Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 21 January 2022 | doi:10.4414/SMW.2022.w30108
Cite this as: Swiss Med Wkly. 2022;152:w30108

Has the profile of heart transplantation recipients changed within the last three decades?

An analysis from the Lausanne Heart Transplantation Centre

Anouck Zurbuchen[a], Piergiorgio Tozzi[b], Julien Regamey[a], Tamila Abdurashidova[a], Philippe Meyer[c], Karl Lefol[d], Manuel Pascual[d], Patrick Yerly[a], Vincent Aubert[d], Stefania Aur[a], Valentina Rancati[e], Carlo Marcucci[e], Marco Rusca[f], Sam Rotman[g], Rene Pretre[b], Matthias Kirsch[b], Roger Hullin[a]

[a] Cardiology, Cardiovascular Department, University Hospital Lausanne, Switzerland
[b] Cardiac surgery, Cardiovascular Department, University Hospital Lausanne, Switzerland
[c] Cardiogy, Department of Medical Specialties, University Hospital Geneva, Switzerland
[d] Solid Organ Transplantation Centre
[e] Anaesthesiology, Department of Abdominal Surgery and Anesthesiology, University Hospital Lausanne, University of Lausanne, Switzerland
[f] Department of Intensive Care, University Hospital Lausanne, University of Lausanne, Switzerland
[g] Pathology, University Hospital Lausanne, University of Lausanne, Switzerland

Summary

BACKGROUND: Heart transplantation remains the most durable treatment for patients with end-stage heart failure refractory to medical treatment. Central elements of the listing criteria for heart transplantation have remained largely unchanged in the last three decades whereas treatment of heart failure has significantly increased survival and reduced disease-related symptoms. It remains unknown whether the improvement of heart failure therapy changed the profile of heart transplantation candidates or affected post-transplant survival.

METHODS: The study investigated a total of 323 heart transplant recipients of the Lausanne University Hospital with 328 transplant operations between 1987 and 2018. Patients were separated into three groups on the basis of availability of heart failure therapy: period 1 (1987–1998; n = 115) when renin-angiotensin system blockade and diuretic treatment were available; period 2 (1999–2010; n = 106) marked by the addition of beta-blocker and mineralocorticoid receptor antagonist treatment in severe heart failure, and the establishment of cardiac defibrillator and resynchronisation therapy; period 3 (2011–2018; n = 107) characterised by the increasing use of ventricular assist devices for bridge to transplantation.

RESULTS: The patient characteristics age (all: 53.4 years), male sex (all: 79%) and body mass index (all: 24.5 kg/m^2) did not differ between periods. History of arterial hypertension was less prevalent in period 2 (period 1 vs 2 vs 3: 44 vs 28 vs 43%, p = 0.04) whereas other cardiovascular risk factors were equally distributed. Left ventricular ejection fraction, VO_2max, and pulmonary vascular resistance were not different between the three periods. The prevalence of ischaemic cardiomyopathy was higher in periods 1 and 3; dilated non-ischaemic cardiomyopathy was more frequent in period 2. Post-transplant 1-year survival was highest in period 3 (1 vs 2 vs 3: 87.2 ± 3.2% vs 70.8 ± 4.4% vs 93.0 ± 2.6%, p always ≤0.02), and the Kaplan-Meier estimates of survivors of the first year post-transplant were not different between the three periods. In descriptive analysis, early mortality was not associated with acknowledged pretransplant predictors of post-transplant mortality.

CONCLUSION: Availability of different medical heart failure treatments did not result in greatly different pretransplant characteristics of heart transplantation recipients across the three periods. This suggests that the maintained central criteria of listing for heart transplantation still identify end-stage heart failure patients with a similar profile. This finding can explain the unchanged overall mortality on condition of 1-year survival across the three periods, since pretransplant characteristics are relevant for long-term survival after heart transplantation.

Correspondence:
Roger Hullin, MD
Associate Professor for Severe Heart Failure and Heart Transplantation
Cardiology, Cardiovascular Department
Centre Hospitalier Universitaire Vaudois
BH10-509
Rue du Bugnon 46
CH-1011 Lausanne
roger.hullin[at]chuv.ch

Introduction

As of 1967, heart transplantation has remained the treatment of choice in end-stage heart failure [1]. However, this therapeutic option turned into a success story only after the early 1980s when ciclosporin became available for anti-rejection treatment. At the Lausanne University Hospital, heart transplantation started in 1987 and this uninterrupted activity resulted in a total of 328 heart transplantations up to 31 December 2018. The continuation of this activity for more than 31 years indicates that heart transplantation remains an indispensable option for heart failure treatment despite of the significant progress during the last decades, in particularly in the treatment of heart failure with reduced left ventricular ejection fraction (HFrEF).

Since 1987, angiotensin converting enzyme inhibitors (ACE-Is) have been shown to decrease mortality in

HFrEF patients [2, 3]. In 1999, antagonists of the beta-adrenergic receptor and the mineralocorticoid receptor (MRA) were established as effective pharmacological therapies in severe heart failure when added to ACE-I [4, 5]. In 2001, angiotensin II type 1 receptor blockers (ARB) were shown to reduce the incidence of heart failure-related hospitalisations [6] and, in 2003, to decrease cardiovascular mortality [7]. Finally, since 2005, internal defibrillators and resynchronisation devices have become established HFrEF treatment because of a significant decrease in mortality when added to optimal pharmacological treatment [8, 9]. These achievements have reduced case fatality with heart failure in the real world [9, 10]. However, heart failure treatment only slows progression of the disease, which is why ventricular assist device (VAD) treatment has become a welcome therapeutic option for those patients progressing towards terminal heart failure, in particular while waiting for heart transplantation [10, 11].

Despite the dynamic development of therapeutic options for heart failure treatment, key listing criteria for heart transplantation have remained largely unchanged [12–14]. We hypothesised that improvement in heart failure therapy with a reduction of morbidity should result in selection of heart transplantation recipients of older age, since heart failure patients are less symptomatic for a longer period of time. Comorbidity load increases with age and the time living with heart failure. Therefore, we supposed that heart transplant recipients may present with a higher comorbidity load, which is known to affect post-transplant survival [14].

Methods

Study population

This cohort includes consecutive heart transplantation recipients at the Lausanne University Hospital from the first transplant operation on 5 June 1987 until study end on 31 December 2018. All patients were censored on the 31 December 2019. The protocol was approved by the local research ethics committee (CER VD 2019-704) and the study was conducted in accordance with the Declaration of Helsinki [15].

Study aim

The primary aim of this retrospective monocentric cohort study was to investigate whether pretransplant characteristics of patients undergoing heart transplantation at the University Hospital of Lausanne differed in the periods 1987–1998 (period 1) versus 1999–2010 (period 2) versus 2011–2018 (period 3). The secondary aim was to investigate whether post-transplant mortality differed between these periods based on the hypothesis that differences in pretransplant patientcharacteristics may affect post-transplant survival.

Data collection on characteristics of heart transplantation candidates and mortality

Recipient-related demographic, anthropometric, biological and clinical data, as well as medical history and basic information on the transplant operation were collected from the individual patients' electronic health report of the Lausanne University Hospital (AZ). For some old files, data were extracted from paper medical records. Biological and clinical data always refer to the day of transplant operation. Donor-related demographic, clinical and biological data were extracted either from the respective recipients' electronic/paper medical file (AZ) or from the Swiss Organ Allocation System data bank (KL). Left ventricular ejection fraction of the donor heart was always assessed with echocardiography as of 1988. Data availability always varied between 92 and 100% but forserum iron levels which were available for 83% of all cohort patients. Data accuracy was confirmed by revisiting 20% patients' data, revealing 97% accuracy (TA). Comprehensive pretransplant transthoracic echocardiography, right heart catheterisation and cardiopulmonary exercise testing were performed by board-certified cardiologists and represent the last examination before the transplant operation. All-cause mortality data derived from the Swiss national mortality registry and local documentation in the electronic/paper file of the individual patient.

Grading of acute cellular rejection after heart transplantation

For each patient, the acute cellular rejection score of the first postoperative year was calculated as the sum of histopathological results from all endomyocardial biopsies obtained divided by the number of endomyocardial biopsies [16]. Endomyocardial biopsies were graded according to the revised criteria of the International Society of Heart and Lung Transplantation, ISHLT–2004 [17]. For the purpose of this study, endomyocardial biopsy results graded by ISHLT-1990 recommendations (endomyocardial biopsies procured 1990–2004) or by the Texas Heart Institute classification (endomyocardial biopsies before 1990) [17, 18] were all converted into the ISHLT-2004 grading system [17].

Statistical analysis

Statistical analysis was performed using SPSS BASE 17.0 statistical software (SPSS Inc. Chicago, IL, USA). Categorical variables were expressed as percentages and compared using the Pearson's chi-square or Fisher's exact test (when $n \leq 5$). Continuous variables were expressed as medians and interquartile ranges (IQRs). The groups were compared using the non-parametric Kruskal-Wallis test, in order to waive the assumption of normal distribution of variables. Post-hoc intergroup differences were assessed using the non-parametric Mann-Whitney test with Bonferroni correction. Survival data were analysed with standard Kaplan-Meier actuarial techniques for estimation of survival probabilities and compared using the log-rank test. A two-tailed p-value <0.05 was taken to indicate statistical significance.

Results

Cohort

A total of 323 patients underwent heart transplantation at the Lausanne University Hospital between 5 June 1987 and 31 December 2018 and were included in this study. Five of them had a retransplant, expanding the number

of transplant operations to 328. Separation of the cohort by the time of operation resulted in 115 heart transplantation recipients for the first period, 106 for the second period, and 107 for the third period. The annual number of heart transplant operations varied between 3 (1987) and 22 (2018), yielding a mean of 10.6 heart transplantations/year (supplementary fig. S1 in the appendix). Three-month and 1-year all-cause mortality were not different when years with <12 heart transplantations/year and other years were compared (14 vs 10%, p = 0.27; 18 vs 15%, p = 0.42, respectively).

At the time of the transplant operation, 57 (17%) heart transplant recipients had urgent status on the waiting list, with 50 patients on positive inotropic treatment and 2 patients on veno-arterial extracorporeal membrane oxygenation support. In addition, three cases waited in urgent status because of multiple pre-existing anti-HLA antibodies and two patients suffered from persisting severe infection of the implanted left ventricular assist device (LVAD).

Recipients characteristics

Table 1 shows patients' characteristics. Median age at heart transplantation was 53.4 years; age was not different between groups. Twelve patients were <18 years old, representing altogether 4% of the total cohort; more patients <18 years had heart transplantation in the third period (period 1 vs 2 vs 3: 0 vs 3 vs 9, p = 0.003). Male gender was preponderant (79%) and not different between groups (83 vs 76 vs 77%, p = 0.34). Body mass index (BMI) and associated anthropometric measures were not different between groups (p = 0.29). The prevalence of a history of arterial hypertension was higher in the first and third period (38.3 vs 26 vs 40.2%, p = 0.04). The proportion of recipients with a history of tobacco use tended to be higher in the first and third era (57 vs 45.3 vs 54%, p = 0.1). In absolute numbers, more patients had diabetes in the third era (15.7 vs 14 vs 23%, p = 0.2). The prevalence of dyslipidaemia, chronic obstructive pulmonary disease (COPD) and renal replacement therapy was not different between groups.

Heart failure aetiology

Table 2 shows heart failure aetiology classified according to Maron et al. [19]. Non-ischaemic and ischaemic cardiomyopathy were the overall most prevalent aetiologies in the study cohort (36.8 and 34.7%, respectively). Less prevalent were congenital heart disease (4.9%) and secondary cardiomyopathies (4.8%), with half of them due to cardiotoxicity (2.4%). The distribution of the aetiologies of heart failure differed between the three periods with a higher prevalence of ischaemic cardiomyopathy in periods 1 and 3, whereas non-ischaemic cardiomyopathy was less frequent in period 3.

Table 1:
Demographic and clinical parameters.

Variable		All patients (n = 328)	1987–1998 (n = 115)	1999–2010 (n = 106)	2011–2018 (n = 107)	p-value
Demographics	Caucasians	97%	98%	99%	94%	
	Age (years), median (IQR)	53.4 (14.3)	52.4 (13.0)	53.7 (15.0)	53.6 (18.9)	0.71
	Recipients <18 years(%)	12 (4%)	0 (0%)	3 (3%)	9 (8%)	0.003
	Male gender	79%	83%	76%	77%	0.34
Clinical data	Height (m), median (IQR)	1.71 (0.13)	1.72 (0.11)	1.72 (0.14)	1.70 (0.14)	0.68
	BMI (kg/m^2), median (IQR)	24.5 (6.8)	24.0 (6.4)	23.8 (7.0)	24.9 (6.6)	0.29
	BSA (m^2), median (IQR)	1.86 (0.30)	1.85 (0.25)	1.85 (0.32)	1.88 (0.32)	0.51
Comorbidity	Smoking	171 (52%)	65 (57%)	48 (45.3%)	58 (54%)	0.10
	Arterial hypertension	115 (35%)	44 (38.3%)	28 (26%)	43 (40.2%)	0.04
	Diabetes	58 (18%)	18 (15.7%)	15 (14%)	25 (23%)	0.20
	Dyslipidaemia	147 (45%)	49 (42.6%)	48 (45.3%)	50 (47%)	0.99
	COPD	37 (11%)	14 (12.2%)	12 (11%)	11 (10%)	0.85
	Haemodialysis	10 (3%)	3 (3%)	3 (3%)	4 (4%)	0.90
Cardiovascular parameters	LVEF (%), median (IQR)	20.0 (14.0)	20.0 (8.0)	20 (10.0)	22.5 (20.0)	0.23
	PVR, median (IQR)	2.19 (1.49)	1.76 (1.5)	2.44 (2.1)	2.22 (1.3)	0.51
	VO_2max, (median IQR)	13.0 (4.7)	12.5 (4.9)	12.2 (4.1)	13.3 (4.5)	0.36
	HR (bpm), median (IQR)	80.0 (18.0)	88.0 (21.0)	84.0 (27.0)	76.5 (14.0)	0.008
	HR ≥80 bpm	184 (56.1%)	74 (64.3%)	65 (61.3%)	45 (42.1%)	0.001
Medical therapy	Beta-blockers	132 (40%)	3 (3%)	51 (39%)	78 (73%)	0.0001
	RAS antagonist	247 (75%)	95 (83%)	78 (74%)	74 (69%)	0.06
	Diuretics	261 (80%)	90 (78%)	91 (86%)	80 (75%)	0.122
	MRA	172 (52%)	27 (24%)	64 (60%)	81 (76%)	0.0001
	CRT	60 (18.3%)	0 (0%)	23 (21.7%)	37 (35%)	0.0001
	Pre-heart transplantation VAD	54 (16.5%)	0 (0%)	16 (15%)	38 (35.5%)	<0.0001
	– VAD-type PF (n)	14		10	4	<0.0001
	– VAD-type CF (n)	40		6	34	<0.0001

Data are expressed in absolute numbers and percentages, if not otherwise specified, or as median (IQR).

ACE-I: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; BSA: body surface area; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; HR: heart rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; PVR: pulmonary vascular resistance in Wood Units; VO_2max: maximal oxygen consumption in ml/kg/min; RAS: renin-angiotensin system; VAD-type PF: ventricular assist device with pulsatile flow; VAD-type CF: ventricular assist device with continuous flow

Pretransplant heart failure therapy

As shown in table 1, pretransplant beta-blocker or MRA treatment increased from period 1 to 3 (3 vs 39 vs 73%, p = 0.0001; 24 vs 60 vs 76%, p = 0.0001, respectively) whereas renin-angiotensin system antagonist treatment and use of diuretics were not significantly different between periods (83 vs 74 vs 69%, p = 0.06; 78 vs 86 vs 75%, p = 0.122, respectively). The percentage of recipients with cardiac resynchronisation therapy (CRT) significantly increased between the second and third period (0 vs 21.7 vs 35%, p = 0.0001). Furthermore, the number of patients waiting for heart transplantation while on VAD treatment increased from period 2 to 3 (15 vs 35.5%, p <0.0001). The number of continuous-flow (CF) LVADs increased from 6 to 34 (p <0.0001) while the number of LVADs with a pulsatile flow (PF) decreased between periods 2 and 3 from 10 to 4 and was limited in period 3 to paediatric cases (p <0.0001).

Pretransplant cardiovascular function and biological parameters

Table 1 shows that the overall median left ventricular ejection fraction (LVEF) was 20% with LVEF being numerically higher in the third decade (20 vs 20 vs 22.5%, p = 0.23). Median pulmonary vascular resistance (PVR) was 2.19 Wood Units (WU) and median VO_2max was 13 m/kg/min; PVR and peak VO_2 did not significantly differ between groups. Median heart rate decreased over time (period 1 vs 2 vs 3: 88 vs 84 vs 76.5 bpm, p = 0.008) with a corresponding decrease of the proportion of patients with a heart rate ≥80 bpm (64.3 vs 61.3 vs 45%, p = 0.001) consistent with the increasing use of beta-blockade after 1999.

Supplementary table S2 (in the appendix) demonstrates that the haemoglobin levels were lower in period 2 and 3 (147 vs 130 vs 130 g/l, p = 0.0001), whereas leucocyte and platelet counts were not different between groups. Bilirubin and creatinine levels were lower in the third period (18.0 vs 15.0 vs 10.0 µmol/l, p = 0.0001; 110 vs 114 vs 98 µmol/l, p = 0.08). Aspartate and alanine aminotransferase (ASAT and ALAT) levels were always within normal range but varied between groups (30.0 vs 27.0 vs 31 U/l, p = 0.56; 36.0 vs 21.0 vs 31.0 U/l, p = 0.017; respectively) and the proportion of patients with ASAT or ALAT >3 times above the upper limit of normal was lowest in period 3 (p = 0.006, p = 0.0001, respectively). On the basis of the biological measures, heart transplantation recipients in period 3 seemed healthier and this may relate to lower serum levels of creatinine and ASAT in patients on LVAD treatment at the time of the transplant operation. In fact, patients with a VAD had significantly lower (always p <0.0001) median preoperative values of creatinine (85.0, IQR 53.5 vs 110.0, IQR 42.0 µmol/l), blood urea nitrogen (6.3, IQR5.3 vs 8.8, IQR 5.9 mmol/l) and total bilirubin (9.0, IQR 11.8 vs 16.0, IQR 14.5 µmol/l). Serum iron was significantly lower in the second period (13.1 vs 10.1 vs 14.2 µmol/l, p = 0.001) and the proportion of recipients with a serum iron <10 µmol/l was highest during period 2 (30 vs 46.7 vs 22%, p = 0.001).

Details of heart transplant operations

Table 3 shows that median waiting time for heart transplantation was shortest during period 1 and longest for period 3 patients (1 vs 2 vs 3: 90 vs 129 vs 185 days, p = 0.006). Cold ischaemia time was 154 minutes for the total cohort and was lower in the first period (123.6 vs 180.0 vs 169.8 min, p = 0.0001). Significantly more heart transplant recipients had pretransplant cardiac surgery in the third era (32 vs 39 vs 58%, p = 0.001). The overall proportion of recipient/donor sex mismatches was 37% and was not significantly different between the three periods. Donor age was lower in period 1 and increased in periods 2 and 3 (32.0 vs 41.0 vs 49.0 years; p = 0.0001).

Follow-up and all-cause mortality

From 1987 to 2018, one patient was lost to follow-up, five patients are known to be dead but the date and cause of death are unknown and five patients underwent a second heart transplantation. As shown in table 4, the median follow-up time was 85.3 months. Total follow-up was 2989.1 patient-years.

Figure 1 and the attached table show the Kaplan-Meier estimate of overall survival as censored by survival status on 31 December 2019. The 1-year overall survival was 83.6 ± 2.1%; the 10-year survival was estimated to be 68.4 ± 2.9%. A total of 12% of all heart transplant recipients died within the first 3 months; the deaths were related to graft failure (5%) and haemorrhagic shock (4%), whereas infection (2%), acute rejection (1%) and neurological

Table 2:
Aetiologies of heart failure.

Aetiologies of heart failure	**All patients (n = 328)**	**1987–1998** (n = 115)	**1999–2010 (n = 106)**	**2011–2018 (n = 107)**
Primary cardiomyopathy				
– Mixed	121 (36.8%)	50 (44%)	46 (43%)	25 (23%)
– Genetic	26 (7.9%)	2 (1.7%)	8 (7.5%)	16 (15%)
– Acquired	12 (3.7%)	3 (2.6%)	4 (3.8%)	5 (4.7%)
Ischaemic heart disease	114 (34.7%)	40 (34.8%)	32 (30.2%)	42 (39.3%)
Valvular heart disease	8 (2.4%)	6 (5.2%)	0 (0%)	2 (1.9%)
Congenital heart disease	16 (4.9%)	3 (2.6%)	6 (5.7%)	7 (6.5%)
Cardiac allograft vasculopathy	5 (1.5%)	0 (0%)	2 (1.9%)	3 (2.8%)
COPD related	1 (0.3%)	1 (0.9%)	0 (0%)	0 (0%)
HTA, coarctation	5 (1.5%)	4 (3.5%)	1 (0.9%)	0 (0%)
Secondary cardiomyopathy	16 (4.8%)	2 (1.7%)	7 (6.6%)	7 (6.5)
Unknown	4 (1.2%)	4 (3.5%)	0 (0%)	0 (0%)

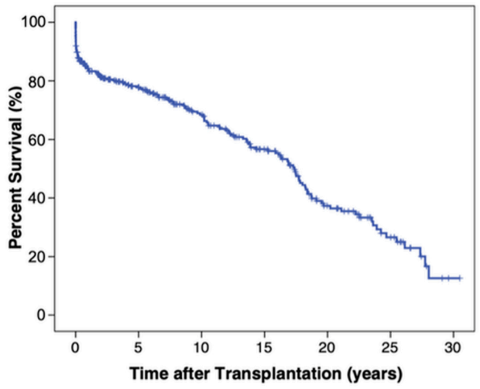
Data are expressed in absolute numbers and percentages.

COPD: chronic obstructive pulmonary disease; HTA: systemic arterial hypertension; always p = 0.0001 between periods

causes (0.6%) were less frequent (supplementary table S3 in the appendix).

Survival analyses of each period is presented in figure 2 and the attached table. Early mortality was significantly different between periods (period 1 vs 2 vs 3: 7 vs 26 vs 4%, p <0.0001). The difference in early mortality contributed to the significant difference in 1-year survival, which was 87.2% in period 1, 70.9% in period 2 and 93.0% in period 3 (p <0.022). The difference remained significant for 3- and 5-year survival. However, all-cause mortality in patients surviving at 1 year was not different between groups (figure 3) suggesting that the risk of mortality was largely associated with fatalities occurring within the first post-transplant year.

Figure 1: Kaplan-Meier estimate of overall survival after heart transplantation in the years 1987–2018.



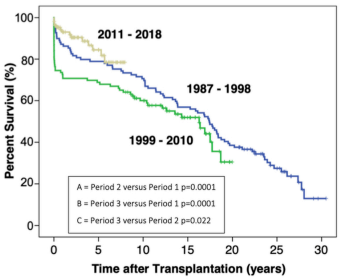
Time after HTx	% Survival	Patients at risk
1 year	83.6±2.1	248
3 years	80.1±2.3	215
5 years	77.8±2.4	193
10 years	68.4±2.9	131
15 years	56.7±3.3	89
20 years	37.3±3.8	42

Data are expressed in % ± SD

Discussion

Since the first cardiac allograft implantation in 1967, heart transplantation has remained the treatment option of choice for selected patients with advanced-stage heart failure refractory to standard treatment. This retrospective monocentric study tested whether characteristics of heart transplantation candidates have changed since heart failure therapy has substantially improved quality of life and sur-

Figure 2: Survival after heart transplantation according to period (1987–1998, 1999–2010 and 2011–2018).



	1987 – 1998 n=110 Events: n=81	1999 – 2010 n=106 Events: n= 54	2011 – 2018 n=107 Events: n=14
1 year	87.2±3.2	70.8±4.4	93.0±2.6
3 years	79.8±3.8	70.8±4.4	90.4±3.1
5 years	78.9±3.9	68.9±4.5	84.5±4.4
10 years	70.6±4.4	60.0±4.8	-
15 years	56.9±4.7	-	-
20 years	38.5±4.7	-	-

Data are expressed in % ± SD

Table 3:
Risk factors for heart transplantation surgery.

Variable	All patients (n = 328)	1987–1998 (n = 115)	1999–2010 (n = 106)	2011–2018 (n = 107)	p-value
Time on waiting list (days) median (IQR)	118.0 (289)	90 (225)	129 (229)	184 (347)	0.006; B 0.002
Urgent status on waiting list	57 (17%)	6 (5%)	32 (30%)	19 (18%)	0.0001
Cold ischaemic time (min) median (IQR)	154.0 (57.3)	123.6 (82.7)	180.0 (69.8)	169.8 (62.3)	0.0001; B, P1 vs (P2+P3)
Previous cardiac surgery	136 (41.5%)	35 (32%)	39 (29%)	62 (58%)	0.001
Donor age (years) median (IQR)	41.5 (25.0)	32.0 (22.0)	41.0 (25.0)	49.0 (22.0)	0.0001; B, P1 vs (P2+P3)
Recipient/donor sex mismatch	92 (37%)	29 (32%)	39 (38%)	24 (26%)	0.40

Data are presented as absolute numbers and percentages or median (IQR).

P1: period 1 (1987–1998); P2: period 2 (19992010); P3: period 3 (2011-2018)

Table 4:
Follow-up and outcome.

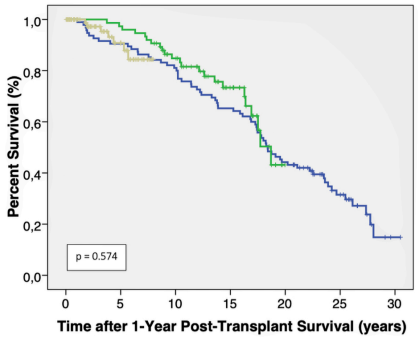
Variable	All patients (n = 328)	1987–1998 (n = 115)	1999–2010 (n = 106)	2011–2018 (n = 107)	p-value
Mean follow-up time (months) median (IQR)	85.3 (174.6)	209.0 (194.2)	121.4 (181.2)	33.1 (57.0)	<0.0001; B, P3 vs (P2+P1) and P1 vs P2
Early mortality <3 months	39 (12%)	8 (7%)	27 (26%)	4 (4%)	<0.0001
Mean rejection score, median (IQR)	0.54 (0.82)	1.0 (0.10)	0.49 (0.55)	0.16 (0.23)	<0.0001; B, P1 vs (P2+P3) and P1 vs P2

Data are presented as median (IQR) or absolute numbers and percentages. Median rejection score was calculated as the sum of the results of endomyocardial biopises divided by the number of biopsies.

P1: period 1 (1987–1998); P2: period 2 (1999–2010); P3: period 3 (2011—2018)

A: period 2 versus period 1; B: period 3 versus period 1; C: period 3 versus period 2

Figure 3: Kaplan-Meier estimate of all-cause mortality of patients surviving at 1 year post-transplant for the years 1987–1998, 1999–2010 and 2011–2018.



Blue survival curve: period 1 (1987-1998); green survival curve: period 2 (1999-2010); yellow survival curve: period 3 (2011-2018)

(n=270, 97 events)

Time after Tx	1987 – 1998 (n=95) Events 67	1999 – 2010 (n=75) Events 23	2011 – 2018 (n=100) Events 7
1 year	100	100	100
3 years	91.6±2.8	100	97.2±1.9
5 years	90.5±3.0	97.3±1.9	90.8±4.0
10 years	81.1±4.0	84.8±4.2	-
15 years	65.3±4.9	73.4 ±5.7	-
20 years	44.2±5.1	-	-

Data represents % survival. Data are expressed in % ± standard deviation.

vival of patients while central elements of the listing criteria for heart transplantation remained largely unchanged. Neither demographic, clinical or biological patient characteristics, nor survival of patients surviving the first year posttransplant differed greatly between periods, suggesting that the largely unchanged listing criteria still select similar patients. However, early mortality was significantly higher in period 2 and therefore its relation to pretransplant patient characteristics was investigated further.

Pretransplant characteristics of heart transplant recipients

During the last decades the key elements indicating eligibility for heart transplantation listing, in particular peak VO_2 and pulmonary vascular resistance, have been maintained without change of the respective cut-offs [12–14]. This could explain why these two parameters were not significantly different between the three periods. However, we were surprised that median patient age was also not different between the periods since drug treatment of heart failure not only prolongs survival but also retards progression of clinical symptoms and signs. Likewise, distribution between female and male gender remained unchanged, despite of the fact that more females survive acute myocardial infarction [20]. Furthermore, during the last two 2 decades the guidelines for listing of heart transplant recipients had less stringent comorbidity-related contraindications to heart transplantation . While this change should render patients with higher BMI, more severe renal dysfunction, or more severe diabetes eligible for heart transplantation [13, 14], neither BMI nor renal function parameters were significantly different between the three periods, although the prevalence of diabetes was numerically higher in period 3.

Altogether, these results suggest that patient selection remained conservative across the three periods and candidates with the best chances for long-term favourable outcome post-transplant were listed. In accordance with this conclusion, heart transplantation recipients across the three periods presented with a relatively benign comorbidity profile when compared with other patients with advanced heart failure [9]. In fact, pretransplant comorbidity was a determinant of postoperative long-term survival [21] and the superposition of the Kaplan-Meier estimates on the condition of 1-year survival across the three periods is in accordance with the not significantly different and overall benign comorbidity profile.

However, ischaemic cardiomyopathy was more prevalent in periods 1 and 3, which is of interest since this pathology is associated with an increased post-transplant mortality, as reported in a retrospective analysis by the International Society of Heart and Lung Transplantation (ISHLT) [22]. In fact, survival after heart transplantation was best in periods 1 and 3, with a 1-year survival of 87.2 / 93% and a 5-year survival of 78.9/84.5%, indicating that period 3 survival was even superior to the survival reported from the registry of the ISHLT for the years 2010–2017 [10]. In contrast, the Kaplan-Meier estimates of survival indicated a higher mortality in period 2 due to a significantly higher mortality within the first year post-transplant.

Pretransplant characteristics and post-transplant mortality

In order to better understand the increased early mortality in period 2, we compared across the three periods acknowledged pretransplant risk factors for early mortality post-transplant such as serum bilirubin, serum creatinine, haemoglobin, PVR and donor age [21, 22]. As monitoring and care in the operating room and in the intensive care unit, and patients' management in the immediate and early postoperative period improved significantly between 1987 and 2018, we chose a descriptive approach for statistical analysis.

Serum bilirubin was significantly higher in the first period whereas mortality was lower in period 1 than period 2, suggesting that this parameter of hepatic function does not explain the high early mortality in period 2. Likewise, serum creatinine was numerically higher in the second period, which could theoretically explain the increased early mortality in this period, but serum creatinine levels were not significantly different when survivors were compared with non-survivors in period 2 (as shown in the supplementary table S4). In contrast, pretransplant VAD therapy decreased bilirubin and creatinine serum levels significantly, suggesting that this treatment might have contributed to the improved outcomes in period 3.

Furthermore, the haemoglobin level was lower in the second period, which is interesting since low pretransplant haemoglobin levels have been associated with increased 1-year mortality after transplantation [23]. Furthermore, the serum iron level was low in period 2 and the combination of low haemoglobin level and low serum iron suggests the presence of iron deficiency as common underlying pathology. Iron deficiency is highly prevalent in severe heart failure and is also associated with increased mortality [24]. Therefore, it is conceivable that heart transplant re-

cipients from period 2 suffered from iron deficiency, although we cannot confirm this hypothesis since ferritin and transferrin saturation were at that time not regularly measured before transplantation. However, peak VO_2 levels were lower in 1-year non-survivors of the second period when compared with survivors (10.4 ± 3.5 vs 13.7 ± 3.7 ml/min/kg, p = 0.03), in accordance with the negative impact of iron deficiency on maximum exercise capacity observed in heart failure patients [25]. Nonetheless, it remains to be shown whether pretransplant iron deficiency is associated with increased post-transplant mortality.

Last but not least, PVR and donor age have been associated with increased early mortality. However PVR was not different between groups and not related in univariate analysis. Donor age was highest in period 3 whereas all-cause mortality was lowest, suggesting that donor age alone cannot explain the increased early mortality in period 2.

Transplant operation-associated risk factors and post-transplant survival

Perioperative or post-transplant factors such as cold ischaemia time may explain the higher early mortality observed in period 2, since cold ischaemia time is an important determinant of early postoperative mortality [26, 27]. Cold ischaemia time was significantly longer in period 2 as compared with other periods and long cold ischaemia time increases the risk of early mortality, especially when combined with older donor age (>34 years) [26, 27]. However, early mortality predicted by the cold ischaemia time was similar for periods 2 and 3 on the basis of analyses in the the United Network of Organ Sharing (UNOS) and the ISHLT registry. This suggests that cold ischaemia time alone cannot explain the increased mortality in period 2. The longer cold ischaemia time in periods 2 and 3 as compared with period 1 are surprising, but may reflect changes in the organ allocation system, which was regional until 2007 and national thereafter [28].

More recently, a propensity-matching analysis of the UNOS showed that both 1-year and 5-year mortality is higher in heart transplantation recipients with LVAD implantation preceding transplant surgery [29]. In contrast, survival was best in period 3 when 38 of the 62 heart transplantation recipients had pretransplant VAD implantation. This is in accordance with other reports that CF-LVAD treatment results in more favourable clinical and biological presentation on the day of heart transplantation [30, 31] and this was more true for those patients on HeartMate 3 support [32].

Post-transplant factors may likewise impact on early postoperative mortality and, in particular, acute cellular rejection can play an important role. However, the mean rejection score significantly decreased from period 1 to period 3, although most of the immunosuppressive drugs were already available in period 1. A similar decrease of the mean rejection score was also documented in a more recent analysis of the ISHLT registry and this decrease was associated with improved survival [33]. Therefore, the decrease in the rejection score may have contributed to the favourable results in period 3, but its progressive decrease from period 1 to period 3 does not suggest that acute cellular rejection explains the high early mortality in period 2.

Last but not least, changes in immediate post-transplant care may also explain the favourable results in period 3. In 2010, a multidisciplinary team was established at the Lausanne University Hospital for the care of the heart transplantation patients. This team is composed of local transplant cardiologists and cardiac surgeons, trained cardiac anaesthesiologists, together with dedicated intensive care and infectious disease specialists, as well as transplant immunology specialists. This multidisciplinary team approach was shown to improve morbidity and mortality after heart transplantation in our cohort, whether heart transplantation recipients had been on pretransplant LVAD support or not [30, 34]. This multidisciplinary approach is not limited to heart transplantation candidates but extends to the follow-up of patients with advanced heart failure and can likewise explain why substantially more heart failure patients were on beta-blocker, MRA, and CRT treatment in period 3. This integrated approach to advanced heart failure care corresponds to the quality of care centre strategy set out by te European Society of Cardiology [35]. Follow-up by such structures was shown to improve heart failure symptoms and cardiac function [36, 37] and may explain why LVEF was numerically higher in period 3.

Limitations

This retrospective cohort study spans 31 years of uninterrupted heart transplantation at the Lausanne University Hospital. The study stratified heart transplantation recipients as a function of the heart failure therapies available at the time of transplant operation, but we cannot exclude that heart transplantation outcome was affected by the great improvement in monitoring and care in the operating room and in the intensive care unit, and in patients' management thereafter. In acknowledgement that this presents a confounder for any association with post-transplant mortality, we limited the analysis to descriptive statistics. Furthermore, we cannot exclude that changes in the availability of immunosuppressive medicines may have impacted on post-transplant survival too. In fact, ciclosporin arrived on the market in 1982, tacrolimus in 1989, mycophenolate mofetil in 1992, and everolimus after 2004. However, the guideline-based local immunosuppressive regimen initiated at our institution has remained largely unchanged since 1995 [38], suggesting that change in immunosuppression may not explain the increased early mortality in period 2.

Conclusion

The results of the present heart transplantation cohort study indicate that the overall profile of the local heart transplantation recipients has not changed between 1987 and 2018. This observation is in accordance with the current guidelines for the selection of heart transplantation candidates, which perpetuated central criteria of earlier guidelines on the one hand. On the other hand, other criteria for heart transplantation listing softened, in particular with respect to severity of comorbidity, but we did not observe an effect of this change. This suggests that the medical strategy for heart transplantation listing has remained conservative, most likely related to the intention to select the heart transplantation candidates with the best option for long-term survival post-transplant. In the absence of any significant association of survival with demographic, clinical and

biological parameters in the descriptive statistical analysis, we hypothesise that the superior survival in the years 2011–2018 is based on the implementation of a multidisciplinary team approach achieving optimal arrival of the heart transplantation candidates at the time of their transplant operation. However, we cannot exclude a contribution of the favourable pretransplant characteristics in heart transplantation recipients with pretransplant LVAD treatment.

Acknowledgement
We acknowledge the support of the local team of transplant coordinators (Breton, MC, Chappuis N, Church C, Peuble C, Pilon N, Rogati G) and the nurses implicated in the follow-up of patients on CF-LVAD support (Collins J, Froideveaux O, Revelly ML).

Conflicts of interest
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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Appendix: Supplementary data

Figure S1: Number of annual heart transplantation operations from 1987 to 2018. Bars represent absolute numbers.

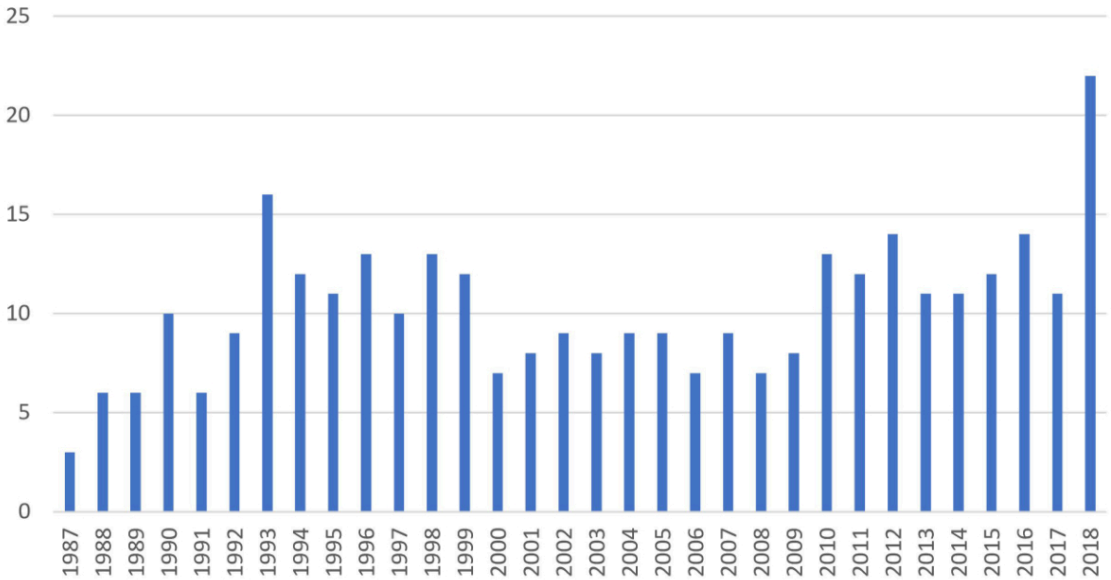

Table S1 :
Kaplan-Meier estimate of 1-year mortality of patients surviving at 1 year post-transplant (n = 270, 97 events).

Time after transplantation	% Survival	Patients at risk
1 year	100%	270
3 years	95.8 ± 1.3	215
5 years	93.0 ± 1.7	193
10 years	81.9 ± 2.8	131
15 years	67.8 ± 3.6	89
20 years	44.6 ± 4.4	42

Data are expressed as % ± standard deviation

Table S2:
Pretransplantation laboratory values.

Variable	All patients(n = 328)	1987–1998(n = 115)	1999–2010(n = 106)	2011–2018(n = 107)	p-value
Renal function					
Creatinine (µmol/l), median (IQR)	103.5 (48.3)	110.0 (33.0)	114.0 (57.0)	98.0 (45.8)	0.08
Creatinine >150 µmol/l	42 (12.8%)	12 (10.4%)	17 (16%)	13 (12.1%)	0.66
BUN (mmol/l), median (IQR)	8.2 (5.4)	8.4 (5.7)	9.9 (11.6)	7.7 (4.4)	0.06
Blood count					
Hb (g/l), median (IQR)	131.5 (26.8)	147.0 (32.0)	130.0 (31.0)	130.0 (244.0)	0.0001 B, P1 vs (P2+P3)
Leucocytes (G/l), median (IQR)	7.7 (3.1)	7.9 (5(IQR).0)	7.6 (3.1)	7.6 (2.8)	0.16
Platelets (G/l), median (IQR)	209.5 (92.3)	208.0 (237.0)	217.0 (93.0)	204.5 (96.8)	0.96
Hepatic function					
Total bilirubin (µmol/l), median (IQR)	13.0 (10.0)	18.0 (23.0)	15.0 (12.0)	10.0 (10.8)	0.0001 B
Total bilirubin >3N (63 U/l)	1 (0.6%)	1 (2.4%)	0 (0%)	0 (0%)	0.24
ASAT (U/l), median (IQR)	29.0 (17.0)	30.0 (18.0)	27.0 (10.0)	31.0 (17.8)	0.56 B 0.04
ASAT >3N (150 U/l)	15 (5.3%)	9 (11.7)	5 (5.0%)	1 (0.9%)	0.006
ALAT (U/l), median (IQR)	27.5 (25.3)	36.0 (29.0)	21.0 (10.0)	31.0 (25.8)	0.017 A,B
ALAT >3N (180 U/l)	11 (3.9%)	9 (11.5%)	1 (1.0%)	1 (0.9%)	0.0001
Iron level					
Iron (µmol/l), median (IQR)	13.3 (9.4)	13.1 (5.9)	10.1 (10.9)	14.2 (8.7)	0.0001 B,C
Iron <10 µmol/l	76 (33%)	12 (30%)	42 (46.7%)	22 (22%)	0.001

Data are presented as absolute number and percentage or median (IQR).

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; BUN: blood urea nitrogen; Hb: haemoglobin

A: period 2 versus period 1; B: period 3 versus period 1; C: period 3 versus period 2

Table S3:
Causes of death <3 months in the total cohort (n = 39).

Cardiac	16 (5%)
Bleeding	12 (4%)
Infection	6 (2%)
Rejection	3 (1%)
Neurological	2 (0.6%)

Table S4:
Comparison of survivors and non-survivors in period 2.

	1 year survivors (n = 75)	**1 year non-survivors (n = 31)**	**p-value**
Sex (M/F)	58/17	23/8	0.8
Age (years)	50 ± 13.9	50 ± 15.4	0.9
Smoking	36 (49%)	12 (39%)	0.4
Arterial hypertension	19 (25%)	9 (29%)	0.7
Diabetes	9 (12%)	6 (19%)	0.3
Dyslipidaemia	32 (44%)	16 (53%)	0.4
COPD	8 (11%)	4 (13%)	0.7
Dialysis	2 (3%)	1 (3%)	0.9
Time on waiting list (days)	210.3 ± 239	247.4 ± 208	0.5
LVEF (%)	22.9 ± 11.8	26.6 ± 13.7	0.2
PVR	2.7 ± 1.6	2.6 ± 0.8	0.5
VO_2max	13.7 ± 3.7	10.4 ± 3.5	0.03
HR >80 bpm	13 (19%)	8 (26%)	0.4
CRT	18 (24%)	5 (16%)	0.4
Preoperative LVAD	12 (16%)	4 (13%)	0.7
Diuretic	65 (87%)	26 (84%)	0.8
MRA	45 (60%)	19 (61%)	1.0
ACE-I or ARB	59 (79%)	19 (61%)	0.07
Beta-blocker	37 (49%)	14 (45%)	0.7
Creatinine (µmol/l)	131.0 ± 85.8	121.3 ± 68.1	0.6
Creatinine >150 µmol/l	14 (19%)	3 /10%)	0.23
BUN (mmol/l)	12.0±8.8	10.7±6.1	0.5
Total bilirubin (µmol/l)	17.8±7.5	23.6±9.7	0.03
Total bilirubin >3N	0 (0%)	0 (0%)	-
ASAT (U/l)	46.0 ± 69.4	59.7 ± 127.6	0.5
ASAT >3N	4 (6%)	1 (3%)	0.6
ALAT (U/l)	43.8 ± 70.9	28.4 ± 17.5	0.3
ALAT >3N	1 (1%)	0 (0%)	1.0
Iron <10 µmol/l	36 (55%)	12 (48%)	0.5
Hb (g/l)	124.9 ± 19.3	127.2 ± 24.7	0.6
WBC (G/l)	8.8 ± 3.5 (n = 73)	7.2 ± 2.0 (n = 31)	0.02
Platelets (G/l)	225.1 ± 78.7	206.9 ± 68.8	0.3
Time on waiting list (days)	210.3 ± 239	247.4 ± 208	0.5
Cold ischaemia time (min)	180.5 ± 47.2	185.3 ± 58.4	0.7
Redo surgery	27 (36%)	12 (39%)	0.8
Gender mismatch	28 (38%)	11 (36%)	0.8

ALAT: alanine aminotransferase; AST: aspartate aminotransferase; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; LVEF: left ventricular ejection fraction; Hb: haemoglobin; HR: heart rate; LVAD: left ventricular assist device; MRA: mineralocorticoid receptor antagonist; PVR: pulmonary vascular resistance in Wood Units; VO_2max: maximal oxygen consumption in ml/kg/min; WBC: white blood cell count.