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Post-transplant survival with pre-transplant durable continuous-flow mechanical circulatory support in a Swiss cohort of heart transplant recipients

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Summary

BACKGROUND: Worldwide, almost half of all heart transplantation candidates arrive today at their transplant operation with durable continuous-flow mechanical circulatory support (CF-MCS). This evolution is due to a progressive increase of waiting list time and hence an increased risk of haemodynamic worsening. Longer duration of CF-MCS is associated with a higher risk of device-related complications with potential adverse impact on post-transplant outcome as suggested by recent results from the United Network of Organ Sharing of the United States.

METHODS: A 2-centre Swiss heart transplantation programme conducted a retrospective observational study of consecutive patients of theirs who underwent a transplant in the period 2008–2020. The primary aim was to determine whether post-transplant all-cause mortality is different between heart transplant recipients without or with pre-transplant CF-MCS. The secondary outcome was the acute cellular rejection score within the first year post-transplant.

RESULTS: The study participants had a median age of 54 years; 38/158 (24%) were females. 53/158 study participants (34%) had pre-transplant CF-MCS with a median treatment duration of 280 days. In heart transplant recipients with pre-transplant CF-MCS, the prevalence of ischaemic cardiomyopathy was higher (51 vs 32%; p = 0.013), the left ventricular ejection fraction was lower (20 vs 25; p = 0.047) and pulmonary vascular resistance was higher (2.3 vs 2.1 Wood Units; p = 0.047). Over the study period, the proportion of heart transplant recipients with pre-transplant CF-MCS and the duration of pre-transplant CF-MCS treatment increased (2008–2014 vs 2015–2020: 22% vs 45%, p = 0.009; increase of treatment days per year: 34.4 ± 11.2 days, p = 0.003; respectively). The primary and secondary outcomes were not different between heart transplant recipients with pre-transplant CF-MCS or direct heart transplantation (log-rank p = 0.515; 0.16 vs 0.14, respectively; p = 0.81).

CONCLUSION: This data indicates that the strategy of pre-transplant CF-MCS with subsequent orthotopic heart transplantation provides post-transplant outcomes not different to direct heart transplantation despite the fact that the duration of pre-transplant assist device treatment has progressively increased.

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Introduction

Modern medical therapy has significantly prolonged the survival of heart failure patients resulting in a large increase in the number of patients living with advanced-stage heart failure [1, 2]. To date, orthotopic heart transplantation has remained the treatment of choice for selected patients with advanced heart failure. Intensive efforts have increased the availability of donor hearts and the number of heart transplants performed worldwide [3, 4]. Nonetheless, the overall donor heart supply still falls short of demand [5], resulting in prolonged waiting list time. In Switzerland, the mean waiting list time increased from 181 to 307 days at a regional heart transplantation centre from the period 1987–1999 to 2011–2018 [6].

A longer waiting list time carries the risks of worsening central haemodynamics, progressive deterioration of end-organ function and increased waiting list mortality [7, 8]. For a long time, heart transplantation under urgent status remained the only option for shortening the waiting list time. In recent years, long-term continuous-flow mechanical circulatory support (CF-MCS) has been shown to improve haemodynamics, to decrease end-organ dysfunction [9] and to reduce waiting list mortality of heart transplant candidates [7, 8]. This may explain why the number of

heart transplant candidates with a bridge to transplant by means of durable CF-MCS has increased worldwide, as reflected by the International Society of Heart and Lung Transplantation (ISHLT) registry demonstrating that 42.9% of heart transplant recipients had pre-transplant long-term CF-MCS in the years 2011–2018 [4, 10, 11].

However, studies investigating post-transplant survival of heart transplant recipients with pre-transplant CF-MCS have provided heterogeneous results, with some reports suggesting similar survival when compared with direct heart transplantation [12, 13] and others indicating inferior outcomes [14–18]. In October 2018, the US national heart organ allocation system changed priorities resulting in prolonged CF-MCS duration and inferior post-transplant outcomes of these patients when compared to direct heart transplantation [16, 17]. Different priorities of national allocation systems for heart transplantation can therefore explain the inhomogeneous results of post-transplant survival reported for pre-transplant CF-MCS patients and prolonged duration of CF-MCS may therein play a role [14–17]. The heterogeneous results may also relate to the different CF-MCS types that have been implanted in recent years, given that the HeartMate II®, the HVAD® and the HeartMate 3® differ with respect to the incidence of device-related complications [19, 20]. And this difference may have been accentuated by varying implantation rates across different world regions. Finally, dissimilarity of the post-transplant care protocol and the annual rate of locally performed transplant operations may also affect post-transplant outcome [3, 4].

In Switzerland, the national donor heart allocation system has remained largely unchanged since 2007. In particular, a high-urgency status has always been limited to approximately 30% of the annual number of all heart transplants. Given that the pre- and post-transplant follow-up protocols for our regional heart transplant cohort has not changed significantly since 2008, the present observational study compares against this stable background post-transplant survival in patients without or with pre-transplant CF-MCS both for the total of all CF-MCS devices implanted and for each CF-MCS type separately.

Methods

Study inclusion and exclusion criteria

The inclusion criteria for this observational study were: transplant operation carried out between 1 January 2008 and 31 December 2020; and consent provided by the heart transplant recipient. The study excluded patients undergoing retransplantation and patients who had received extra- or paracorporeal ventricular support pre-transplant.

Study population

This 2-centre observational study included 175 consecutive patients who underwent 176 heart transplant operations in the years 2008 to 2020. Study participants were all under follow-up by the Heart Transplantation Programme of Suisse Romande established at the University Hospitals of Lausanne and of Geneva. Addition of patients to the waiting list of heart transplant candidates was decided in regularly scheduled joint sessions of the dedicated multidisciplinary teams at both sites, as described elsewhere [21]. Each centre provided pre-transplant and post-transplant care to their local patients [21]. In contrast, the transplant surgery and immediate postoperative follow-up were always carried out at the University Hospital of Lausanne.

Four of 175 heart transplant recipients were excluded from the final analysis because retransplantation of heart transplant recipients with transplant operation before 2008 precluded these patients from pre-transplant CF-MCS. Likewise, a retransplantation of a heart transplant recipient with first transplant within the study period was not considered and censored as a primary outcome event. Of the remaining 171 heart transplant recipients, 13 were excluded because pre-transplant long-term MCS support used extra- or para-corporeal devices (figure S1 in the appendix).

Acquisition of anthropometric, biological, clinical and outcome data

Patient characteristics were collected from the electronic health reports of individual patients at the Lausanne and Geneva University Hospitals (TA, AZ). Data accuracy was confirmed by revisiting all patients' data, which demonstrated 98.6% correctness (TA). Donor-specific characteristics were extracted from the Swisstransplant organ allocation system (KL). The acute cellular rejection score was calculated from corresponding data extracted from the Swiss Transplant Cohort study (BPG). Comprehensive transthoracic echocardiography was always acquired on GE Healthcare machines by board-certified cardiologists. LVEF was quantitatively assessed using the biplane Simpson method [22]. All-cause mortality (ACM) was collected from local documentation and confirmed by death dates extracted from the Swiss registry of deaths up to the censor date 31 December 2021 on access date 26 March 2022.

Outcomes

Heart transplant recipients were separated into two groups as a function of pre-transplant CF-MCS.

The primary outcome compares the post-transplant survival time of primary heart transplant recipients with that of heart transplant recipients with pre-transplant CF-MCS.

The secondary outcome compares the acute cellular rejection scores in the first post-operative year [6, 21].

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 Pearson's Chi-square or Fisher's exact test (when expected n $\leq$5). Continuous variables were expressed as medians and interquartile ranges (IQR). The groups were compared using the nonparametric Mann-Whitney test to avoid the assumption of normal distribution of variables. Correlation between two continuous variables was tested using the nonparametric Spearman correlation test.

The mean rejection score within the first year post-transplant was calculated as the sum of the rejection grade of all endomyocardial biopsies taken during the first year post-transplant divided by the number of procurements [21].

Endomyocardial biopsies were graded for acute cellular rejection based on the 2004 ISHLT score.

Simple linear regression analysed the change of the duration of pre-transplant CF-MCS time as a function of the year of CF-MCS implantation after checking the data for linearity.

Survival data was analysed with standard Kaplan-Meier actuarial techniques for estimation of survival probabilities ± standard deviation and were compared using the log-rank test.

A two-tailed p value <0.05 was considered to indicate statistical significance.

Ethics approval

The protocol was approved by the local research ethics committee (CER-VD 2022-00562, CER VD 2019-704); the study was conducted in accordance with the Declaration of Helsinki and complies with the ISHLT Ethics Statement.

Results

Characteristics of heart transplant recipients with or without pre-transplant CF-MCS support

Table 1 shows that most baseline characteristics were not different between patients with direct heart transplantation (n = 105) or heart transplant with pre-transplant CF-MCS (n = 53). There was no difference for non-white ethnicity (11 vs 11%; p = 0.99), median age (overall: 53.7 years; 53.7 vs 54.5 years; p = 0.17) or sex (overall: 24% were females; 27 vs 19%; p = 0.33). In pre-transplant CF-MCS patients, median body mass index (BMI) (27.1 vs 24.8; p = 0.004) and body surface index (BSA) were higher, and the prevalence of smoking history (71 vs 44%; p = 0.001) and of dyslipidaemia (60 vs 38%; p = 0.006) were higher.

Table 2 shows that the proportion of heart transplant patients with ischaemic cardiomyopathy was higher in heart transplant recipients with pre-transplant CF-MCS (51 vs 32%, p = 0.013). The percentage of patients with mixed or acquired cardiomyopathy was not different between groups. Seventeen direct heart transplant recipients presented a cardiac pathology unfavourable for CF-MCS treatment such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, severe left ventricular noncompaction or Danon's disease. The proportion of transplant operations after pre-transplant CF-MCS increased from the period 2008–2014 to 2015–2020 (22 vs 45%; p = 0.009) (table S1 in the appendix).

Table 3 shows that on waitlisting the percentage of patients presenting with NYHA class IV was not different between groups (25 vs 30%; p = 0.56); median left ventricular ejection fraction (LVEF) was lower in pre-transplant CF-MCS than in direct heart transplant recipients (20.0 vs 25.0; p = 0.001); median PVR was higher in pre-transplant CF-MCS patients (2.3 vs 2.1 Wood Units; p = 0.047). In both groups, the proportion of patients on automated intra-cardiac defibrillator (AICD) treatment was high (68% vs 66%; p = 0.86), and many patients were on resynchronisation therapy (pre-transplant CF-MCS vs direct heart transplant (40% vs 32%; p = 0.40). At transplantation, heart transplant candidates with pre-transplant CF-MCS had lower levels of creatinine, urea and haemoglobin while ASAT, ALAT and bilirubin levels were not different (table S2 in the appendix).

Table 4 shows the relative proportions of the 3 different CF-MCS types implanted in the period 2008–2020: the Abbott HeartMate II® (n = 13), the HeartWare HVAD® (n = 13) and the Abbott HeartMate 3® (n = 27). One patient had biventricular long-term mechanical continuous support (LT-MCS) using the HVAD® device. Heart transplant recipients with pre-transplant CF-MCS overall had a median duration of 280.0 days on the device; the median duration of treatment was not significantly different between the 3 different continuous flow (CF) LT-MCS types implanted (HeartMate II® vs HVAD® vs HeartMate 3®: 226.0 vs 232.0 vs 329.0 days; p = 0.186). However, the median duration of treatment increased progressively during the study period (slope linear regression: 34.4 ± 11.2 days/year, p = 0.003) (figure 1).

Table 5 shows that the groups did not differ with respect to donor age, recipient/donor sex mismatch or the proportion of heart transplants under urgent status. Furthermore, cold ischaemic time and transport distance were not different; transport distance was significantly correlated with cold ischaemic time (r = 0.680; p = 0.0001). A total of 30.4% heart transplant patients without pre-transplant CF-MCS had previous cardiac surgery. The median length of the post-transplant stay in hospital was not different be-

Table 1:
Characteristics of heart transplant recipients without or with pre-transplant continuous-flow mechanical circulatory support (CF-MCS) treatment on waitlisting. Categorical values are presented as absolute numbers (n) and percentages; continuous values are presented as medians.

		All patients (n = 158)	No pre-transplant CF-MCS (n = 105)	Pre-transplant CF-MCS (n = 53)	p value
Demographics	Non-white ethnicity	17 (11)	11 (11)	6 (11)	0.99
	Age, in years	53.7	53.7	54.5	0.17
	Sex,#females/# males (% females)	38/120 (24)	28/77 (27)	10/43 (19)	0.33
Anthropometrics	BMI	25.6	24.8	27.1	0.004
	BSA, in m^2	1.88	1.87	1.96	0.018
Pre-transplant risk factors	Smoking	83 (53)	46 (44)	37 (71)	0.001
	COPD	15 (10)	8 (8)	7 (13)	0.26
	Hypertension	62 (40)	35 (33)	27 (52)	0.03
	Diabetes mellitus	34 (22)	20 (19)	14 (26)	0.29
	Dyslipidaemia	71 (45)	39 (38)	32 (60)	0.006
	Dialysis	4 (2.5)	3 (2)	1 (2)	1.0

BMI: body mass index; BSA: body surface index; COBP: chronic obstructive pulmonary disease.

tween groups (direct heart transplant vs pre-transplant CF-MCS: 33 vs 33 days; p = 0.28). No pre-transplant CF-MCS patient had a combined heart and kidney transplant operation.

The mean post-transplant follow-up time was 42.4 months for all study participants and not different between patients without or with pre-transplant CF-MCS (38.3 vs 45.9; p = 0.71). Furthermore, the mean rejection score within the first year post-transplant was not different (0.16 vs 0.14; p = 0.81).

Figure 2 represents the Kaplan-Meier estimates of overall post-transplant survival, which were 88.9 ± 2.5% for the first year post-transplant and 87.3 ± 2.7%, 83.8 ± 3.3% and 77.8 ± 4.7% for 3-, 5- and 10-year survival, respectively.

Survival was not different when Kaplan-Meier estimates compared heart transplant recipients with or without pre-transplant CF-MCS (log-rank p = 0.515) (figure 3).

No significant difference was evident when survival was compared between heart transplant recipients without or with CF-MCS with the former HeartMate II® or HVAD® devices, or with the current HeartMate 3® (log-rank p = 0.681) (figure 4).

Table 2:
Aetiology of end-stage heart failure on waitlisting. Categorical values are presented as absolute numbers (n) and percentages.

Aetiology		No pre-transplant CF-MCS (n = 105)	Pre-transplant CF-MCS (n = 53)	p value
Ischaemic heart disease		34 (32)	27 (51)	0.013
Congenital heart disease		12 (11)	2 (4)	0.11
Primary cardiomyopathies				
Genetic	Hypertrophic cardiomyopathy	8 (8)	0 (0)	0.002
	ARVC	4 (4)	0 (0)	
	Left ventricular noncompaction	3 (2)	0 (0)	
	Glycogen storage disease (Danon)	2 (2)	0 (0)	
Mixed	Dilated cardiomyopathy	24 (23)	18 (34)	0.28
	Restrictive cardiomyopathy	3 (3)	0 (0)	
Acquired	Inflammatory (myocarditis)	3 (3)	3 (6)	0.38
Secondary cardiomyopathies	Infiltrative	3 (3)	0 (0)	0.24
	Inflammatory (sarcoidosis)	2 (2)	0 (0)	
	Consequence of cancer therapy/Toxicity	4 (4)	1 (2)	
	Neuromuscular	1 (1)	0 (0)	
	Valvular heart disease	2 (2)	2 (4)	
Total		105 (100)	53 (100)	

ARVC: arrhythmogenic right ventricular cardiomyopathy; CF-MCS: continuous-flow mechanical circulatory support.

Table 3:
Functional characteristics and device treatment on waitlisting. Categorical values are presented as absolute numbers (n) and percentages; continuous values are presented as medians.

	All patients (n = 158)	No pre-transplant CF-MCS (n = 105)	Pre-transplant CF-MCS (n = 53)	p value
NYHA class IV	39 (27)	25 (25)	14 (30)	0.56
VO_2 max, in ml $O_2 \cdot kg^{-1} \cdot min^{-1}$	13.0	13.4	12.6	0.17
LVEF (%)	22.0	25.0	20.0	0.001
PVR (Wood Units)	2.2	2.1	2.3	0.047
Heart rate ≥100 bpm	13 (9)	9 (9)	4 (10)	0.98
CRT	55 (35)	34 (32)	21 (40)	0.40
AICD	106 (67)	71 (68)	35 (66)	0.86

AICD: automated internal cardiac defibrillator; CF-MCS: continuous-flow mechanical circulatory support; CRT: cardiac resynchronisation therapy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; PM: pacemaker; PVR: peripheral vascular resistance.

Table 4:
Characteristics of continuous-flow mechanical circulatory support (CF-MCS) at time of transplant operation. Categorical values are presented as absolute numbers (n) and percentages; continuous values are presented as medians.

Implanted CF-MCS		53 (100%)
HeartMate II®		13
HVAD®		13
HeartMate 3®		27
Left ventricular CF-MCS / biventricular CF-MCS		52 (98%) / 1 (2%)
Duration of CF-MCS (any CF device)		280.0 days (range: 36– 1343 days; sum: 19,908 patient-days)
Duration, by CF-MCS type	HeartMate II®	226.0 days (range: 36–567 days)
	HVAD®	232.0 days (range: 87–917 days)
	HeartMate 3®	329.0 days (range: 42–1343 days) p = 0.186

Sum = total number of days on CF-MCS.

Discussion

In this regional cohort of heart transplant recipients, one-third arrived at transplant surgery while on CF-MCS. Long-term post-transplant survival was not significantly different between heart transplant recipients with or without pre-transplant CF-MCS. During the observation period, the median time on CF-MCS increased progressively and was longest in the HeartMate 3® group. Post-transplant survival was not significantly different between device type groups but visually superior in patients with the HeartMate 3® despite their longer duration on CF-MCS.

Heart transplantation still remains the long-term treatment of choice for advanced heart failure patients and a major reason is the 10-year survival of up to 75% [4]. From 2009 to 2018, the worldwide number of heart transplant candidates increased substantially due to an increasing proportion of heart transplant candidates aged 65 years and older [23]. Advanced heart failure patients in this age group are usually considered candidates for destination therapy [24].

Figure 1: Increase in the duration of continuous-flow mechanical circulatory support as a function of the year of transplant operation. The beta slope of the regression line represents the change in the outcome (duration on support in days) with unit change in the predictor (year of ventricular assist device implantation).

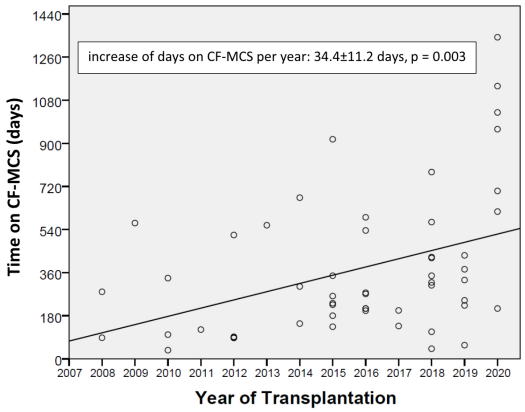
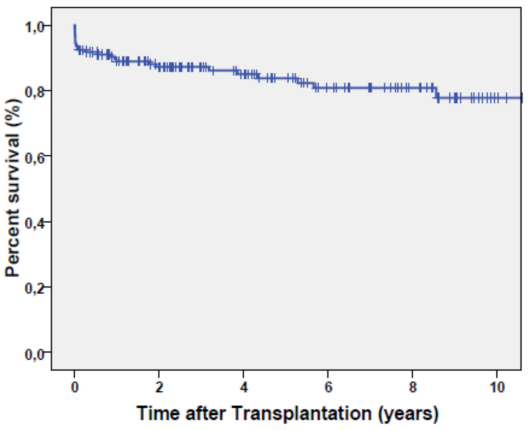
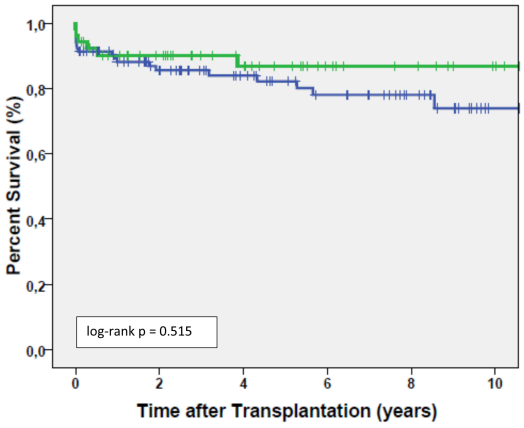


Figure 2: Overall survival of the 158 heart transplant recipients.



Time after Tx	% survival ± SD	Study participants at risk
1 year	88.9 ± 2.5	123
3 years	87.3 ± 2.7	83
5 years	83.8 ± 3.3	61
10 years	77.8 ± 4.7	12

Figure 3: Kaplan-Meier estimates of survival after heart transplantation comparing direct heart transplant patients (n = 105) with pre-transplant continuous-flow mechanical circulatory support (CF-MCS) patients (n = 53). Colour code: Blue line, post-transplant survival with direct heart transplant; Green line, post-transplant survival with pre-transplant CF-MCS. Heart transplant recipients without pre-transplant ventricular assist device (n = 105) had 19 events during the observation period while heart transplant recipients with pre-transplant mechanical circulatory support had 7 events (log-rank, p = 0.515). Results are expressed as percent survival ± standard deviation.



Time after Tx	All patients (n = 158)	No pretransplant CF-MCS (n = 105)	Pretransplant CF-MCS (n = 53)
1 year	88.9 ± 2.5 (n = 123)	88.2 ± 3.2 (n = 81)	90.3 ± 4.1 (n = 42)
3 years	87.3 ± 2.7 (n = 83)	85.7 ± 3.6 (n = 55)	90.3 ± 4.1 (n = 28)
5 years	83.8 ± 3.3 (n = 61)	82.2 ± 4.2 (n = 42)	86.8 ± 5.2 (n = 19)
8 years	77.8 ± 4.7 (n = 12)	78.1 ± 4.9 (n = 23)	86.8 ± 5.2 (n = 9)

Table 5:
Parameters of transplant surgery known to be associated with post-surgical outcome. Categorical values are presented as absolute numbers (n) and percentages; continuous values are presented as medians.

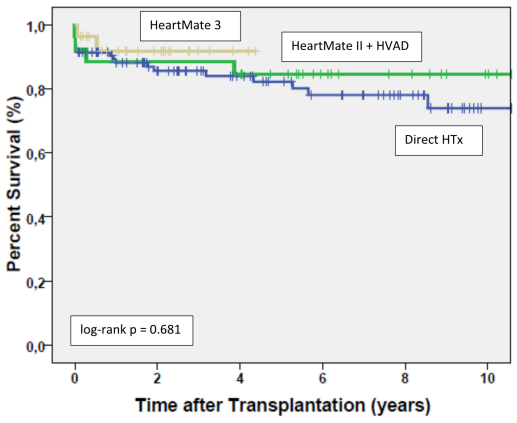
	All patients (n = 158)	No pre-transplant CF-MCS (n = 105)	Pre-transplant CF-MCS (n = 53)	p value
Previous cardiac surgery	85 (54%)	32 (31%)	53 (100%)	<0.0001
High-urgency status	29 (18%)	19 (18%)	10 (19%)	0.90
Time on urgent list (days)	21.0	11.5	47.5	0.003
Transport distance (km)	55.0	55.0	50.0	0.26
Cold ischaemic time (minutes)	162.6	170.0	151.8	0.14
Donor age (years)	47.0	47.0	49.0	0.37
Recipient/donor sex mismatch	64 (41%)	48 (46%)	16 (30%)	0.06
Heart + kidney transplantation	4 (2.5%)	4 (4%)	0 (0%)	0.15
Length of stay after heart transplantation (days)	33.0	33.0	33.0	0.28

CF-MCS: continuous-flow mechanical circulatory support.

In fact, for the 25,551 CF-MCS implantations for the period 2010–2019 documented by the INTERMACS registry, the mean age was 57 years and 50.4% of these implantations were intended as destination therapy [25]. However, the 5-year survival for CF-MCS treatment was only 43.3% in these patients [25], falling short of reported post-transplant 10-year survival of heart transplant recipients documented by the ISHLT registry [4]. This may explain the preference for heart transplantation waitlisting particularly when advanced heart failure presents as monopathology [24]. However, this attitude has worsened the worldwide imbalance between the number of heart transplantation candidates and the number of available donor hearts explaining the worldwide increase in waiting list time [5, 6, 26].

Today's clinical importance of pre-transplant CF-MCS is evident from various registries: the INTERMACS registry shows that almost 50% of all CF-MCS implantations are intended as either a bridge to transplant or a bridge to candidacy for heart transplantation [25]; the ISHLT registry documents that 42.9% of all heart transplantation recipients arrived at transplant surgery with pre-transplant MCS [4]; the United Network of Organ Sharing (UNOS) registry reported a proportion of 37.3% heart transplantation recipients with pre-transplant MCS [26]; European or Asian centres specify pre-transplant CF-MCS in 22% to 47% of their local heart transplantation recipient cohorts [27–30]. In accordance, the present cohort indicates pre-transplant CF-MCS in 33.5% of all heart transplantation recipients.

Figure 4: Kaplan-Meier estimates of survival after heart transplantation comparing direct heart transplant recipients (n = 105) with heart transplant recipients with pre-transplant HeartMate II® or HVAD® (n = 26), or HeartMate 3® (n = 27).Colour code: Blue line, post-transplant survival with direct heart transplantation; Green line, post-transplant survival with pre-transplant Heart Mate II® or HVAD®; Yellow line, post-transplant survival with pre-transplant HeartMate 3®. Survival after heart transplantation in patients without prior CF-MCS support and those with HeartMate 2® or HVAD®, and those with HeartMate 3®. Results are expressed as percent survival ± standard deviation.



Time after Tx	Direct HTx n = 105, events = 19	Pretransplant HeartMate II or HVAD n = 26, events = 5	Pretransplant HeartMate 3 n = 27, events = 2
1 year	88.2 ± 3.2 (n = 81)	88.5 ± 6.3 (n = 23)	91.9 ± 5.5 (n = 19)
3 years	85.7 ± 3.6 (n = 55)	84.6 ± 7.1 (n = 23)	91.9 ± 5.5 (n = 5)
5 years	82.2 ± 4.2 (n = 42)	84.6 ± 7.1 (n = 19)	–
8 years	78.1 ± 4.9 (n = 23)	–	–

Heart transplantation recipients on bridge to transplant were older and more overweight in the present study population; furthermore, LVEF was lower and pulmonary vascular resistance on waitlisting was higher suggesting that heart failure was more advanced. These findings correspond to reports from other cohorts [27–30] and match the profile of waiting list patients implanted with a HeartMate II® device or the HVAD® in the pivotal studies [31, 32]. However, 51% of the bridge-to-transplant patients in the present study population had end-stage heart failure of ischaemic origin while this proportion was lower elsewhere [29, 30]. This observation may relate to the decrease of waitlisted heart transplant candidates with cardiomyopathy of non-ischaemic origin as reported previously from our cohort [6]. However, we cannot exclude a selection bias since patients with heart failure of non-ischaemic origin are prone to a higher incidence of early postoperative right heart failure after CF-MCS implantation [33] and therefore more often considered for urgent transplant surgery [24, 34].

In view of this large use of pre-transplant CF-MCS, post-transplant survival is an important point of interest. In the UNOS registry, heart transplantation recipients with pre-transplant CF-MCS and transplant surgery in the years 2007 to 2017 presented a minor increase in 5-year mortality when compared with direct heart transplantation [35]. This increase resulted from a 2% higher upfront mortality within the first 3 post-transplant months which was related with redo sternotomy and device explantation [35]. Since long-term survival conditional on 90-day survival was in this analysis similar between direct heart transplantation and heart transplantation with pre-transplant CF-MCS, the authors of this study argued that live years gained with MCS should counterbalance the small increase of mortality early after MCS implantation [35]. The effect of redo sternotomy and device explantation on post-transplant mortality was no longer present in another analysis of the UNOS database restricted to the years 2015–2018. This analysis also included heart transplantation recipients with pre-transplant HeartMate3® support (n = 177) in addition to patients with pre-transplant HeartMate II® (n = 881) or HVAD® support (n = 920). In detail, 6-month post-transplant mortality was not different between direct heart transplantation and heart transplantation with pre-transplant CF-MCS and similarly not different between either CF LT-MCS type. However, survival was numerically best in heart transplantation recipients with pre-transplant HeartMate 3® support [36]. In accordance, no difference in post-transplant 1-year survival was reported by Alwair et al. comparing heart transplantation recipients arriving at transplant operation with HVAD® or HeartMate 3® support before the change of the national donor heart allocation in 2018 [37]. The present study is in accordance with these results, expanding the observations discussed above by the first report on 3-year post-transplant survival for heart transplantation recipients on pre-transplant HeartMate 3® device treatment.

The above-mentioned results were obtained in US heart transplantation recipients with transplant operation before October 2018 when heart transplantation candidates with durable CF-MCS (26) were prioritised by the national allocation system [12]. The duration of CF-MCS was shorter

in US heart transplantation recipients before October 2018 and longer thereafter [16, 17]. In contrast, the donor heart allocation algorithms of Eurotransplant and of Switzerland prioritise pre-transplant CF-MCS patients only when severe device complications warrant urgent transplant surgery, which can explain the longer waiting list time documented for heart transplantation candidates with pre-transplant CF-MCS by the EUROMACS registry [38] or the present study. Longer duration of CF LT-MCS treatment, however, is associated with a significant increase in device-related complications such as pump-related infection, gastrointestinal bleeding or stroke which occur in 20–25% of patients surviving the first post-implantation year [39]. CF-MCS-related complications prolong hospitalisation after transplant operation [40] but have also been associated with worse outcomes in heart transplantation recipients with >1 year of pre-transplant CF-MCS [13, 14, 41], especially when pump exchange had been required prior to transplant surgery [42]. In contrast, post-transplant mortality was in the present study population not different between heart transplantation recipients with direct transplant operation or pre-transplant CF-MCS. Of note, survival was numerically best with pre-transplant HeartMate 3® similar to other reports [36] despite having the longest duration of CF-MCS. Reasons for these favourable results are manifold and may relate to the low complication rate of the HeartMate 3® device [43]; however, local care of heart transplantation candidates with or without CF LT-MCS and post-transplant follow-up of patients in a Swiss medium size-volume centre may explain the overall excellent outcomes as well [44, 45].

Limitations

This observational study reports post-transplant outcomes from a Swiss medium-volume heart transplantation centre with a median annual caseload of 13.5 heart transplant operations/year for the period 2008–2020. Furthermore, three different CF-MCS types were implanted during the study period, which may have impacted on the results if numbers had been larger. In addition, the small numbers predispose to bias since patient selection for heart transplantation waitlisting may not have been representative and decision-making on when to implant long-term CF MCS was not standardised but based on clinical appraisal. Furthermore, change in perioperative and postoperative management during the study period may have impacted on outcomes. These considerations may limit broad applicability of the study results; however, the clinical characteristics of heart transplantation candidates are compatible with current indications as reported previously [3, 6] and the decision for CF-MCS was in concordance with the EACTS expert consensus on long-term MCS [46]. Since these results were obtained on the background of the Swiss national donor heart allocation algorithm, we cannot exclude that these results are not applicable to countries with other allocation algorithms.

Conclusion

The lack of a difference in post-transplant survival between patients with direct heart transplant and those with pre-transplant CF-MCS is encouraging and indicates that a bridge-to-transplant strategy is a valid option in patients with haemodynamic compromise while on the waiting list for heart transplantation in Switzerland. This result warrants further study in a larger Swiss national cohort since confirmation would provide additional evidence in favour of the equity of the current Swiss donor heart allocation policy.

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Potential competing interests
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 related to the content of this manuscript was disclosed.

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Appendix: supplementary figure and tables

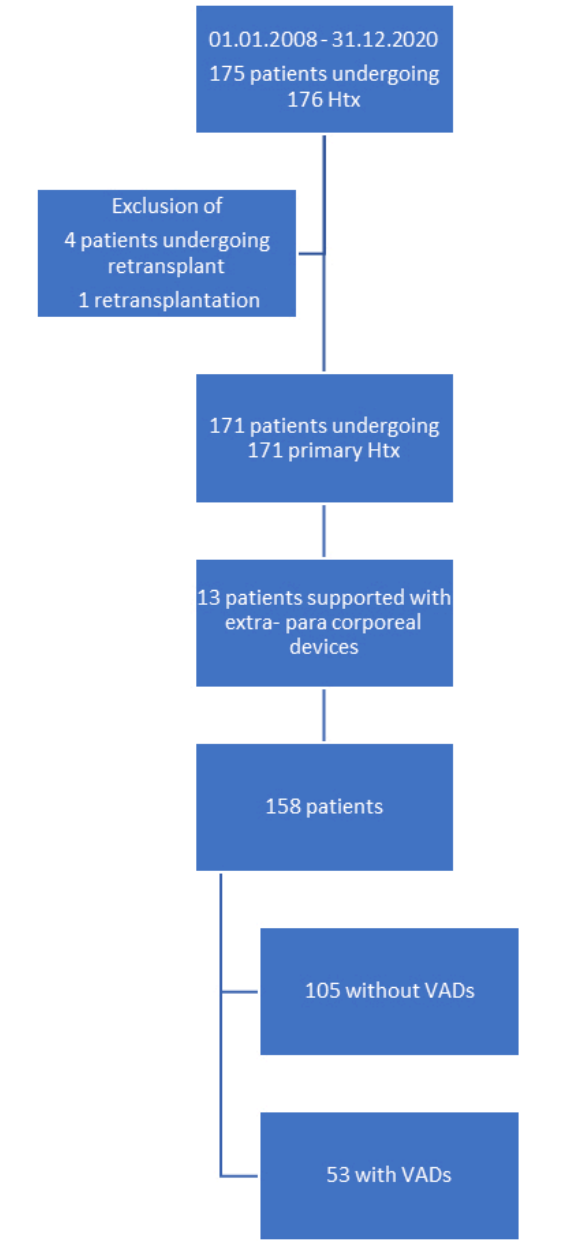

Figure S1: Study population with heart transplantation from 1 January 2008 to 31 December 2020 and minimal follow-up of 12 months. Htx: heart transplantation; VAD: ventricular assist device.

Table S1:
Number of heart transplants performed during the study period with proportion of patients with pre-transplant CF-MCS.

	Heart transplants performed	No pre-transplant CF-MCS	Pre-transplant CF-MCS	% of patients with CF-MCS
2008	6	4	2	33%
2009	5	4	1	20%
2010	12	9	3	25%
2011	11	10	1	9%
2012	13	9	4	31%
2013	11	10	1	9%
2014	11	8	3	27%
2015	11	4	7	64%
2016	13	6	7	54%
2017	7	5	2	29%
2018	20	11	9	45%
2019	19	13	6	31%
2020	19	12	7	37%
Total	n = 158	n = 105	n = 53	34%

CF-MCS: continuous-flow mechanical circulatory support.

Table S2:
Pre-transplant laboratory values. Continuous values are presented as medians.

	All patients (n = 158)	No pre-transplant CF-MCS (n = 105)	Pre-transplant CF-MCS (n = 53)	p value
Creatinine (µmol/l)	101.0	104.0	95.0	0.03
Urea (mmol/l)	8.0	8.4	6.4	0.0001
Haemoglobin (g/l)	129.0	131.0	126.0	0.04
Leucocytes (10^9/l)	7.6	7.6	7.7	0.97
Platelets (10^9/l)	214.5	218.0	200.0	0.80
Total bilirubin (µmol/l)	10.0	11.0	7.5	0.07
ASAT (U/l)	30.0	30.0	28.0	0.15
ALAT (U/l)	28.0	27.5	28.0	0.65
Serum albumin (g/l)	30.0	31.0	25.5	0.42
Serum iron (µmol/l)	13.3	14.0	12.6	0.06
CRP (mg/l)	6.0	6.0	6.5	0.68

ASAT: alanine-serine aminotransferase, ALAT: alanine-leucine aminotransferase, CRP: C-reactive protein; CF-MCS: continuous-flow mechanical circulatory support.