAD hospitalization volume also increased more rapidly than HT volume, rising from 2,205 to 3,645 cases compared with 1,795 to 2,140 for HT. Annual expenditure nearly doubled from \$400 million to \$800 million for LVAD implantation and from \$288 million to \$451 million for HT. (43) These older data are not HeartMate 3-specific but show the growing system-level burden of durable mechanical support. (55) As LVAD technology has evolved to better suit patient needs and become more available, costs and investment tied to its adoption have also seemingly increased. (43,45,56) This is particularly important considering the fact that HT is critically limited by available donors, meaning continued investment and expansion related to LVAD is both necessary and inevitable. (4)

Readmission data also shows higher recurrent utilization after LVAD implantation than after HT in older national cohorts. The National Readmissions Database analysis of 12,111 patients showed 30-day readmissions were 29% after ventricular assist device implantation versus 24% after HT, and 6-month readmissions were 62% versus 46%. (30) Readmission costs were also higher after ventricular assist device implantation: \$29,115 vs \$21,586 at 30 days and \$34,878 vs \$20,144 at 6 months. (30) However, readmissions were common after both therapies, with HT readmissions driven mainly by transplanted-heart complications, renal dysfunction, pulmonary embolism and other previously mentioned adverse events, whereas LVAD readmissions were driven by device infection, hemocompatibility issues, mechanical complications and recurrent HF. It is worth mentioning that this data comes from previous generation LVADs—in theory, improved HM3 should present significantly less complications for patients and therefore reduce readmissions and healthcare burden. This is an area where more mature, long-term datasets are missing due to the relatively recent adoption of HM3. Moreover, several studies demonstrated that healthcare utilization for both therapies were strongly front-loaded—in other words, the vast majority of expenditure was tied to index hospitalization. (30,44,45) This means costs tied to readmission contribute relatively less to overall resource and financial burden. Lastly, cost-effectiveness models of HM3 showed higher total cost than GDMT but substantial benefit to patients in terms of quality-adjusted survival. Both UK and Singapore

models showed that HM3 produced more QALYs compared with medical management, proving that from a patient-centered perspective, associated costs are worthwhile for health and longevity. (47,48)

The main utilization finding here, therefore, is that early costs within the first 3-6 months are similarly high for both HT and LVAD therapy, but the pattern of later utilization differs. While LVAD utilization is driven by factors tied to complications specific to the therapy (such as infections, device complications, and so forth), HT utilization is also driven by its own unique set of complications tied to graft surveillance, rejection monitoring, immunosuppression and malignancy surveillance. The most contemporary data from the Finnish HM3-era cohort suggests that elective HM3 LVAD and primary HT have very similar early cost profiles, whereas urgent LVAD is the most resource-intensive pathway. (42)

4.2 Patient Selection and Timing of Therapy

Patient selection and timing are central to interpreting the comparison between LVAD therapy and HT. *The outcomes reviewed in this thesis show that survival, complications, quality of life and costs are not determined by therapy alone, but by who receives the therapy, when it is delivered, and why it is chosen.* HT recipients are highly selected for key factors such as transplant eligibility, operative fitness, acceptable pulmonary vascular resistance, psychosocial stability, and their ability to adhere to lifelong immunosuppression. LVAD cohorts, meanwhile, are broader and include BTT, bridge-to-candidacy (BTC) and DT patients, many of whom are older or have comorbidities that exclude them from transplantation. (57)

Advanced therapy evaluation according to the Journal of the American College of Cardiology (JACC) follows an algorithmic three-step process:

- first, determining whether HT or LVAD is indicated (in other words, if the patient's prognosis on GDMT is poor enough that advanced therapies must be evaluated)
- second, identifying contraindications
- and last, deciding whether the patient should undergo HT, LVAD implantation, both sequentially, or neither. (7)

Their central algorithm begins with clinical assessment, imaging and right heart catheterization, then separates patients according to low-output syndrome, severe congestion, end-organ dysfunction, and eligibility for HT and/or LVAD. Patients eligible for both may be listed for HT but receive LVAD support if unstable; patients temporarily ineligible for HT may receive LVAD as BTT; and patients permanently ineligible for HT may receive LVAD as DT. Patients unsuitable for either therapy according to this algorithm are generally directed towards GDMT, inotropes, palliative care or hospice. (7)

The most important timing issue is referral before irreversible deterioration. Multicenter studies and cohort data seem to emphasize that, unfortunately, referrals are often delayed until patients have already progressed beyond optimal candidacy. (58) The “I NEED HELP” mnemonic mentioned in the introduction of this thesis for AHF patients identifies practical referral triggers: inotrope requirement, persistent NYHA III–IV symptoms or high natriuretic peptides, worsening renal or liver dysfunction, low ejection fraction, recurrent defibrillator shocks, HF hospitalization, persistent edema or escalating diuretics, low BP, and inability to tolerate prognostic medical therapy. (7) These features indicate that the patient is moving from chronic AHF into a stage where elective intervention may soon become urgent. This is consistent with the healthcare utilization findings of this thesis. In the aforementioned contemporary Finnish HM3 cohort, elective HM3 LVAD and primary HT had broadly similar early costs, whereas urgent LVAD was substantially more expensive. (42) Urgent LVAD patients were shown to require longer ICU stay, ventilator time, total hospitalization, dialysis and RVAD support than elective LVAD patients. They were also shown to have the poorest survival outcomes compared with any other group at 24 months, with progressive decline to 62.5% compared with 93.4% of elective LVADs and 84% of HTs without prior LVADs. (42) Thus, delayed referral and implantation after shock or extracorporeal membrane oxygenation-level illness may convert LVAD from a planned advanced therapy into a higher-risk rescue intervention.

Contraindications to HT also strongly influence whether LVAD becomes the preferred option. Typical HT candidates are usually under 70 years old, with single-organ failure, acceptable pulmonary hemodynamics, no active infection or malignancy, adequate social

support, and adherence to GDMT. (21) Contraindications include active substance abuse, irreversible end-organ dysfunction, severe obesity with a BMI >35 kg/m², significant cerebral or peripheral vascular disease, severe psychiatric illness, and fixed pulmonary hypertension. (59) LVAD may be appropriate when these factors are relative or potentially reversible, but still requires adequate patient LV size, absence of RV failure, commitment of the patient to care for the device, and dedicated caregiver or community support. (7,21,54)

Pulmonary hypertension and right ventricular (RV) function are especially important in choosing between therapies. Fixed pulmonary vascular resistance can make HT unsafe because the donor RV may fail against pulmonary afterload. (7) In some patients, LVAD unloading can reduce left-sided filling pressures and reverse pulmonary hypertension, allowing later transplant eligibility. Conversely, severe right ventricular dysfunction may make isolated LVAD support dangerous, because the LVAD depends on the native RV to deliver blood through the pulmonary circulation. The JACC therefore emphasizes the importance of distinguishing pulmonary hypertension, which may improve with LVAD support, from right ventricular failure, which may contraindicate isolated LVAD implantation. (20) This concern remains clinically important in the HM3 era. As mentioned previously, despite improved survival and reduced hemocompatibility-related adverse events with HM3, right heart failure remains a major limitation. (20)

Organ allocation policy also shapes timing. In 2018, the US allocation system replaced the older three-tier system with six active statuses, prioritizing patients on extracorporeal membrane oxygenation, temporary mechanical support, non-dischargeable biventricular support, intra-aortic balloon pump, life-threatening arrhythmias, or durable LVAD complications. (7) Stable LVAD patients after 30 days are generally status 4, meaning that stable durable LVAD support may increase waiting time compared with temporary support or severe device-related complications. This policy environment has changed LVAD use. In the U.S., LVAD implantation as BTT declined from 29.2% in 2014 to 8.9% in 2019, and the 2022 INTERMACS report showed that only about 5% of LVAD implants in 2021 were BTT, while 81% were DT. (7,60) This reflects not only changing context around policy, but also the increased effectiveness of HM3 as a viable DT therapy, rather than a temporary intermediary. In Europe, BTT LVAD use

increased from 33% in 2011 to 43% in 2020, likely reflecting lower donor availability and longer waiting times; reports reveal 4.2 heart donors per million population in Europe compared with 11.8 in the United States. (7,20)

Risk prediction tools can further refine selection. The Heartmate 3 Risk Score (HM3RS) used in the MOMENTUM-3 trial used six pre-implant variables: age, prior coronary artery bypass grafting, blood urea nitrogen, serum sodium, LV end-diastolic diameter less than 5.5 cm, and RA pressure to pulmonary capillary wedge ratio. (20) The score stratified patients into groups with 2-year survival of high-survival, average survival and low survival ($91\% \pm 2\%$, $83\% \pm 3\%$, and $68\% \pm 4\%$ respectively). These predictors reflect age, surgical complexity, renal/end-organ function, neurohormonal severity, ventricular size, and right-sided reserve. Predictors of 5-year mortality after HM3 implantation have also been described: elevated blood urea nitrogen, prior coronary artery bypass grafting or valve procedures, hemocompatibility-related adverse events, ventricular arrhythmias, and estimated GFR below 60 ml/min/1.73 m² at discharge. Patients without these predictors had a 5-year mortality of 22.6%, compared with 45.7% among those with at least one predictor. This reinforces that LVAD outcomes depend not only on device type, but also on baseline physiology, perioperative events, and post-discharge organ function. (20)

The terms BTT and DT are useful but imperfect. Patients in real-world clinical practice may move between categories: pulmonary hypertension reversal, weight loss, improved social support, or completion of a malignancy-free interval may convert a patient into a transplant candidate, while stroke, nonadherence, substance use, or weight gain may remove transplant eligibility. MOMENTUM-3 found no major outcome difference by preoperative BTT versus DT intent, suggesting that rigid labels may be less informative than patient-specific goals of survival, function, and quality of life. (7,20)

Overall, patient selection and timing explain much of the apparent outcome difference between LVAD and HT. HT is generally favored when the patient is transplant-eligible, has acceptable or reversible pulmonary vascular resistance, lacks prohibitive comorbidity, and can tolerate immunosuppression. LVAD is favored when durable support is needed but HT is unavailable, contraindicated, or temporarily unsuitable. Elective LVAD may stabilize patients

and improve candidacy, whereas urgent LVAD after shock, renal failure, respiratory failure, or right ventricular collapse is associated with higher cost and worse outcomes. (13,21,42) Therefore, the clinically meaningful comparison is not simply LVAD versus HT, but timely allocation of HT, elective LVAD, bridge-to-candidacy LVAD, destination LVAD, or palliative therapy according to patient biology, reversibility, organ availability, and treatment goals.

4.3 Limitations of the Current Evidence

Several limitations affect the strength of the current evidence comparing durable LVAD therapy with HT. The first limitation relates to the methodology of this thesis itself. Although this review used a structured search strategy, explicit inclusion and exclusion criteria, and organized extraction across survival, complications, quality of life, and healthcare utilization, it was not conducted as a formal systematic review. It therefore did not include protocol registration, formal risk-of-bias assessment, or quantitative meta-analysis. This limits the ability to generate pooled effect estimates and means that the conclusions should be interpreted as a structured qualitative synthesis rather than a definitive comparative meta-analysis.

A major limitation is the absence of truly equivalent comparison groups. HT recipients are highly selected for transplant eligibility, operative fitness, pulmonary vascular status, end-organ function, psychosocial support, and adherence. LVAD cohorts include a broader mixture of BTT, bridge-to-candidacy, and DT patients, many of whom are older or have contraindications to HT. Therefore, survival differences between LVAD and HT may reflect patient selection and treatment indication as much as the therapies themselves. Even propensity-matched analyses cannot fully adjust for unmeasured factors such as frailty, right ventricular reserve, reversibility of renal dysfunction, social support, or clinician judgment at the time of listing or implantation.

A second limitation is the imbalance in long-term follow-up. HT has decades of registry data, allowing evaluation of median survival, 10-year survival, chronic rejection, cardiac allograft vasculopathy, renal dysfunction, malignancy, and late graft failure. By contrast, HM3 data are still relatively immature. Contemporary HM3 studies provide strong 2- and 5-year data, including MOMENTUM-3 and ELEVATE, but 10-year survival and very long-term

complication data remain limited. (50,61–63) Long-term data beyond 5 years are still limited for HM3 because of its more recent introduction into clinical practice. This makes long-term comparison asymmetric: HT can be evaluated across decades, while HM3 must still be judged largely through mid-term follow-up. Device-era heterogeneity further complicates interpretation. Many studies include older pulsatile-flow devices, HeartMate II, HeartWare HVAD, or mixed continuous-flow cohorts rather than isolated HM3 populations. (16,25,64) This matters because outcomes differ substantially by device generation. HM3 reduced pump thrombosis, stroke, and reoperation for device malfunction compared with prior-generation devices, so older LVAD data may overestimate the risks of contemporary LVAD therapy. (65) Conversely, HM3-only studies may underestimate later complications that require longer follow-up to emerge, such as chronic infection, aortic regurgitation, right heart failure, device exchange, and cumulative quality-of-life burden. (17,66,67)

Inconsistent definitions of outcomes are another important limitation. Right heart failure is one clear example. In the reviewed literature, reported RHF incidence varies from approximately 5% when defined by postoperative RVAD requirement to as high as 40% when prolonged inotropic support is included. Similar issues affect infection, bleeding, neurological events, device malfunction, and quality-of-life endpoints. Without standardized definitions, differences between studies may reflect measurement variation rather than true clinical differences. Quality-of-life evidence is also limited by survivorship and response bias. Patients who die early, remain hospitalized, experience disabling stroke, require institutional care, or are too unwell to complete questionnaires are less likely to be represented in follow-up assessments. This may make both LVAD and HT quality-of-life outcomes appear more favorable than they are in the full treated population. In addition, generic instruments such as EQ-5D, SF-36, and KCCQ may not fully capture LVAD-specific limitations such as driveline care, battery dependence, inability to swim, equipment burden, sleep disruption, infection anxiety, and caregiver dependence. (40,41)

Finally, cost, utilization, and survival data are difficult to generalize across healthcare systems because they are influenced by national transplant policy, donor availability, insurance coverage, registry structure, patient selection, and center-level practice. This is evident in the

variability between LVAD registries. INTERMACS reported LVAD survival of 83.1%, 70.0%, and 60.8% at 1, 3, and 5 years, respectively, whereas EUROMACS reported lower survival of 70.4%, 55.6%, and 44.5% at the same intervals. (20) In contrast, the Japanese J-MACS registry reported higher early survival, with 1-year survival of 92% and 2-year survival of 88%. (20) These differences may reflect not only device performance, but also regional differences in transplant eligibility, waiting-list duration, BTT strategy, hospital authorization requirements, follow-up intensity, and national insurance policy. In Japan specifically, long waiting times for transplantation and a historically BTT-based LVAD system mean that registry patients may differ substantially from DT cohorts in the United States or Europe. (37,39,64) Therefore, registry outcomes should not be interpreted as directly interchangeable estimates of LVAD performance across healthcare systems.

Overall, the evidence supports several consistent conclusions, particularly that HM3 has improved LVAD outcomes, that HT has the most mature long-term survival data, and that both therapies improve function and quality of life. However, precise direct comparison remains limited by selection bias, unequal follow-up duration, device-era heterogeneity, variable outcome definitions, survivorship bias, and healthcare-system-specific cost data. These limitations mean that LVAD and HT outcomes should be interpreted as context-dependent rather than as fixed, directly interchangeable treatment effects.

4.4 Future Directions

Future research should first address the major evidence gap in long-term contemporary LVAD outcomes. Heart transplantation has mature registry data extending to 10 years and beyond, whereas HeartMate 3 (HM3) data remain strongest at 2–5 years, with limited evidence beyond that timeframe. (21) This imbalance makes long-term comparison inherently difficult. Future studies should therefore prioritize 10-year HM3 survival when that data becomes available, including late right heart failure, chronic infection, aortic regurgitation, device exchange, quality of life, caregiver burden, and cost trajectories, ideally in cohorts that distinguish elective LVAD, urgent LVAD, BTT, bridge-to-candidacy, and DT. HM3 long-term data beyond 5 years remain limited because of its relatively recent clinical introduction. (9)

The next major direction is device innovation. Contemporary HM3 technology has reduced pump thrombosis and stroke, but persistent limitations remain, particularly driveline infection, bleeding, right heart failure, rehospitalization, and device-related lifestyle burden. The future of LVAD therapy could involve “bioengineered LVADs,” including biocompatible blood-contact surfaces that may reduce coagulation activation, fully internalized driveline-free systems, physiologically responsive flow that adapts to patient demand, and transaortic flow designed to better preserve von Willebrand factor and septal function. (18,68) Future LVADs could potentially introduce innovations that provide better therapeutic outcomes: biocompatible devices, “forgettable” internalized devices, pulsatile/autoregulatory flow, and transaortic flow.

Right ventricular failure remains one of the most important unresolved barriers to durable LVAD success. Future work should improve pre-implant phenotyping of right ventricular reserve, develop better prediction models beyond simple hemodynamic thresholds, and refine strategies for temporary or durable right-sided support. Current models for predicting post-LVAD right ventricular failure perform poorly and the unsupported right ventricle remains a major limitation of isolated LVAD therapy. Future biventricular support and total artificial heart systems, including devices such as Bivacor and CARMAT, may become increasingly relevant for patients with biventricular failure or anatomy unsuitable for isolated LVAD support. (18,69) Future transplantation strategies could also focus on expanding donor availability and reducing long-term graft-related morbidity. Donation after circulatory death, ex vivo perfusion, hypothermic oxygenated machine perfusion, improved preservation systems, xenotransplantation, renal-sparing immunosuppression, and non-invasive rejection monitoring may all improve access and outcomes. (21)

Finally, future comparative research should also directly evaluate durable MCS and heart transplantation within the same healthcare systems. Much of the evidence synthesized in this thesis necessarily draws from separate LVAD trials, transplant registries, national inpatient datasets, cost-effectiveness models, and single-center cohorts, each with different patient populations, selection criteria, follow-up durations, outcome definitions, and reimbursement structures. This makes cross-study comparison informative but imperfect. Future studies should

compare contemporary HM3 LVAD therapy and HT head-to-head across survival, complications, quality of life, functional recovery, psychological outcomes, readmissions, healthcare utilization, and costs, while distinguishing elective LVAD, urgent LVAD, BTT, bridge-to-candidacy, and DT pathways. Ideally, these analyses should be conducted within the same national or regional healthcare system, using standardized definitions and comparable follow-up periods, so that differences reflect therapeutic strategy rather than registry structure, health-system context, or study design.

Conclusion

This thesis evaluated contemporary evidence comparing durable mechanical circulatory support, particularly HeartMate 3 left ventricular assist device (LVAD) therapy, and orthotopic heart transplantation (HT) in patients with advanced heart failure, with emphasis on survival, complications, quality of life, and healthcare utilization.

1. In terms of survival outcomes, contemporary HeartMate 3 LVAD therapy has significantly improved short- and intermediate-term survival, narrowing the gap with heart transplantation at 1- and 3-year follow-up. Across registries and clinical trials, early survival between LVAD and HT cohorts is broadly comparable; however, heart transplantation continues to demonstrate superior long-term survival.

Survival comparisons should not be interpreted, therefore, as absolute treatment superiority, but in the context of device generation, follow-up duration, treatment indication, and patient selection.

2. The complication profiles of LVAD therapy and HT differ fundamentally.
 - a. LVAD-related morbidity is driven primarily by device-related and hemocompatibility-associated complications, including bleeding, infection, stroke, right heart failure, arrhythmias, aortic regurgitation, and device malfunction. Although HM3 has markedly reduced pump thrombosis and stroke compared with earlier devices, complications such as driveline infection, gastrointestinal bleeding, and right heart failure remain clinically important.

- b. HT complications are primarily related to graft dysfunction, rejection, cardiac allograft vasculopathy, lifelong immunosuppression, renal dysfunction, infection, and malignancy.

These therapies are therefore not distinguished simply by having more or fewer complications, but by exposing patients to different long-term risks.

- 3. Both treatment strategies result in substantial improvements in quality of life and functional status in patients with advanced heart failure.
 - a. LVAD therapy produces substantial early improvement in NYHA functional class, patient-reported health status, and exercise capacity, particularly in patients who survive the index hospitalization and avoid major complications.
 - b. HT also provides durable functional recovery among selected recipients and removes the burden of external device dependence.

However, neither therapy restores a completely uncomplicated health state: LVAD recipients remain limited by device care, battery dependence, driveline management, infection risk, psychological burden, and readmissions, while HT recipients require lifelong surveillance for graft- and immunosuppression-related complications.

- 4. Healthcare utilization and cost analyses show that both LVAD therapy and HT are resource-intensive, especially during the early post-intervention period. Elective HM3 LVAD and primary HT may have similar early cost trajectories, whereas urgent LVAD is substantially more costly because of greater intensive care use, ventilation, dialysis, right ventricular assist device support, and prolonged hospitalization. Readmissions remain frequent after both therapies but are generally higher after LVAD implantation, especially over longer follow-up. These findings indicate that cost and utilization are strongly influenced by timing, acuity, complications, and healthcare-system structure.

Taken together, the findings of this thesis support the conclusion that durable left ventricular assist device therapy and orthotopic heart transplantation are best understood as complementary rather than competing strategies for advanced heart failure. Patient

selection and timing emerged as central determinants of outcome. HT recipients are highly selected, whereas LVAD populations include bridge-to-transplant, bridge-to-candidacy, and destination-therapy patients with broader comorbidity profiles. Delayed referral may convert a potentially elective advanced-therapy candidate into an urgent, higher-risk patient with worse outcomes and greater resource use. Findings support individualized, timely, and multidisciplinary decision-making in advanced heart failure. Future research should prioritize longer-term HM3 outcomes, standardized outcome definitions, direct LVAD-versus-HT comparisons within the same healthcare systems, and improved tools for identifying which patients benefit most from each therapeutic pathway.

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