Année 2020/2021 N°

Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

par

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Né le 08/07/1992 à Niort (79)

Caractéristiques et survie des patients avec insuffisance cardiaque terminale traités par assistance mécanique monoventriculaire gauche ou transplantation cardiaque à travers une cohorte nationale française rétrospective.

Présentée et soutenue publiquement le 27/ 09/ 2021 devant un jury composé de :

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre et méprisé de mes confrères
si j'y manque.

Introduction : L'objectif de notre étude était de décrire pour la première fois dans une comparaison exhaustive à l'échelle nationale les caractéristiques et la survie des patients en insuffisance cardiaque avancée traités par assistance mécanique ventriculaire gauche ou transplantation cardiaque.

Méthodes : Les données analysées ont été issues du programme de médicalisation des systèmes d'information (PMSI) français entre 2012 et 2020. La première partie a consisté à analyser la survie selon la prise en charge avec la méthode de Kaplan-Meier et les facteurs prédictifs de mortalité avec un test de Cox multivarié. Un appariement avec un score de propension a été réalisé pour équilibrer les facteurs de risques de morbi-mortalité. La seconde partie de l'analyse s'est intéressée aux différentes populations d'assistance ventriculaire gauche en comparant la morbi-mortalité des patients implantés d'un Heartmate III aux autres générations de LVAD.

Résultats : Cette cohorte rétrospective a regroupé 4843 patients, 3326 transplantés cardiaques et 1517 patients sous assistance ventriculaire gauche. Les patients transplantés étaient plus jeunes (48 ans vs 58 ans), comportaient plus de femmes (28% vs 16%) et avaient moins de cardiopathie ischémique (51% vs 76%). La survie toute cause à 1 an était significativement plus élevée pour les patients ayant eu une transplantation cardiaque 81 % contre 63 % pour les patients implantés d'une assistance ventriculaire gauche (Hazard ratio [HR] après appariement par score de propension 1.92, IC 95% 1.68-2.20 $p<0.001$). L'incidence d'accident vasculaire cérébral, d'hémorragie majeure et de choc septique était significativement plus élevée pour les patients assistés ($p<0.001$). Les patients sous HeartMate III avaient une survie significativement meilleure (HR 0.62, IC 95% 0.51-0.76) et un taux d'accident vasculaire cérébral significativement moins élevé (HR 0.32, IC 95% : 0.16-0.64) par rapport aux autres types d'assistance.

Conclusion : En France, la transplantation cardiaque reste la référence pour le traitement de l'insuffisance cardiaque terminale chez les patients encore jeunes avec peu de comorbidités et est associée à de meilleurs résultats que l'assistance ventriculaire gauche en termes de survie et morbidité. Les taux de survie restent néanmoins inférieurs aux standards nord-américains. Il s'agit, à notre connaissance, de la première étude apportant une différence significative de survie entre le HeartMate III et les autres assistances ventriculaires gauches.

Mots clés : Insuffisance cardiaque - transplantation cardiaque - assistance ventriculaire gauche – survie- accident vasculaire cérébral- HeartMate III

Title: Characteristics and survival of patients with advanced heart failure treated with left ventricular assist device (LVAD) or heart transplantation through a French national retrospective cohort.

Introduction: The aim of our study is to describe for the first time in an exhaustive nationwide comparison the characteristics and survival of patients with advanced heart failure treated with left ventricular assist device or heart transplantation.

Methods: Data were obtained from the French medicalization of information systems program (PMSI) between 2012 and 2020. Survival was analyzed according to patient's management using the Kaplan-Meier method and predictive factors of mortality were determining using a multivariate Cox test. A propensity score matching was performed to balance risk factors for morbidity and mortality. The second part of the analysis focused on the different LVAD populations and compared the morbidity and mortality of Heartmate III patients with the other LVAD.

Results: This retrospective cohort included 4843 patients of which 3326 heart transplant recipients and 1517 patients on LVAD. Transplanted patients were younger (48 vs 58 years), with more women (28% vs 16%), and had less frequent coronary artery disease (51% vs 76%). Survival at 1 year was significantly better in heart transplant patients compared with patients implanted with LVAD (81% vs 63%, Hazard ratio [HR] after propensity score matching 1.92; 95% CI 1.68-2.20 $p<0.001$). The incidence of stroke, major bleeding, and septic shock was significantly higher in LVAD patients ($p<0.001$). HeartMate III assist device was associated with significantly better survival (HR 0.62; 95% CI 0.51-0.76) and a significantly lower stroke rate (HR 0.32; 95% CI 0.16-0.64) in comparison with other devices.

Conclusion: In France, heart transplantation remains the reference treatment for end-stage heart failure in young patients with few comorbidities and is associated with better outcomes than LVAD. The survival rates remain lower than North American standards. To our knowledge, this is the first study to show a significant difference in survival between HeartMate III and other LVAD.

Keywords: Heart failure - heart transplantation - left ventricular assist device - survival- stroke - HeartMate III

Remerciements :

A mon maître et Président du jury, **Monsieur le Professeur Fauchier**,
Merci de me faire l'honneur de présider ce jury de thèse, votre contribution à ce travail a été précieuse tout comme votre enseignement durant mon internat. Merci d'avoir participé à mon attrait pour la rythmologie et de m'y accueillir d'ici quelques mois.

A mon maître et Directeur de thèse, **Monsieur le Docteur Thibaud Genet**,
Merci de m'avoir confié ce travail et de l'avoir dirigé. Merci de ton aide précieuse, de ta patience, de tes remarques et corrections avisés. Tu es un exemple de connaissance, de sérénité et de disponibilité, tu as été une vraie source d'inspiration durant mon internat.

A mon maître et juge, **Monsieur le Professeur Denis Angoulvant**,
Merci d'avoir accepté de juger ce travail. Votre enseignement, votre disponibilité et votre écoute sont un privilège au quotidien.

A mon maître et juge, **Monsieur le Professeur Thierry Bourguignon**,
Merci d'avoir accepté de juger ce travail. Merci pour votre expertise et votre disponibilité pour les dossiers chirurgicaux. Les échanges avec vous, en USCI, comme en staff sont toujours riches d'enseignement.

A mon maître et juge, **Monsieur le Docteur Xavier Bailleul**,
Merci d'avoir accepté de juger ce travail. Merci pour ton aide et de ta bienveillance lors des moments difficiles en garde. Merci pour ton expertise sur les cas complexes qu'on a pu te présenter en USCI.

Aux équipes médicales et paramédicales de la cardiologie du CHU de Tours : merci pour ces 4 dernières années qui sont passées à une vitesse incroyable, merci pour votre bienveillance au quotidien.

Aux équipes médicales et paramédicales des centres hospitaliers de Blois et de Bourges : merci de m'avoir accueilli au début de mon internat et d'avoir grandement contribué à ma formation. Franck, Bruno, Régis, Adi, Houssem, Nassim, Thierry, Mr.Lang et Mr.Marcollet : merci pour vos précieux enseignements.

A l'équipe de la réanimation médicale du CHU de Tours.

A l'équipe du CHU de Bordeaux et particulièrement à celle du 2ème étage de m'avoir accueilli et d'avoir partagé vos connaissances en rythmologie... Benjamin, Benjamin, Benjamin et Benjamine ce fut un plaisir de partager ce semestre avec vous, vous êtes des très bons gars !

A l'équipe d'Orléans, merci de m'accorder votre confiance et de m'accueillir pour cette année de docteur junior.

A Patrick et Fabrice : Merci pour votre précieuse aide dans ce travail.

Au Professeur Babuty, Nicolas, Bertrand, Clémentine, Arnaud, Alexandre et Vincent, merci de m'avoir donné envie de faire de la rythmologie vous êtes des monstres de connaissance et m'avez impressionné durant tout mon internat.

A Carl, merci pour ta présence et ton aide précieuse durant toutes ces années. Ta générosité est sans égale.

A Isabelle, merci de m'avoir appris à poser mes premiers pacemakers.

A Marion, Thibaud et Vincent, c'était une chance de débuter la cardiologie à vos côtés, c'en est une encore plus grande de vous avoir comme amis.

A Amélie, Rominou, Antonine, Kissel et Jean Ba: c'était super d'être dans votre promo, ces soirées angevines resteront gravées dans nos mémoires… ou pas !

A Val, Kissel et Jean Ba : merci pour ces semestres de colocation au top !

A mes co-internes, jeunes et moins jeunes : Flavie, Réda, Matthieu D, Jérémy, Matthieu G, Iris, Pascal, Alexis, Jonathan, Hanna, Maeva, Leprat, Roxane, Mickael, Lenormand, Marie, Pierre, Marine, Sihame, Ines, Ahmad, Yassine, Camélia, David, Karole, Léa, Charlotte, Justine, Perrine, Thibaud, Lionel ..

A mes amis d'Echiré, les moments passés avec vous sont toujours une vraie bouffée d'oxygène.

A Vera, Julie et Bastien : le temps passe mais rien ne change.

A ma famille, merci de m'avoir soutenu durant toutes ces années, qu'elle chance de vous avoir à mes côtés.

A Blandine, ma plus belle rencontre de cet internat, je te suis reconnaissant d'avoir été présente durant tous ces moments, les bons comme les (rares) mauvais, j'ai hâte de partager mon quotidien avec toi.

A Bross, elle est pour toi celle-là !

I- Table of contents

List of abbreviations

ABM: Biomedical agency

AHA: American Heart Association

BIVAD: Bi-Ventricular Assist Device

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

ECLS: ExtraCorporeal Life Support

ESC: European Society of Cardiology

EUROMACS: European Registry for Patients with Mechanical Circulatory Support

GRAM: Groupe de réflexion de l'Assistance Mécanique

HF: Heart Failure

HR: Hazard Ratio

HT: Heart Transplantation

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support

LVAD: Left Ventricular Assist Device

LVEF: Left Ventricular Ejection Fraction

MCS: Mechanical Circulatory Support

NYHA: New York Heart Association

PMSI: Programme de Médicalisation des Systèmes d'Information

RV: Right Ventricle

SD: Standard Deviation

TAH: Total Artificial Heart

II- Introduction

1- Advanced heart failure

A) Epidemiology

Heart failure (HF) is a major public health concern affecting 500,000 to one million patients in France, 6 million Americans, and more than 23 million people worldwide (1).

Estimating the prevalence of advanced HF remains an epidemiological challenge because its definition varies. Patients with advanced HF cover an estimated 1% to 10% of the overall HF population (2). Its prevalence increases due to a growing number of the overall HF population due to aging, treatments improvements, and increased survival.

B) Stages of HF

Multiple classifications have been established to identify every stage of HF (*Supplementary Figure 1*). Among the proposed classifications are New York Heart Association (NYHA), American College of Cardiology (ACC) and the American Heart Association (AHA)'s definition, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)'s profiles and a new Universal Definition and Classification of Heart Failure in April 2021 (*Supplementary Figure 2*) (3).

C) Definitions

There are three main definitions of advanced HF, emerging from different societies. In 2018, the European Society of Cardiology defined advanced HF using 4 criteria:

1. Severe and persistent symptoms of heart failure (NYHA class III or IV).
2. Severe cardiac dysfunction defined by a reduced left ventricular ejection fraction (LVEF) $\leq$ 30%, isolated right ventricular (RV) failure or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) Brain natriuretic peptide (BNP) or NT-pro BNP values and data of severe diastolic dysfunction or left ventricular structural abnormalities according to the ESC definition of heart preserved ejection fraction and heart reduced ejection fraction.
3. Episodes of pulmonary or systemic congestion requiring high doses of intravenous diuretics (or diuretics combinations), or episodes of low output requiring inotropes or

vasoactive drugs, or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.

4. Severe impairment of exercise capacity with inability to exercise or low 6 minutes walking test (<300m) or VO^2 Peak (< 12-14ml/kg/min) estimated to be of cardiac origin.

AHA and HF society of America had their own definition (4). *Supplementary Table 1* summarizes the characteristics and criteria for each classification.

D) Course of heart failure and prognosis

The clinical course of HF is progressive but nonlinear and is characterized by a worsened quality of life despite increased care levels (*Supplementary Figure 3*). When HF diagnosis is established, there is a period of drug initiation and titration followed by, when appropriate, resynchronization therapy. Initial response to treatment is of the utmost importance, as the inability to titrate indicates a poor prognosis (5,6). After this first stage, there is usually some improvement from few months to several years. However, as the disease progresses, the functional status declines, resulting in multiple hospitalizations for HF worsening.

When this happens, few therapeutic options remain: palliative inotropes, or advanced therapies, including mechanical circulatory support (MCS), and transplantation for younger patients with few comorbidities. The therapeutic choice for each patient with advanced HF isn't easy and requires multidisciplinary Heart Team approaches.

In the Rematch trial, which involved randomized patients with chronic heart failure who were ineligible for heart transplantation, to receive a LVAD, or optimum medical therapy, the prognosis was poor (7). Patients in the medical therapy arm had survival rates at 1 and 2 years of 25% and 8%, respectively. A retrospective analysis of sample derived from the Framingham Offspring and Third Generation Studies confirmed this poor prognosis for late-stage HF (8).

Accurate prognostic evaluation is particularly important in advanced HF in order to reduce the time for referral to an expert center. A mnemonic has been suggested by Jay Baumwol and reused by the ESC in its position statement in 2018 (9). It lists the main clinical and biological markers for advanced HF to help clinicians with referral considerations for advanced therapies. There are several scores for advanced HF to help clinician assess the evolution of the course of the disease. Among them, the most used are the Seattle Heart Failure Model (SHFM) and the Heart failure Survival score (HFSS) (10,11). A 1- year estimated survival of <80%, as calculated by the SHFM, or a HFSS in the high/medium risk range should be considered reasonable cutoffs for registering a patient on heart transplant lists.

2- Heart transplantation

Heart transplantation (HT) remains the gold standard therapy for selected patients with demonstrable improvements in quality of life, functional status, and longevity when compared with conventional therapy. HT is reserved for younger and less comorbid patients. Main indications and contraindications are well described (12,13). An estimated 6000 heart transplantations are performed worldwide each year (14).

The main concern after heart transplantation is the consequence of both limited effectiveness and complications following immunosuppressive therapy (infections, rejection, late graft dysfunction, malignancy, cardiac allograft vasculopathy, renal dysfunction).

Two surgical procedures have been described since the first transplantation in 1967. The first one was described by Lower and Shumway and consists in keeping native atria from the recipient, and the latest was the bicaval's technique performed by Dreyfus with removal of the right atrium while maintaining the left atrium roof.

In France, about 350 to 450 heart transplantations are performed every year. Patients' registration and graft allocations are managed by the "Agence de la Biomédecine". Despite this number, there are still 500 new registrations per year and about 60 deaths on the waiting list (*Supplementary Figure 4*). In 2018, the allocation system changed to promote transplantation with long-term mechanical support for patients. This contributes to the increase of LVAD implantation in France (*Supplementary Figure 5*).

3- Long-term mechanical circulatory support

Long-term support with durable MCS devices such as LVAD in patients with advanced HF offers survival benefits and improves quality of life compared with conventional treatments in inotrope-dependent patients, or patients with contraindications for heart transplantation.

Using the Intermacs cohorts as a reference, LVAD represents 92% of all assisted patients, Bi-Ventricular Assist Device (BiVAD) 6%, and total artificial heart (TAH) 2% (15).

First mechanical circulatory devices were implanted in 1984 and were equipped with a pulsatile axial system. Next, they evolved towards axial continues flow system (second generation: HeartMate II: Abbott Inc., Chicago, IL, USA; Jarvik 2000: Jarvik Heart Inc., New York, NY, USA) and most recently centrifugal-flow (third generation: HeartWare Medtronic Inc.,Minneapolis, MN, USA) and an intrathoracic left ventricular assist device with fully

magnetically levitated (Heart Mate III Abbott Inc., Chicago, IL, USA) to try to reduce adverse effects (16) (*Supplementary Figure 6*).

Hemocompatibility is the biggest challenge for LVAD, and head of pump thrombosis, thromboembolic bleeding events, and strokes have an increased prevalence after 2 years of implantation (15).

Indications and eligible criteria for LVAD implantation are proposed by HFA and ESC (12,13). In 2019, almost 3200 LVAD were implanted in the world (17).

All LVAD were not implanted in the same purpose. Different strategies have been described:

- Bridge to candidacy: Use of MCS to improve end-organ function in order to make an ineligible patient eligible for heart transplantation.
- Bridge to transplantation: Use of MCS to keep a high-risk patient eligible to transplantation alive until a donor organ becomes available.
- Bridge to recovery: Use of MCS to keep patient alive until cardiac function recovers sufficiently to remove MCS.
- Destination therapy: Long-term use of MCS as an alternative to transplantation in patients with end-stage HF ineligible to transplantation or long-term awaiting for heart transplantation.

In its 2021 recommendations, ESC proposes an algorithm for of patients with advanced HF (*Supplementary figure 7*) (13).

4- Aim of the study

There are several cohort studies on LVAD, particularly in France, e.g. the group for reflection on mechanical circulatory assistance GRAM's cohort and most recently ASSIST-ICD study (18,19). There are also several cohorts worldwide with follow up and outcomes for heart transplantation (14). In France, data come from the "Agence de la Biomédecine" (ABM).

To our knowledge, no national registry or study ever compared LVAD and heart transplant populations. The aim of our study was to compare patient characteristics and outcomes following heart transplantation and LVAD in France. Our secondary endpoint was to analyze the impact of latest LVAD on mortality and morbidity.

III- Methods

1- Study design

This French longitudinal cohort study was based on the national hospitalization database covering hospital care from the entire national population, namely the PMSI (Programme de Médicalisation des Systèmes d'Information) which was inspired by the U.S. Medicare system. Since 2004, the budget of each hospital has been associated to the medical activity described in this specific program, which compiles discharge abstracts related to all admissions for inpatients in the 1 546 French healthcare facilities.

Each hospitalization is encoded in a standardized dataset, which includes information about the patient (age and sex), hospital, stay (date of admission, date and mode of discharge), pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the International Classification of Diseases-10th Revision (ICD-10). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Médicaux. The PMSI contains individual pseudonymized information on each hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for each patient. The reliability of PMSI data has already been assessed, and this database has been previously used to study patients with LVAD (20,21) and heart transplantation (22).

The study was conducted retrospectively and, since patients were not involved in it, there was no impact either or their health or on their care. Therefore, ethical approval was not required, as all data was anonymized. The French Data Protection Authority granted access to the PMSI data. This type of study was approved by the institutional review board of the "*Pôle Coeur Thorax Vaisseaux"* from the Trousseau Medical University on December 1, 2015, and registered as a clinical audit. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés, the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139).

2- Study population

Data of all patients (> 18 years) admitted in French hospitals for LVAD or heart transplantation between 2012 and 2020 were collected to study survival and to identify potential predictors of all-cause and cardiovascular mortality. To identify LVAD implantation and each device we used LPP's code (Liste des produits et prestations, e.g. 3430126 for Jarvik 2000). For transplantation, we excluded from the analysis patients with a prior transplant or a combined transplant, using codes DZEA002 and DZEA003 (Classification Commune des Actes Médicaux). Patient information (demographics, comorbidities, medical history, and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined diagnoses at discharge were obtained. Each variable was identified using ICD-10 codes. Mode of death (cardiovascular or non-cardiovascular) was identified based on the main diagnosis during hospitalization resulting in death.

3- Outcomes

Primary endpoint

Patients were followed from January 1st, 2012 until December 31st, 2020 for the outcomes. We evaluated the incidence of all-cause mortality, cardiovascular mortality, stroke, cerebral bleeding, right heart failure, septic shock, major bleeding, graft rejection and cancer.

Secondary endpoint

We analyzed morbidity and mortality of the latest LVAD generation compared with the others from 2012 and after 2017 to reduce the impact of patient's selection, optimization of care and complication overtime, and thus reduce temporal biases. A sensitivity analysis was performed by excluding patients transplanted after LVAD in each group to minimize a possible allocation bias with too many bridge to transplant patient in one group.

4- Statistical analysis

All analyses were performed using Stata version 16.0 (StataCorp, College station, Texas). Qualitative variables are described as frequency and percentages and quantitative variable as mean with standard deviation (SD). Comparisons were made using chi-square tests for categorical variables and the Student's t-test or nonparametric Mann-Whitney U test, as appropriate, for continuous variables. A multivariable Cox was used to identify predictors of all-cause death. After univariate analysis a matching was done with a propensity score with of all data of characteristics baseline. Survival analysis was produced with Kaplan Meier's methods. HR and two-sided 95% confidence intervals (CI) were estimated using Cox proportional hazards model for all outcomes of interest. All comparisons with a p-value <0.05 were considered statistically significant.

IV- Results

1- Baseline characteristics

Figure 1 displays the flow chart of 4 843 patients included in the cohort from January 2012 to December 2020, of which 3 326 patients (68%) were treated with a heart transplant and 1 517 with a LVAD.

Heart transplant patients' mean age was 48 years, 72% were male, and 51% had coronary heart disease. Comparatively, LVAD patients were more likely to be older (58 years), male (84%), and more frequently had coronary artery disease (76%). They had a higher frailty index at 13 against 10 ($p<0.001$). In addition, 36% of patients in both groups had an ECLS before transplantation or LVAD. These data are presented in **Table 1** with other baseline characteristics.

Figure 2 represents the number of heart transplantation and LVAD implantation for each calendar year, from 2012 to 2020. A more detailed distribution shows that HeartMate III became predominant after 2018.

Figure 1. Flowchart of study population.

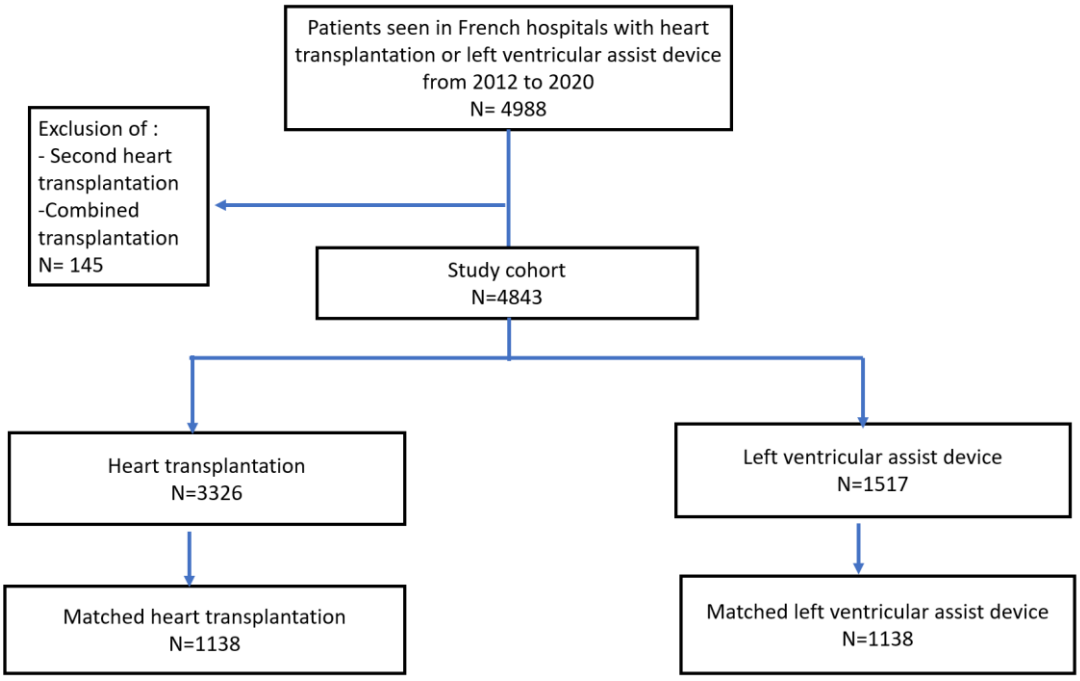
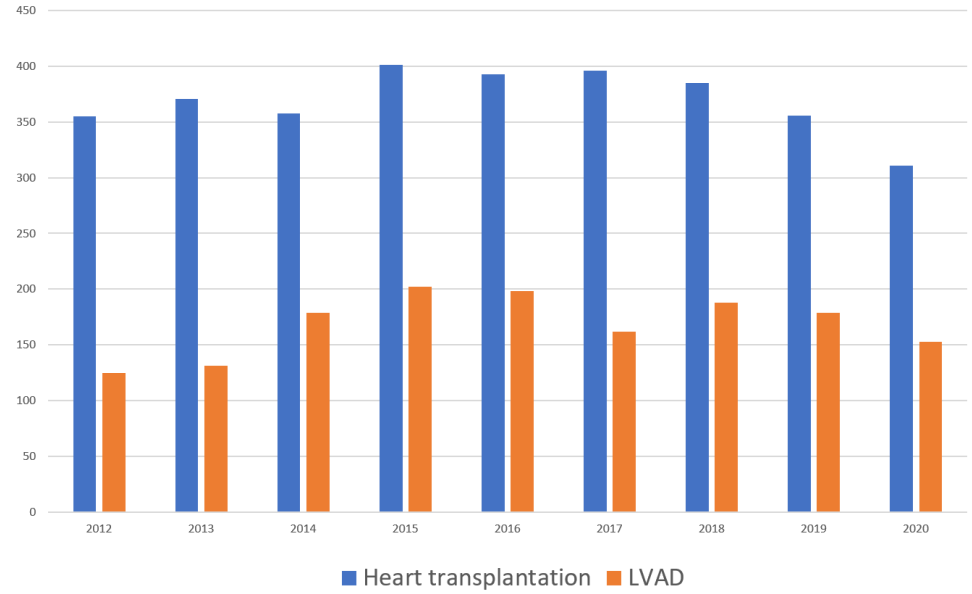


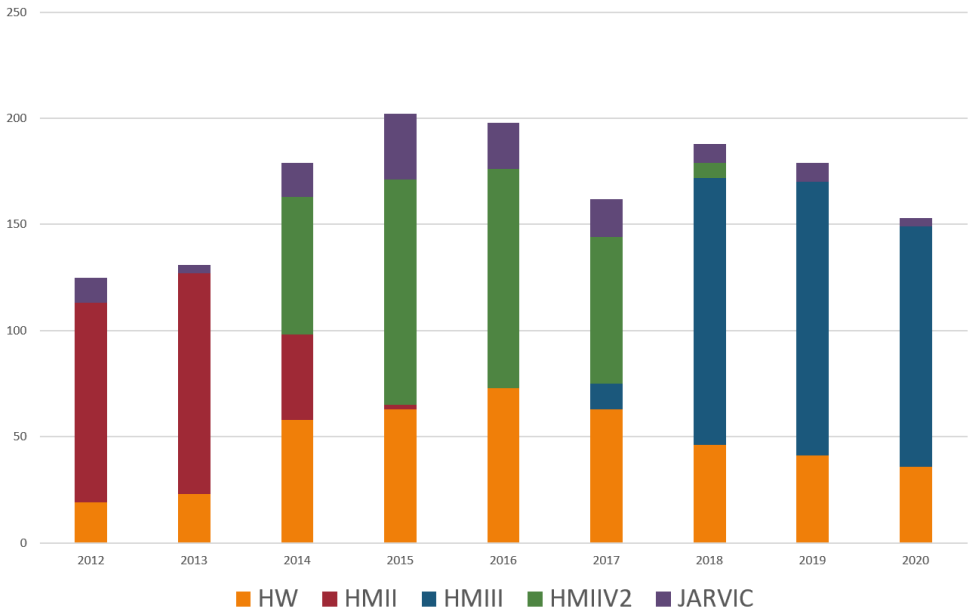
Table 1. Baseline characteristics of patients with heart transplantation or LVAD.

	Heart transplantation	LVAD	p	Total
	(n=3326)	(n=1517)		(n=4843)
Demographics				
Age, years	48±15	58±12	<0.001	51±15
Gender (male)	2399 (72)	1276 (84)	<0.001	3675 (76)
Obesity (> 30kg/m²)	706 (21)	434 (29)	<0.001	1140 (24)
Medical history				
Dyslipidemia	958 (29)	647 (43)	<0.001	1605 (33)
Arterial hypertension	1485 (45)	806 (53)	<0.001	2291 (47)
Smoking status	895 (27)	558 (37)	<0.001	1453 (30)
Diabetes mellitus	652 (20)	444 (29)	<0.001	1096 (23)
Alcohol related diagnoses	341 (10)	183 (12)	0.06	524 (11)
Cardiac condition				
Coronary artery disease	1694 (51)	1157 (76)	<0.001	2851 (59)
Congenital heart disease	300 (9)	33 (2)	<0.001	333 (7)
Dilated or other cardiomyopathy	1332 (40)	327(22)	<0.001	1659 (34)
History of arrhythmia				
Cardiac arrest	468 (14)	299 (20)	<0.001	767 (16)
Ventricular tachycardia	1102 (33)	562 (37)	0.01	1664 (34)
VT ablation	189 (6)	98 (7)	0.29	287 (6)
CRT	565 (17)	227 (15)	0.08	792 (16)
ICD	1557 (47)	629 (42)	0.001	2186 (45)
Pace Maker	323 (10)	124 (8)	0.09	447 (9)
Atrial fibrillation	1755 (53)	864 (57)	0.01	2619 (54)
Initial severity				
Cardiogenic shock	2597 (78)	1290 (85)	<0.001	3887 (80)
Dobutamine infusion	2611 (79)	1231 (81)	0.04	3842 (79)
ECLS	1193 (36)	545 (36)	0.97	1738 (36)
IABP	238 (7)	185 (12)	<0.001	423 (9)
Mechanical ventilation	2086 (63)	939 (62)	0.58	3025 (63)
Comorbidities				
Vascular disease	1235 (37)	977 (64)	<0.001	2212 (46)
Ischemic stroke	291 (9)	190 (13)	<0.001	481 (10)
Lung disease	679 (20)	414 (27)	<0.001	1093 (23)
COPD	246 (7)	207 (14)	<0.001	453 (9)
Sleep apnea syndrome	354 (11)	239 (16)	<0.001	593 (12)
Chronic kidney disease	716 (22)	317 (21)	0.62	1033 (21)
Liver disease	1063 (32)	469 (31)	0.47	1532 (32)
Anaemia	1188 (36)	664 (44)	<0.001	1852 (38)
Poor nutritional status	879 (26)	506 (33)	<0.001	1385 (29)
Previous cancer	179 (5)	111 (7)	0.01	290 (6)
Thyroid disease	630 (19)	282 (19)	0.77	912 (19)
HIV	17 (1)	6 (1)	0.59	23 (1)
Cognitive impairment	21 (1)	12 (1)	0.53	33 (1)
Depressive disorder	407 (12)	203 (13)	0.27	610 (13)
Charlson comorbidity index	5.50±2.76	6.14±2.59	<0.001	6±3
Frailty index	10±8	13±9	<0.001	11±8

Values are n (%) or mean ±SD. COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronisation Therapy; ECLS = Extracorporeal Life Support; HIV = Human Immunodeficiency Viruses; IABP = Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT = Ventricular Tachycardia.

Figure 2. Heart transplantation and LVAD implantations by year.





LVAD= left ventricular assist device; HM = Heartmate®; HW = Heartware®.

2- Survival analyses

In the heart transplant population, all-cause mortality was 24% during a mean follow up of 310±590 days; 1-year survival rate was 81%.

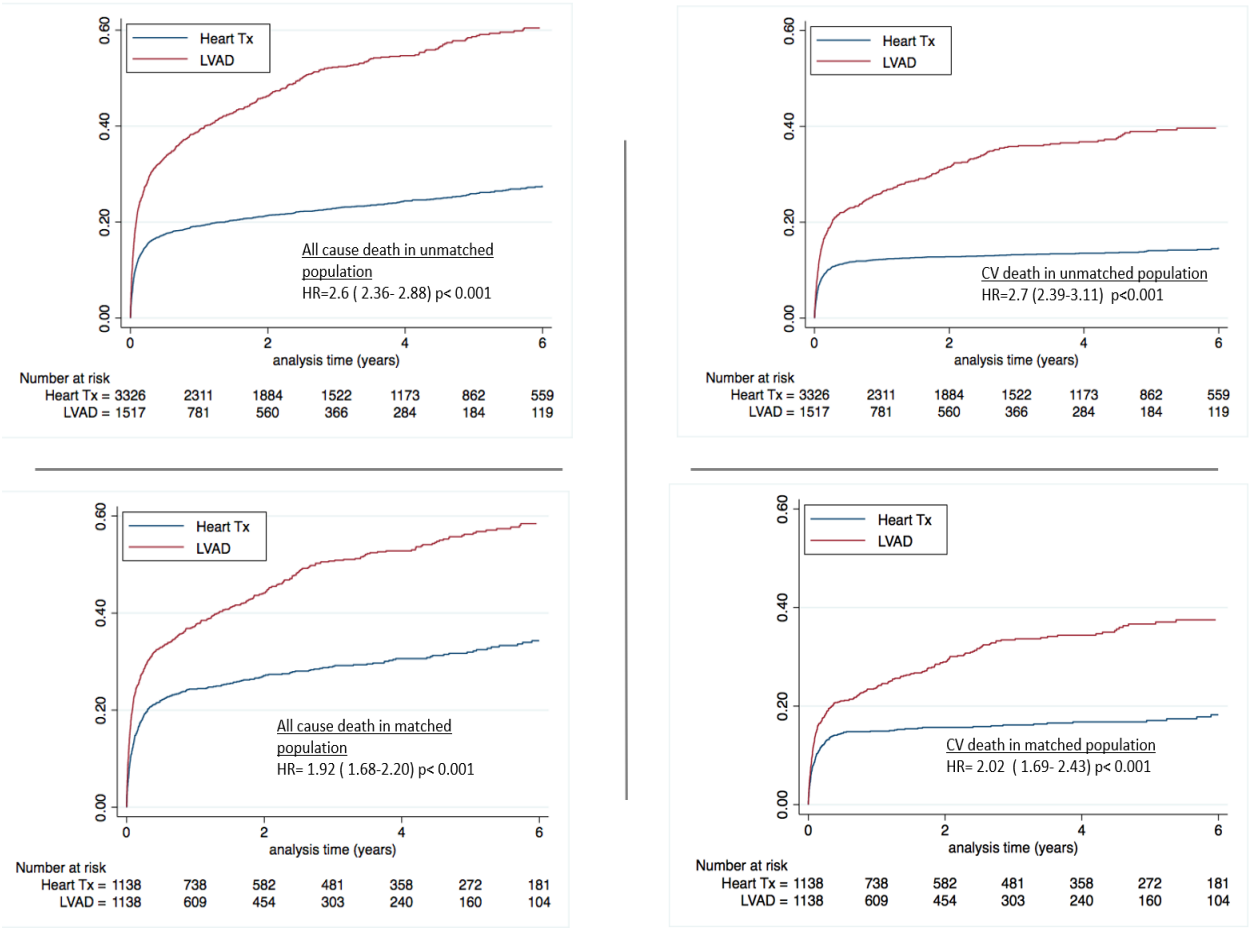
All-cause mortality for LVAD population was 51%; mean follow up was 307±513 days; 1-year survival was 63%. A number of 407 (26.8%) patients were transplanted after LVAD implantation within an average delay of 428 days.

Using propensity score, 1 138 LVAD patients were adequately matched in a 1:1 fashion with 1 138 heart transplant patients. All data are presented in **Table 1**.

The survival for all 4 843 patients and matched populations is illustrated in **Figure 3.**

Characteristics of matched populations and standardized percentage bias across main baseline characteristics are presented in *Supplementary Table 2* and *Supplementary Figure 8*.

Figure 3. Kaplan-Meier survival curves in unmatched and matched populations.



Values are HR with (95% Confidence Interval) and p value; CV = cardiovascular; HR = hazard ratio; LVAD = left ventricular assist device; Tx = transplantation.

In univariate analysis, all-cause and CV mortalities were significantly higher in the LVAD group with an HR of 2.6 (95% CI: 2.36-2.88; p<0.001) and 2.7 (95% CI: 2.4-3.11; p<0.001) respectively.

After propensity matching, all-cause mortality was significantly higher in LVAD patients with a HR of 1.92 (95% CI: 1.68-2.2; p<0.001); HR was 2.02 for CV mortality (95% CI: 1.69-2.43; p<0.001).

Table 2 presents a multivariable analysis of independent predictors of mortality: age, congenital heart disease, ECLS, kidney and liver disease were the most relevant variables together with gender, frailty index, arterial hypertension and diabetes mellitus. In multivariate analysis, considering all variables presented in table 1, all-cause mortality was significantly higher in the LVAD group compared to heart transplant patients, with an HR of 2.13 (95%CI: 1.90- 2.38; p<0.001).

Initial severity had a very negative impact in each group. Cardiogenic shock before transplantation or LVAD was associated with a higher mortality rate: HR of 1.40 (CI 95% 1.20-1.64; p<0.001). ECLS strengthened this information with a HR of 1.92 (CI 95% 1.64-2.24; p<0.001). These data are illustrated in **Figure 4** and in *Supplementary Table 3*.

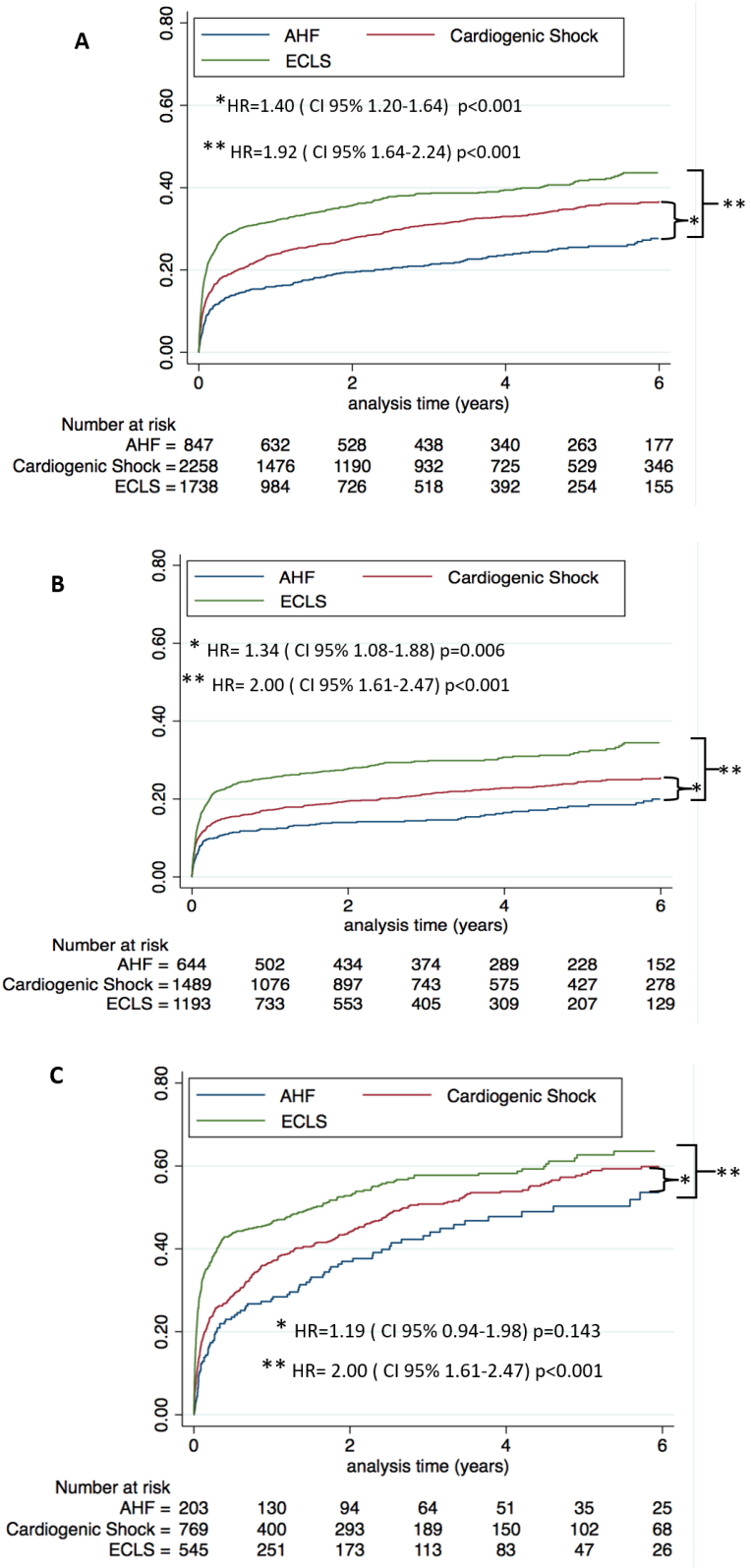
Table 2. Analysis multivariate of predictors of mortality.

	Hazard.Ratio	P>|z|	[95% Conf. Interval]	
Demographics				
Age, years	1.03	<0.001	1.02	1.03
Gender (male)	0.86	0.017	0.76	0.97
Obesity (>30kg/m²)	1.11	0.085	0.98	1.25
Medical history				
Dyslipidemia	1.11	0.064	0.99	1.25
Arterial hypertension	1.14	0.022	1.02	1.28
Smoking status	0.89	0.065	0.79	1.01
Diabetes mellitus	1.23	0.001	1.09	1.40
Alcohol related diagnoses	1.09	0.261	0.93	1.29
Cardiac condition				
Coronary artery disease*	0.99	0.953	0.86	1.14
Congenital heart disease*	1.35	0.010	1.07	1.69
History of arrhythmia				
Cardiac arrest	1.74	<0.001	1.53	1.97
Ventricular tachycardia	0.84	0.003	0.75	0.94
Atrial fibrillation	0.98	0.794	0.88	1.10
CRT	0.96	0.637	0.83	1.12
ICD	0.99	0.884	0.88	1.11
Pace Maker	1.35	<0.001	1.14	1.59
VT ablation	1.19	0.098	0.97	1.47
Initial severity				
ECLS	1.43	<0.001	1.28	1.60
IABP	0.85	0.065	0.71	1.01
Cardiogenic shock	1.17	0.031	1.01	1.35
Mechanical ventilation	0.99	0.856	0.88	1.11
Comorbidities				
Peripheral vascular disease	1.02	0.776	0.89	1.17
Ischemic stroke	1.15	0.088	0.98	1.35
Lung disease	1.07	0.390	0.92	1.23
COPD	1.16	0.143	0.95	1.40
Sleep apnea syndrome	1.01	0.874	0.87	1.17
Chronic kidney disease	1.33	<0.001	1.18	1.50
Liver disease	1.69	<0.001	1.51	1.90
Anaemia	1.04	0.470	0.93	1.16
Poor nutritional status	0.74	<0.001	0.66	0.84
Previous cancer	1.95	<0.001	1.62	2.34
Thyroid disease	0.97	0.719	0.86	1.10
HIV	1.92	0.094	0.89	4.14
Cognitive impairment	0.80	0.461	0.45	1.43
Depressive disorder	0.85	0.036	0.73	0.99
Charlson comorbidity index	0.91	<0.001	0.88	0.93
Frailty index	1.02	<0.001	1.01	1.03
LVAD	2.13	<0.001	1.92	2.38

Values are HR with (95% Confidence Interval) and p value; COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronisation Therapy; ECLS = Extracorporeal Life Support; HIV = Human Immunodeficiency Viruses; IABP = Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT = Ventricular Tachycardia.

* Dilated or other cardiomyopathy as reference.

Figure 4. All-cause mortality according to initial severity for the entire population (A), heart transplant patients (B) and LVAD patients (C).



Values are HR with (95% Confidence Interval) and p value; AHF = adverse heart failure; CI = confidence interval; ECLS = Extracorporeal life support; HR = Hazard ratio; LVAD = left ventricular assist device.

3- Major adverse events

As reported in **Table 3**, incidence of stroke, intracranial bleeding, major bleeding, septic shock and right ventricular heart failure (RHF) were significantly higher in LVAD patients for unmatched and matched populations (p<0.001). In our registry, incidences of ischemic stroke and intracranial bleeding in LVAD patients were 8% and 7% respectively. RHF occurred in 40% of LVAD patients.

Cancer incidence was significantly higher (p<0.001) in transplanted patients. The incidence of graft rejection was 17% during the entire follow-up.

Table 3. Major complications in unmatched and matched populations.

	Unmatched populations			Matched populations		
	LVAD	HTx	Hazard Ratio (95% CI) p value	LVAD	HTx	Hazard Ratio (95% CI) p value
Ischemic Stroke	117 (8)	67 (2)	5.6 (4.17-5.17) p<0.001	83 (7)	23 (2)	4.7 (2.97-7.5) p< 0.001
Intra-cranial bleeding	105 (7)	47 (1)	7.14 (5-10.1) p<0.001	67 (5.8)	23 (2)	3.7 (2.31-5.99) p<0.001
Major bleeding	145 (10)	143 (4)	3.05 (2.42- 3.86) p<0.001	112 (10)	54 (4.7)	2.6 (1.89-3.6) p<0.001
Septic shock	192 (12)	205 (6.2)	3.1 (2.5-3.7) p<0.001	140 (12)	88 (7.7)	2.16 (1.6-2.82) p<0.001
RHF	594 (40)	397 (12)	6.4 (5.6-7.3) p<0.001	451 (40)	143 (12)	5.6 (4.6 – 6.8) p<0.001
Cancer	89 (6)	337 (10)	0.9 (0.7 -1.14) p= 0.393	70 (6)	131 (11.5)	0.7 (0.5-0.94) p<0.001

Values are n (%); CI = confidence interval; HR = Hazard ratio; HTx = heart transplantation; LVAD = left ventricular assist device; RHF = right heart failure.

4- LVAD population analysis of the impact of fully centrifugal devices

Baseline characteristics of HeartMate III® (HM III) patients and other LVAD patients are presented in *Supplementary Table 4*. Their features were mainly similar but we noticed more coronary and congenital heart diseases, as well as more peripheral vascular diseases in HM III patients (p<0.001).

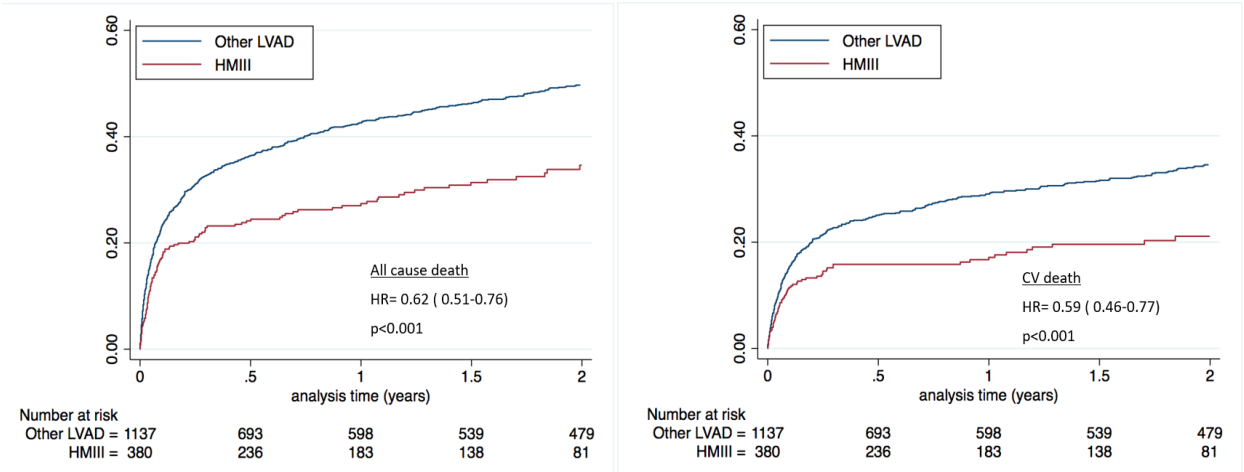
In patients who were implanted by a HM III, all-cause and CV mortality were significantly lower in this group and: HR is 0.62 (CI 95%: 0.51-0.76; p<0.001) and 0.59 (CI 95%: 0.46-0.77; p<0.001) respectively. They had significantly lower incidence of ischemic stroke (HR=0.32; 95% CI: 0.16-0.64; p<0.001) and intracranial bleeding (HR=0.49; 95% CI: 0.26-0.90; p<0.001). These results are depicted in **Figure 5 and 6**.

There was no significant difference for RHF (HR=0.94; 95% CI: 0.74-1.10), septic shock (HR=0.80; 95% CI: 0.53-1.20), and non-cerebral major bleeding (HR= 0.64; 95% CI: 0.41-1.00) between HM III patients and the others.

An analysis of LVAD patients after 2017 (the year of the beginning of implantation of HM III, in France) revealed identical results with the exception of a significantly lower incidence of non-cerebral major bleeding for HM III patients (HR=0.50; 95% CI: 0.29-0.83; p<0.001). Results are presented in *Supplementary Table 5*.

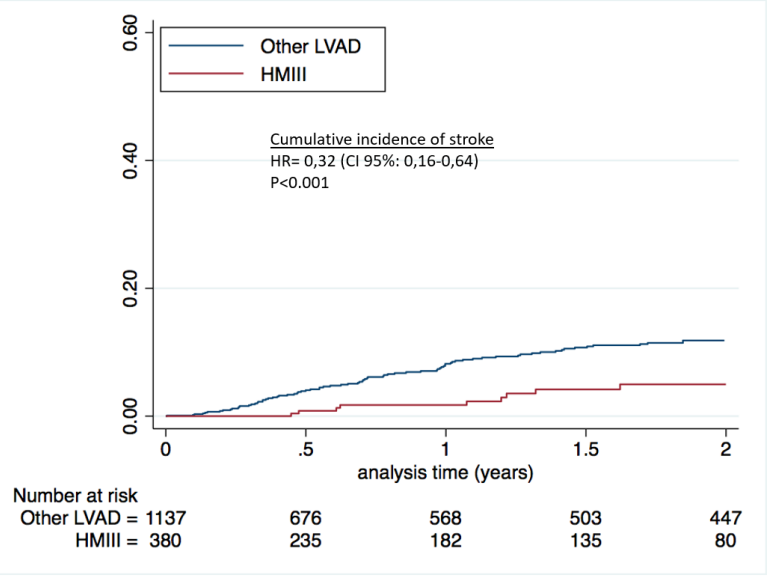
The sensitivity analyses performed by excluding patients transplanted after LVAD in each group (63 in HM III patients and 76 in other LVAD after 2017) were not different. After 2017, we found a HR for all-cause mortality of 0.50 (CI 95%: 0.39-0.64; p<0.001) and a HR for CV mortality of 0.45 (CI 95%: 0.32-0.62; p<0.001) in HM III patients.

Figure 5. Kaplan Meier survival curves for all-cause and cardiovascular mortality in Heartmate III vs other LVAD.



Values are HR with (95% Confidence Interval) and p value; CV = cardiovascular; HM III = HeartMate III®; HR = Hazard Ratio; LVAD = Left Ventricular Assist Device.

Figure 6. Cumulative incidence of ischemic stroke for HM III and other LVAD.



Values are HR with (95% Confidence Interval) and p value; CV= cardiovascular; HM III= HeartMate III®; HR= Hazard Ratio; LVAD= Left Ventricular Assist Device.

V- Discussion

1- Mains results

To our knowledge, this is the first nationwide study that compared LVAD and heart transplantation with matching analyses in a so-called 'real life' population. In this study, we showed that survival rate at 1-year for LVAD therapy was 63% as compared to 81% in heart transplant patients. After propensity matching, all-cause mortality was significantly higher in LVAD patients. Our study's main strength is its exhaustive aspect since it included all patients implanted with a LVAD in France from 2012 to 2020. Our results regarding mortality were comparable to reports from the "Agence de la Biomédecine" and french registry ASSIST-ICD for each group with most recent data and an analysis of a larger population of LVAD with inclusion of all french centers in our cohort (18,23,24).

In ASSIST-ICD, 1-year survival was 65% for the LVAD group, comparable to the 69% survival reported in the Euromacs registry (25). Survival-rate remained lower than the annual results from the Intermacs registry (26). For the latter, 1-year and 2-year survivals were 82,3% and 73,1%, respectively. Such differences may be explained by the initial severity of patients before implantation: only 6% had ECLS before implantation in the Intermacs registry, compared to 36% in our cohort. ECLS before assistance was associated with a higher mortality in our analysis, which could explain the difference in survival. These results should be analyzed taking in consideration the impact of the Intermacs profiles well described in the literature, with an higher mortality associated with profiles 1,2 and 3 (15). These data support that the follow-up of patients with advanced heart failure and their selection for transplantation or assistance are of the utmost importance in order to avoid the situations of refractory cardiogenic shock that impact on short- and long-term mortality. Many prognostic parameters exist in order to reduce late referral of patients to expert teams (13).

Furthermore, prevalence of diabetes mellitus, chronic kidney disease, and COPD in LVAD and heart transplanted European patients and in our cohort are higher than American patients (26). These are among the main independent predictors of mortality found in this study and may again account for the differences of survival with the Intermacs registry.

These observations are similar for transplanted patients and also include many differences in donor's characteristics: for example, North American donors are younger than European donors (30 vs 45 years), with fewer comorbidities, and died more frequently from head trauma whereas stroke is the predominant cause of death in European donors (28). Data from International Society for Heart and Lung Transplantation 5 (ISHLT) show that one-year survival following

cardiac transplantation now approximates 90%, with a median survival of 12.2 years in the USA (27–29). Yet, ECLS was similarly associated with an increased mortality rate in our study.

Regarding morbidity and mortality, LVAD remained associated with worse outcomes than heart transplantation. Age could explain these observations, in addition to more comorbidities and greater initial severity for assisted patients. However, propensity matching analysis did not modify these results.

Our cohort, with patients analyzed in more recent years, testifies the progressive evolution of indications with only 26.8% of assisted patients being transplanted compared to 47% in the French Gram cohort in a 2006 analysis (19). In line with international data, our data validate that destination therapy is now the first indication of LVAD implantation (17,19).

Regarding other major complications, the risk of ischemic stroke, intracranial bleeding or major non-cerebral bleeding was higher in LVAD patients than in heart transplant patients in our registry. They constitute, with pump thrombosis, principal concerns of hemocompatibility-related adverse events due LVAD. Stroke is the most disabling outcome and remains a main cause of death. Fortunately, these complications seem to be reduced with the latest generation LVAD (30).

Again, this was confirmed by our study, which reports that Heart Mate III® was associated with a lower incidence of stroke and cerebral bleeding. This risk was similar than that reported in the literature and in a recent propensity score matched analysis from the Intermacs registry (31). For both outcomes, this association persisted when analysis only included patients after 2017, as well as in the sensitive analysis with the exclusion of transplanted patients. These data seem to be partly explained by an improved preservation of Von Willebrand factor (32). However, we did not observe a significant reduction in the incidence of right heart failure or septic shock. In addition, HM III was associated with a lower risk major bleeding in the analysis after 2017, in line with a reduction of gastro-intestinal bleeding reported in many studies (30,33).

The ELEVATE registry and HM 3 CE-mark study showed a progression of 1- and 2-year survival rates with fully magnetically levitated circulatory support device (34,35). Our study is the first to demonstrate that the risk of mortality was significantly lower in HM III patients in comparison with other devices. These data suggest that French and probably Europeans assisted patients could benefit more from this therapy, because of an increased number of comorbidities and higher frailty. Thus, the release and increased availability of the latest devices might have a positive impact on patients.

RHF remains frequent in LVAD course with an incidence of 40% in our study. This was a substantial proportion of patients, similar to the data from the Euromac's registry with 35% (25), and this appeared consistent since RHF also represented 12% of the causes of death in the latest Intermacs registry (26). Diagnosis of RV failure is not easy in the pre-implantation period and may require a systematic and multiparametric approach by transthoracic echocardiography, magnetic resonance imaging, and right heart catheterization. Many societies propose scores to predict its development after implantation, i.e. the Right ventricular failure risk score, based on vasopressor requirement, blood rate of aspartate aminotransferase, bilirubin, and serum creatinine (36). In such cases, the therapeutic option was implantation of BiVAD or TAH when heart transplantation was not indicated or not achievable, but these situations are often associated with a poorer prognosis (17).

2- Study limitations

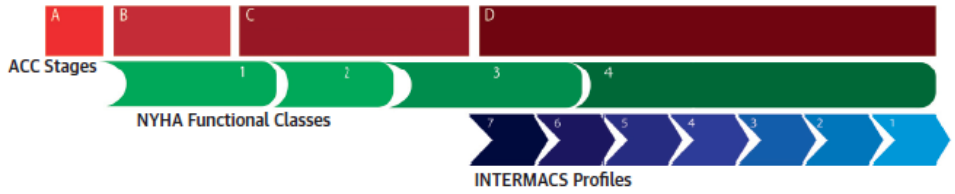
Our work contains several limitations: first, this was an observational and retrospective study, therefore the analyses may have inherent biases. The PMSI database contains diagnoses coded using ICD-10 that are obtained at hospital discharge and are under physicians' responsibility. Data were not systematically checked externally. However, since coding of complications is linked to reimbursement and is regularly controlled, it is anticipated to be accurate and reliable. Second, we only included in-hospital events and were not able to analyze data for out-of-hospital deaths but the patients in our analysis are unlikely to be managed out-of-hospital for clinical cardiovascular and non-cardiovascular events. Third, this system does not allow the collection of echocardiographic data (left and right ventricular ejection fraction), indications for LVAD therapy (bridge to transplant- destination therapy), pump thrombosis and use of drugs. In addition, Intermacs classification of patients was not available. Even with a propensity score matching, LVAD and transplant patients may not be completely comparable because they are complementary with respect to their respective contra-indications, e.g. cancer for HT and RHF for LVAD). Finally, these results were obtained using the French administration database and may not be generalizable in other settings.

VI- Conclusion

The results of our study were obtained in a large and exhaustive analysis of transplantation and assistance activity in France from 2012 to 2020 following the arrival of fully magnetically levitated LVAD.

For patients with advanced heart failure, heart transplantation was associated with a lower risk of mortality and morbidity than LVAD in our propensity score matched analysis. However, LVAD survival is improving and patients implanted with newer generations of devices have a lower risk of ischemic stroke, cerebral bleeding, all-cause and CV mortality. This improvement, coupled with the lack of cardiac grafts, explains the growing use of LVAD, in particular as a destination therapy. These results need to be confirmed in other cohorts including patients from different healthcare systems and should cover a longer period following the introduction of the latest generation of LVAD.

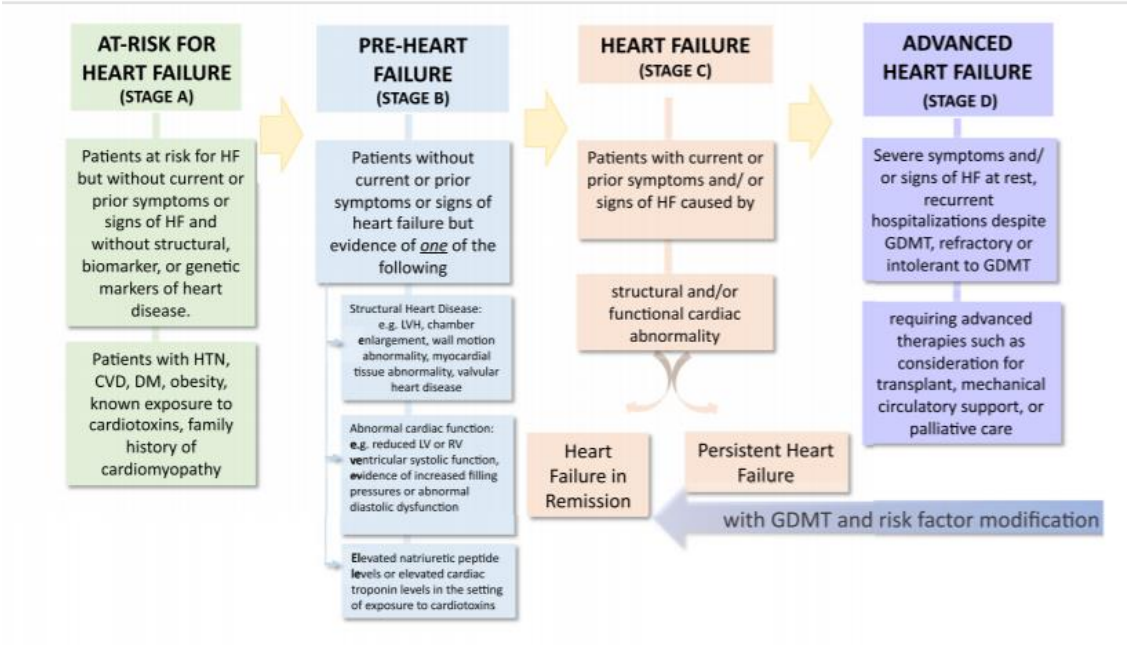
VII- Supplementary data



ACC Stages	NYHA Functional Classes	INTERMACS Profiles
A: Patient is at high risk for developing heart failure but has no functional or structural heart disorder	I: No limitation in normal physical activity	Profile 1: Critical Cardiogenic Shock
B: Structural heart disorder without symptoms	II: Mild symptoms with normal activity	Profile 2: Progressive Decline
C: Past or current symptoms or heart failure associated with structural disorder	III: Markedly symptomatic during daily activities, asymptomatic only at rest	Profile 3: Stable, But Inotrope Dependent
D: Advanced heart disease requiring hospital-based support, transplant, or palliative care	IV: Severe limitations, symptoms even at rest	Profile 4: Resting Symptoms
		Profile 5: Exertion Intolerant
		Profile 6: Exertion Limited
		Profile 7: Advanced NYHA Class III

Supplementary Figure 1. Association between different classification of Heart Failure from Truby *et al.* Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. JACC: Heart Failure 2020.

ACC = American College of Cardiology; Intermacs = Interagency Registry for Mechanically Assisted Circulatory Support; NYHA = New York Heart Association.



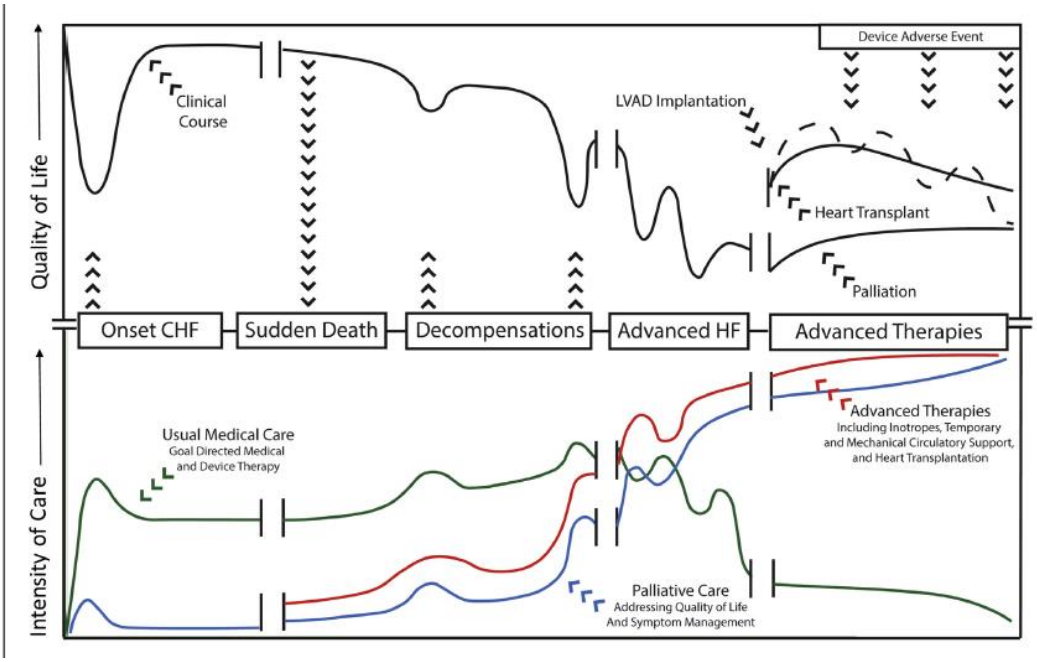
Supplementary Figure 2. New stages of Heart Failure from Bozkurt *et al.* Universal Definition and Classification of Heart Failure. Journal of Cardiac Failure. 2021.

CVD = cardiovascular disease; DM = diabetes mellitus; GMT = guideline-directed medical therapy; HF = heart failure; HTN = hypertension.

Supplementary Table 1. Summary and characteristics of each definition of advanced heart failure from Chaudhry *et al*. Advanced Heart Failure Heart Failure Clinics 2016.

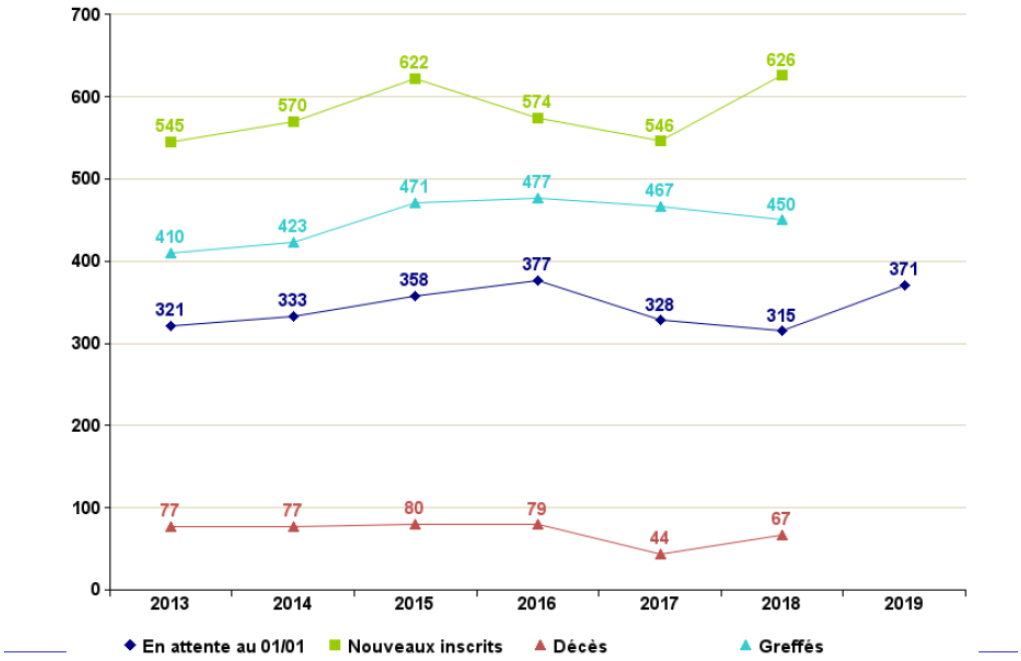
	Refractory Symptoms					Exercise Intolerance	Objective Evidence of Severe Cardiac Dysfunction			
	Severe Symptoms	Multiple Hospitalizations	Optimal Therapy	Inotropic Support	Fluid Retention and/or Peripheral Hypoperfusion	Severe Functional Capacity Impairment	Reduced Ejection Fraction	Doppler Echocardiography	Hemodynamics	Elevated Natriuretic Peptides
ACC/AHA	x	x	x	—	—	x	x	—	—	—
HFSA	x	x	x	x	—	x	—	—	—	—
ESC	x	x	x	—	x	x	x	x	x	x

ACC = American College of Cardiology; HSFA = Heart Failure Society of America; ESC = European Society of Cardiology.

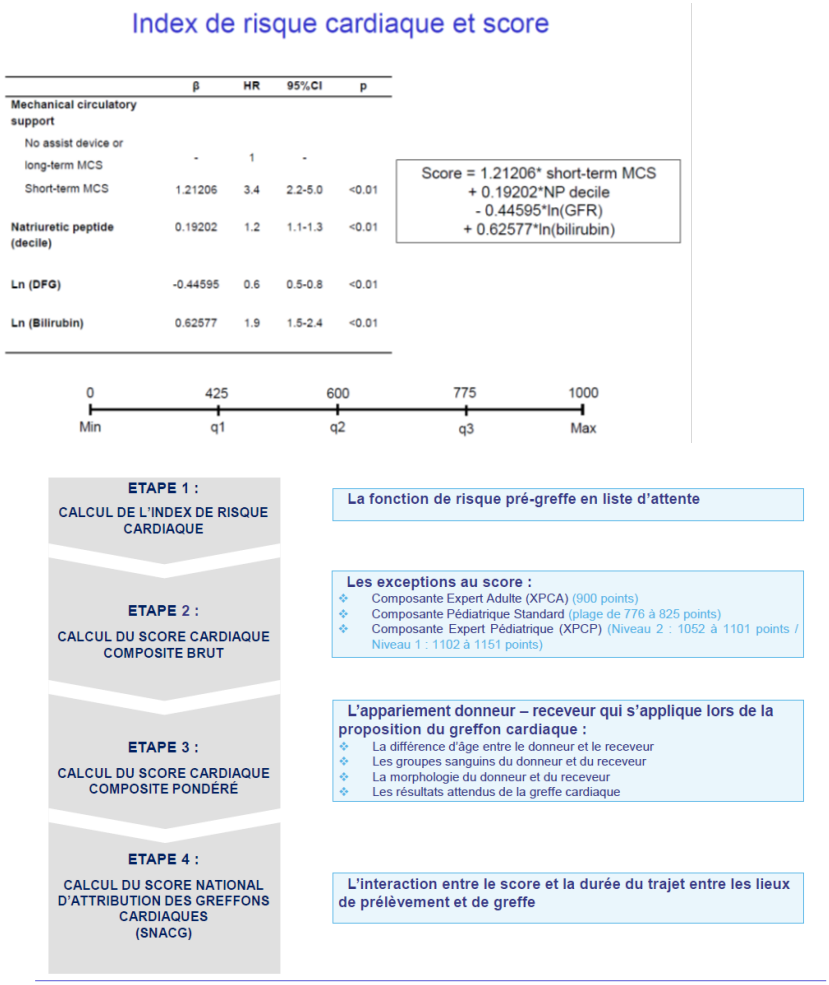


Supplementary Figure 3. Natural history of heart failure. (from Allen *et al.* Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation 2012 and adapted by Truby *et al.* Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. JACC: Heart Failure 2020).

HF = Heart failure.

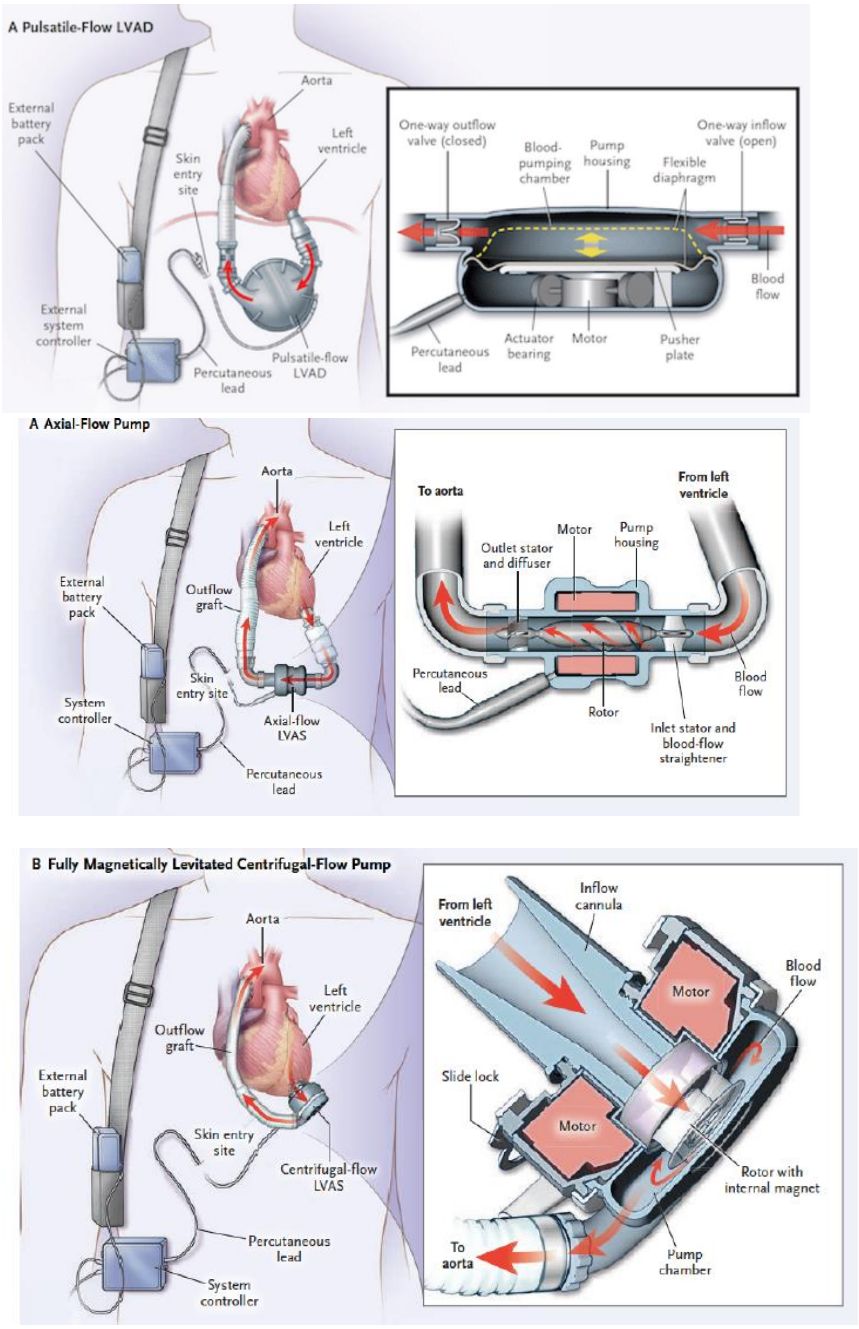


Supplementary Figure 4. Progression of supply and demand in the graft list in France. "Agence de la biomédecine" 2018.



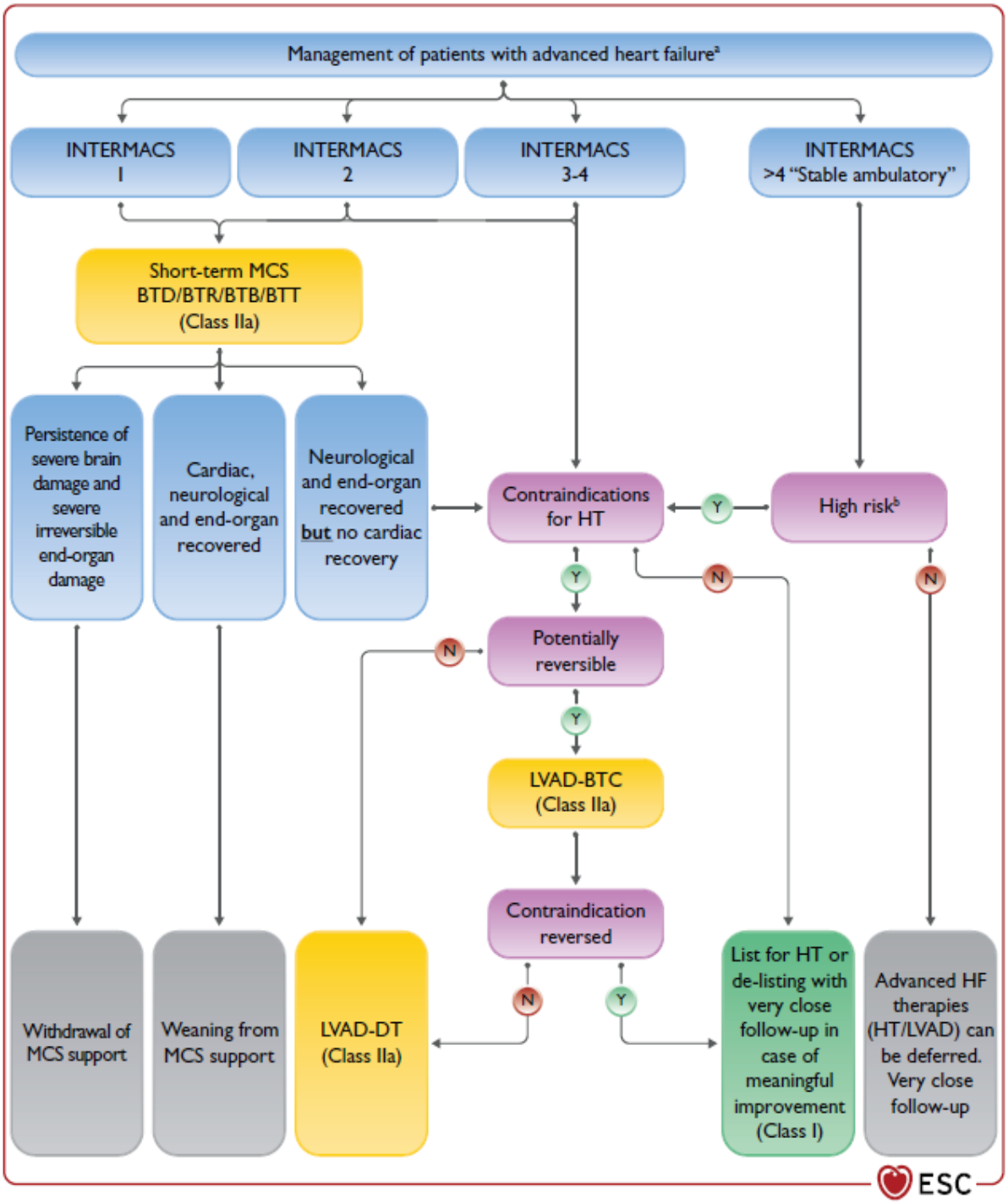
Supplementary Figure 5. Cardiac risk index and distribution score for heart transplants in France. From "Agence de la Biomedecine" in 2018.

MCS = Mechanical Circulatory Support; DFG = débit de filtration glomérulaire.



Supplementary Figure 6. Evolution LVAD technology from Mandeep R. Mehra *et al.*, "A Fully Magnetically Levitated Left Ventricular Assist Device — Final Report", *New England Journal of Medicine* 2017.

LVAD = Left ventricular assist device.



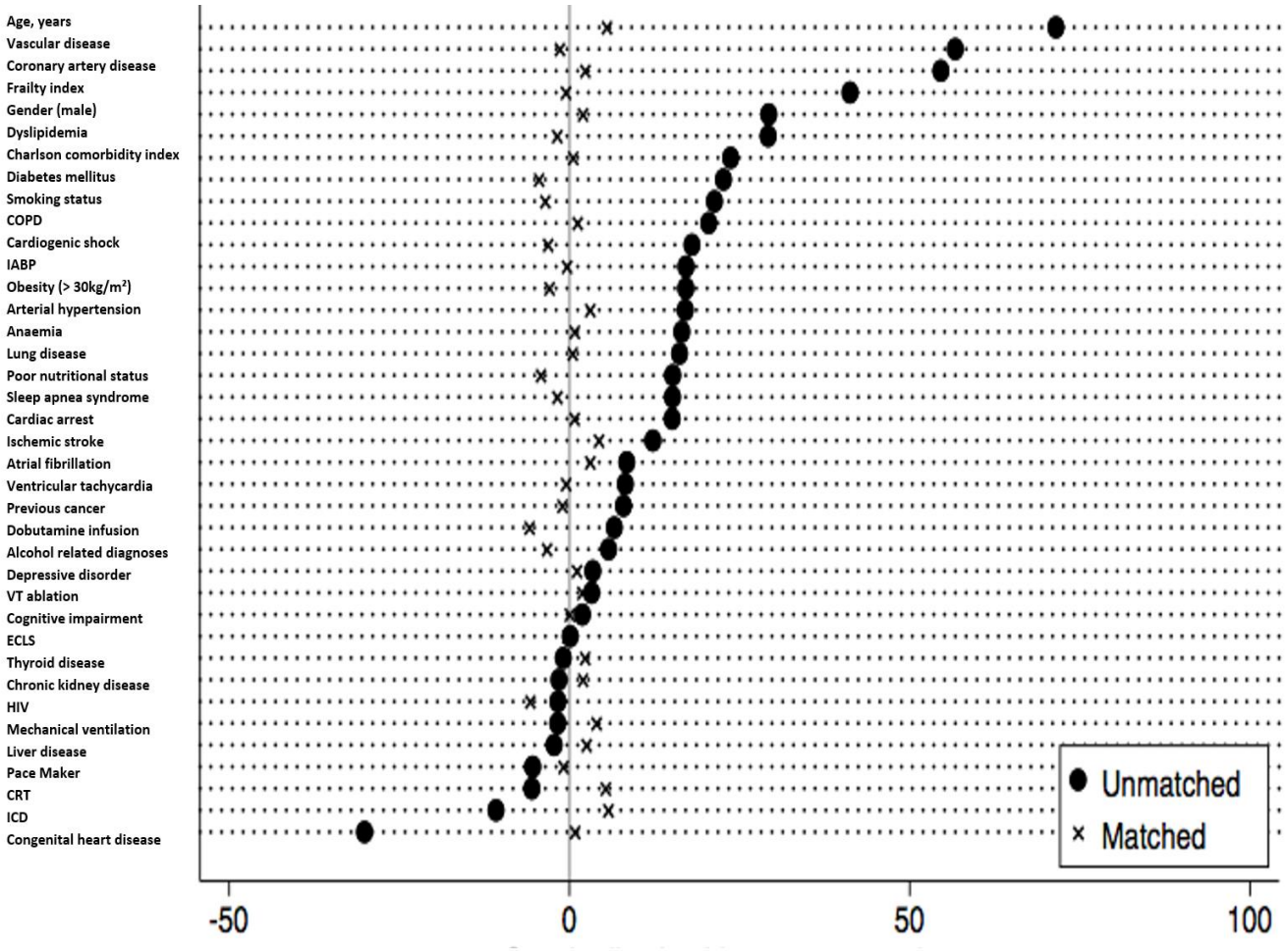
Supplementary Figure 7. Algorithm for the treatment of patients with advanced heart failure from Theresa A. *et al*, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, European Heart Journal, 2021.

BTB=bridge to bridge; BTC=bridge to candidacy; BTD=bridge to decision; BTR=bridge to recovery; BTT=bridge to transplantation; CA=cardiac amyloidosis; DT=destination therapy; ESC= European Society of Cardiology; HCM=hypertrophic cardiomyopathy; HF=heart failure; HFA=Heart Failure Association; HT=heart transplantation; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; LVAD=left ventricular assist device; LVAD-BTC=left ventricular assist device -bridge to candidacy; LVAD-DT= left ventricular assist device-destination therapy; MCS=mechanical circulatory support. This algorithm can be applied to all patients with advanced HF defined according to the ESC/HFA criteria, with exception of HCM, CA, arrhythmic storm, adult congenital heart disease, refractory angina. Recurrent hospitalization, progressive end-organ failure, refractory congestion, inability to perform cardiopulmonary exercise test or peak oxygen consumption <12 mL/min/kg or <50% of expected value.

Supplementary Table 2. Baseline characteristics of matched population.

	Heart transplant (n=1138)	LVAD (n=1138)	p	Total (n=2276)
Demographics				
Age. years	55±10	56±12	0.11	56±11
Gender (male)	931 (82)	940 (83)	0.62	1871 (82)
Obesity (> 30kg/m²)	311 (27)	309 (27)	0.93	620 (27)
Medical history				
Dyslipidemia	466 (41)	456 (40)	0.67	922 (41)
Arterial hypertension	568 (50)	585 (51)	0.48	1153 (51)
Smoking status	413 (36)	394 (35)	0.41	807 (36)
Diabetes mellitus	331 (29)	309 (27)	0.31	640 (28)
Alcohol related diagnoses	149 (13)	137 (12)	0.45	286 (13)
Cardiac condition				
Coronary artery disease	798 (70)	810 (71)	0.58	1608 (71)
Congenital heart disease	27 (2)	29 (3)	0.79	56 (3)
Dilated or other cardiomyopathy	313 (28)	299 (26)	0.61	612 (26)
History of arrhythmia				
Cardiac arrest	202 (18)	205 (18)	0.87	407 (18)
CRT	170 (15)	192 (17)	0.21	362 (16)
ICD	505 (44)	537 (47)	0.18	1042 (46)
Pace Maker	108 (10)	105 (09)	0.83	213 (9)
Ventricular tachycardia	404 (36)	401 (35)	0.9	805 (35)
VT ablation	68 (6)	73 (6)	0.66	141 (6)
Atrial fibrillation	628 (55)	645 (57)	0.47	1273 (56)
Initial severity				
Cardiogenic shock	965 (85)	951 (84)	0.42	1916 (84)
Dobutamine infusion	933 (82)	906 (80)	0.15	1839 (81)
ECLS	430 (38)	428 (38)	0.93	858 (38)
IABP	116 (10)	106 (9)	0.48	222 (10)
Mechanical ventilation	720 (63)	688 (61)	0.17	1408 (62)
Comorbidities				
Vascular disease	661 (58)	653 (57)	0.73	1314 (58)
Ischemic stroke	106 (9)	121 (11)	0.29	227 (10)
Lung disease	293 (26)	295 (26)	0.92	588 (26)
COPD	135 (12)	139 (12)	0.8	274 (12)
Sleep apnea syndrome	177 (16)	170 (15)	0.68	347 (15)
Chronic kidney disease	247 (22)	256 (23)	0.65	503 (22)
Liver disease	342 (30)	355 (31)	0.55	697 (31)
Anaemia	449 (40)	453 (40)	0.86	902 (40)
Poor nutritional status	348 (31)	326 (29)	0.31	674 (30)
Previous cancer	72 (6)	69 (6)	0.79	141 (6)
Thyroid disease	206 (18)	216 (19)	0.59	422 (19)
HIV	2 (1)	5 (1)	0.26	7 (1)
Cognitive impairment	8 (1)	8 (1)	1	16 (1)
Depressive disorder	140 (12)	144 (13)	0.8	284 (13)
Charlson comorbidity index	6±3	6±3	0.91	6±3
Frailty index	12±9	12±8	0.89	12±8

Values are n (%) or mean ±SD. COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronisation Therapy; ECLS = Extracorporeal Life Support; HIV = Human Immunodeficiency Viruses; IABP = Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT = Ventricular Tachycardia.



Supplementary Figure 8. Standardized percentage bias across main baseline characteristics in unmatched and matched population.

COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronisation Therapy; ECLS = Extracorporeal Life Support; HIV = Human Immunodeficiency Viruses; IABP = Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT = Ventricular Tachycardia.

Supplementary Table 3. Baseline of characteristics according to initial severity.

	AHF (n=847)	ECLS (n=1738)	CS (n=2258)	Total (n=4843)
Demographics				
Age, years	50±17	50±14	52±14	51±15
Gender (male)	610 (72)	1329 (77)	1736 (77)	3675 (76)
Obesity (>30kg/m²)	197 (23)	374 (22)	569 (25)	1140 (24)
Medical History				
Dyslipidemia	296 (35)	493 (28)	816 (36)	1605 (33)
Arterial hypertension	406 (48)	757 (44)	1128 (50)	2291 (47)
Smoking status	224 (26)	516 (30)	713 (32)	1453 (30)
Diabetes mellitus	173 (20)	379 (22)	544 (24)	1096 (23)
Alcohol related diagnoses	67 (8)	213 (12)	244 (11)	524 (11)
Cardiac condition				
Coronary artery disease	434 (51)	1051 (61)	1366 (61)	2851 (59)
Congenital heart disease	84 (10)	89 (5)	160 (7)	333 (7)
Dilated or other cardiomyopathy	329(39)	598(34)	732(32)	1659 (34)
History of arrhythmia				
Cardiac arrest	58 (7)	442 (25)	267 (12)	767 (16)
Ventricular tachycardia	258 (31)	603 (35)	803 (36)	1664 (34)
Atrial fibrillation	439 (52)	907 (52)	1273 (56)	2619 (54)
VT ablation	58 (7)	106 (6)	123 (5)	287 (6)
CRT	144 (17)	224 (13)	424 (19)	792 (16)
ICD	448 (53)	636 (37)	1102 (49)	2186 (45)
Pace Maker	85 (10)	136 (8)	226 (10)	447 (9)
Comorbidities				
Vascular disease	297 (35)	874 (50)	1041 (46)	2212 (46)
Ischemic stroke	73 (9)	214 (12)	194 (9)	481 (10)
Lung disease	176 (21)	430 (25)	487 (22)	1093 (23)
COPD	85 (10)	129 (7)	239 (11)	453 (9)
Sleep apnea syndrome	134 (16)	152 (09)	307 (14)	593 (12)
Chronic kidney disease	176 (21)	359 (21)	498 (22)	1033 (21)
Liver disease	157 (19)	741 (43)	634 (28)	1532 (32)
Anaemia	274 (32)	684 (39)	894 (40)	1852 (38)
Poor nutritional status	199 (24)	524 (30)	662 (29)	1385 (29)
Previous cancer	44 (5)	103 (6)	143 (6)	290 (6)
Thyroid disease	180 (21)	280 (16)	452 (20)	912 (19)
HIV	6 (1)	9 (1)	8 (1)	23 (1)
Cognitive impairment	6 (1)	12 (1)	15 (1)	33 (1)
Depressive disorder	98 (12)	219 (13)	293 (13)	610 (13)
Charlson comorbidity index	5±3	6±3	6±3	6±3
Frailty index	9±8	12±8	10±8	11±8

Values are n (%) or mean ±SD; AHF = adverse heart failure; CS = cardiogenic shock; COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronisation Therapy; ECLS = Extracorporeal Life Support; HIV = Human Immunodeficiency Viruses; IABP = Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT = Ventricular Tachycardia.

Supplementary Table 4. Baseline characteristics HM III patients vs others LVAD.

	Other LVAD (n=1137)	HM III (n=380)	p	Total (n=1517)
Demographics				
Age. years	58±12	57±12	0.3	58±12
Gender (male)	949 (84)	327 (86)	0.23	1276 (84)
Obesity (>30kg/m²)	293 (26)	141 (37)	<0.001	434 (29)
Medical history				
Dyslipidemia	475 (42)	172 (45)	0.23	647 (43)
Arterial hypertension	600 (53)	206 (54)	0.63	806 (53)
Smoking status	371 (33)	187 (49)	<0.001	558 (37)
Diabetes mellitus	334 (29)	110 (29)	0.87	444 (29)
Alcohol related diagnoses	128 (11)	55 (15)	0.1	183 (12)
Cardiac condition				
Coronary artery disease	839 (74)	318 (84)	<0.001	1157 (76)
Congenital heart disease	18 (2)	15 (4)	0.01	33 (2)
Dilated or other cardiomyopathy	280 (24)	47 (12)	<0.001	327 (22)
History of arrhythmia				
Cardiac arrest	224 (20)	75 (20)	0.99	299 (20)
CRT	170 (15)	57 (15)	0.98	227 (15)
ICD	463 (41)	166 (44)	0.31	629 (42)
Pace Maker	84 (7)	40 (11)	0.05	124 (8)
Ventricular tachycardia	412 (36)	150 (40)	0.26	562 (37)
Atrial fibrillation	652 (57)	212 (56)	0.6	864 (57)
VT ablation	67 (6)	31 (8)	0.12	98 (7)
Initial severity				
Cardiogenic shock	975 (86)	315 (83)	0.18	1290 (85)
Dobutamine infusion	918 (81)	313 (82)	0.48	1231 (81)
ECLS	418 (37)	127 (33)	0.24	545 (36)
IABP	153 (14)	32 (8)	0.01	185 (12)
Mechanical ventilation	709 (62)	230 (61)	0.52	939 (62)
Comorbidities				
Vascular disease	701 (62)	276 (73)	<0.001	977 (65)
Ischemic stroke	137 (12)	53 (14)	0.33	190 (13)
Lung disease	309 (27)	105 (28)	0.86	414 (27)
COPD	156 (14)	51 (13)	0.88	207 (14)
Sleep apnea syndrome	171 (15)	68 (18)	0.19	239 (16)
Chronic kidney disease	238 (21)	79 (21)	0.95	317 (21)
Liver disease	360 (32)	109 (29)	0.28	469 (31)
Anaemia	473 (42)	191 (50)	0.003	664 (44)
Poor nutritional status	335 (30)	171 (45)	<0.001	506 (33)
Previous cancer	84 (7)	27 (7)	0.85	111 (7)
Thyroid disease	223 (20)	59 (16)	0.08	282 (19)
HIV	5 (1)	1 (1)	0.64	6 (1)
Cognitive impairment	7 (1)	5 (1)	0.18	12 (1)
Depressive disorder	141 (12)	62 (16)	0.05	203 (13)
Charlson comorbidity index	6±3	6±3	0.004	6±3
Frailty index	13±9	14±10	0.02	13±9

Values are n (%) or mean ±SD. COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronisation Therapy; ECLS = Extracorporeal Life Support; HIV = Human Immunodeficiency Viruses; HM = HeartMate®; IABP = Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT = Ventricular Tachycardia.

Supplementary Table 5. Baseline characteristics HM III patients and others LVAD after 2017.

	Other LVAD (n=302)	HM III (n=380)	p	Total (n=682)
Demographics				
Age. years	59±11	57±12	0.02	58±11
Gender (male)	248 (82)	327 (86)	0.16	575 (85)
Obesity (>30kg/m²)	83 (28)	141 (37)	0.01	224 (33)
Medical history				
Dyslipidemia	130 (43)	172 (45)	0.56	302 (44)
Arterial hypertension	171 (57)	206 (54)	0.53	377 (55)
Smoking status	117 (39)	187 (49)	0.01	304 (45)
Diabetes mellitus	93 (31)	110 (29)	0.6	203 (30)
Alcohol related diagnoses	38 (13)	55 (15)	0.48	93 (14)
Cardiac condition				
Coronary artery disease	244 (81)	318 (84)	0.33	562 (83)
Congenital heart disease	3 (1)	15 (4)	0.02	18 (3)
Dilated or other cardiomyopathy	55 (18)	47 (12)	0.07	102 (14)
History of arrhythmia				
Cardiac arrest	61 (20)	75 (20)	0.88	136 (20)
CRT	59 (20)	57 (15)	0.12	116 (17)
ICD	136 (45)	166 (44)	0.73	302 (44)
Pace Maker	30 (10)	40 (11)	0.8	70 (10)
Ventricular tachycardia	120 (40)	150 (40)	0.94	270 (40)
Atrial fibrillation	168 (56)	212 (56)	0.97	380 (56)
VT ablation	23 (8)	31 (8)	0.79	54 (8)
Initial severity				
Cardiogenic shock	273 (90)	315 (83)	0.005	588 (87)
Dobutamine infusion	256 (85)	313 (82)	0.4	569 (84)
ECLS	141 (47)	127 (33)	0.0004	268 (39)
IABP	37 (12)	32 (8)	0.1	69 (10)
Mechanical ventilation	201 (67)	230 (61)	0.11	431 (63)
Comorbidities				
Vascular disease	210 (70)	276 (73)	0.38	486 (72)
Ischemic stroke	41 (14)	53 (14)	0.89	94 (14)
Lung disease	90 (30)	105 (28)	0.53	195 (29)
COPD	40 (13)	51 (13)	0.95	91 (13)
Sleep apnea syndrome	55 (18)	68 (18)	0.91	123 (18)
Chronic kidney disease	63 (21)	79 (21)	0.98	142 (21)
Liver disease	110 (36)	109 (29)	0.03	219 (32)
Anaemia	135 (45)	191 (50)	0.15	326 (48)
Poor nutritional status	95 (32)	171 (45)	0.0003	266 (39)
Previous cancer	26 (9)	27 (7)	0.47	53 (8)
Thyroid disease	60 (20)	59 (16)	0.14	119 (18)
HIV	1 (1)	1 (1)	0.87	2 (1)
Cognitive impairment	2 (1)	5 (1)	0.4	7 (1)
Depressive disorder	46 (15)	62 (16)	0.7	108 (16)
Charlson comorbidity index	6±3	6±3	0.03	6±3
Frailty index	15±9	14±1	0.48	14±9

Values are n (%) or mean ±SD. COPD = Chronic Obstructive Pulmonary Disease; CRT= Cardiac Resynchronisation Therapy; ECLS= Extracorporeal Life Support; HIV=Human Immunodeficiency Viruses; HM= HeartMate®; IABP= Intra-Aortic Balloon Pump Therapy; ICD = Implantable Cardioverter Defibrillator; LVAD = Left Ventricular Assist Device; SD = Standard Deviation; VT= Ventricular Tachycardia.

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53 pages – 8 tableaux – 13 figures –1 illustration

Résumé : Introduction : L'objectif de notre étude était de décrire pour la première fois dans une comparaison exhaustive à l'échelle nationale les caractéristiques et la survie des patients en insuffisance cardiaque avancée traités par assistance mécanique ventriculaire gauche ou transplantation cardiaque.

Méthode : Les données analysées ont été issues du programme de médicalisation des systèmes d'information (PMSI) français entre 2012 et 2020. La première partie a consisté à analyser la survie selon la prise en charge avec la méthode de Kaplan-Meier et les facteurs prédictifs de mortalité avec un test de Cox multivarié. Un appariement avec un score de propension a été réalisé pour équilibrer les facteurs de risques de morbi-mortalité. La seconde partie de l'analyse s'est intéressée aux différentes populations d'assistance ventriculaire gauche en comparant la morbi-mortalité des patients implantés d'un Heartmate III aux autres générations de LVAD.

Résultats : Cette cohorte rétrospective a regroupé 4843 patients, 3326 transplantés cardiaques et 1517 patients sous assistance ventriculaire gauche. Les patients transplantés étaient plus jeunes (48 ans vs 58 ans), comportaient plus de femmes (28% vs 16%) et avaient moins de cardiopathie ischémique (51% vs 76%). La survie toute cause à 1 an était significativement plus élevée pour les patients ayant eu une transplantation cardiaque 81 % contre 63 % pour les patients implantés d'une assistance ventriculaire gauche (Hazard ratio [HR] après appariement par score de propension 1.92, IC 95% 1.68-2.20 $p<0.001$). L'incidence d'accident vasculaire cérébral, d'hémorragie majeure et de choc septique était significativement plus élevée pour les patients assistés ($p<0.001$). Les patients sous HeartMate III avaient une survie significativement meilleure (HR 0.62, IC 95% 0.51-0.76) et un taux d'accident vasculaire cérébral significativement moins élevé (HR 0.32, IC 95% : 0.16-0.64) par rapport aux autres types d'assistance.

Conclusion : En France, la transplantation cardiaque reste la référence pour le traitement de l'insuffisance cardiaque terminale chez les patients encore jeunes avec peu de comorbidités et est associée à de meilleurs résultats que l'assistance ventriculaire gauche en termes de survie et morbidité. Les taux de survie restent néanmoins inférieurs aux standards nord-américains. Il s'agit, à notre connaissance, de la première étude apportant une différence significative de survie entre le HeartMate III et les autres assistances ventriculaires gauches.

Mots clés : Insuffisance cardiaque- transplantation cardiaque- assistance ventriculaire gauche- survie- accident vasculaire cérébral- HeartMate III

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Date de soutenance : 27 septembre 2021.