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ORIGINAL ARTICLE

Mid-term survival after continuous-flow left ventricular assist device versus heart transplantation

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Abstract There is a paucity of data about mid-term outcome of patients with advanced heart failure (HF) treated with left ventricular assist device (LVAD) in Europe, where donor shortage and their aging limit the availability and the probability of success of heart transplantation (HTx). The aim of this study is to compare Italian single-centre mid-term outcome in prospective patients treated with LVAD vs. HTx. We evaluated 213 consecutive patients with advanced HF who underwent continuous-flow LVAD implant or HTx from 1/2006 to 2/2012, with complete follow-up at 1 year (3/2013). We compared outcome in patients who received a LVAD ($n = 49$) with those who underwent HTx ($n = 164$) and in matched groups of 39 LVAD and 39 HTx patients. Patients that were treated with LVAD had a worse risk profile in comparison with HTx patients. Kaplan–Meier survival curves estimated a one-year survival of 75.5 % in LVAD vs. 82.3 % in HTx patients, a difference that was non-statistically significant [hazard ratio (HR) 1.46; 95 % confidence interval (CI) 0.74–2.86; $p = 0.27$ for LVAD vs. HTx]. After group matching 1-year survival was similar between LVAD (76.9 %) and HTx (79.5 %; HR 1.15; 95 % CI 0.44–2.98; $p = 0.78$). Concordant data was observed at 2-year follow-up. Patients treated with LVAD as bridge-to-transplant indication ($n = 22$) showed a non significant better outcome compared with HTx with a 95.5 and 90.9 % survival, at 1- and 2-year follow-up, respectively. Despite worse pre-operative conditions, survival is not significantly lower after LVAD than after HTx at 2-year follow-up. Given the scarce number of donors for HTx, LVAD therapy represents a valid option, potentially affecting the current allocation strategy of heart donors also in Europe.

Keywords LEFT ventricular assist device · Heart transplantation · Advanced heart failure · Outcome

Introduction

Heart transplantation (HTx) is believed to be the best treatment for refractory and advanced heart failure (HF) [1, 2], but it is available only for a minority of patients, due to paucity of donor hearts, and to the presence of contraindications or multiple risk factors in many HF patients. Expanding the donor pool by utilizing increasingly old donors may limit the probability of success of HTx [3]. Patients listed for HTx have a prolonged waiting time, that in Italy was about 2.3 years in the 2006–2010 time period (http://www.trapianti.salute.gov.it/), with continuing deterioration, poor quality of life and, 8–10 % annual mortality, despite an allocation system that prioritizes candidates in critical conditions. Another 10–15 % of HTx candidates are removed from the waiting list each year because they are no longer suitable for transplantation. Eurotransplant International Foundation (including 7 European Countries) yearly statistics showed that the percentage of HTx candidates receiving a heart at the end of each year decreased from 63 %

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in 2006 to 45 % in 2011 (Annual report 2011, http://www.eurotransplant.org), stressing an unmatched need.

Continuous-flow left ventricular assist devices (LVADs) have been demonstrated to improve the hemodynamic and functional status together with the quality of life of advanced/refractory HF patients [4–6], making LVAD therapy an approved strategy both for bridging patients to transplantation [6] or as destination therapy (DT) in patients ineligible for HTx [5, 7] Furthermore, the durability of currently available LVADs has extended the period of time that patients can live on support [5, 6], with a degree of acceptability near to that of HTx [8]. These remarkable results had led to the addition of LVAD as a recommended therapeutical option for advanced HF in European and United States (US) guidelines [1, 2].

To prevent adverse outcomes while awaiting HTx, an increasing number of centres started to use continuous-flow LVADs as a bridge-to-transplantation (BTT) in patients listed for HTx who are failing medical therapy with signs of deteriorating end-organ function [7]. Decision-making regarding timing of device implantation varies across countries and centres. In the US, a larger number of centres compared with Europe appeared to apply a strategy of early LVAD implant for many patients who meet clinical criteria for listing for HTx [6]. Data from controlled trials using LVAD either as BTT or DT reported a 1-year survival varying from 68 % in 2005–2007 series [5, 6] to 73 % (DT indication) in 2007–2010 series [9, 10], and 85 % (BTT indication) in 2008–2010 series [11, 12]. Results of the post-US Food and Drug Administration (FDA)-approval study with a continuous-flow LVAD as BTT using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) showed a survival at 1-year of 85 %, although about 50 % of those patients received an HTx within the first 6 months from LVAD implant [13].

Comparing with US, reports on LVAD indication, use and outcome in Europe are still limited [14, 15]. Furthermore, reports directly comparing the characteristics and outcomes of consecutive patients with advanced HF treated either with HTx or continuous-flow LVAD are still missing. Small series comparing HTx vs. LVAD have been reported, but most of HTx patients enlisted in those series had previously undergone LVAD support [16] or the HTx vs. LVAD comparison included mostly pulsatile LVAD [17].

The aim of this study is to describe the clinical risk profile and compare the outcome of consecutive patients with advanced HF treated with either HTx or continuous-flow LVADs. The study comes from a single Italian centre with a large volume of transplants. Clinical and instrumental parameters associated with increased peri-operative death in LVAD patients are also analysed.

Methods

Study population

Prospective data collection utilized for this study was approved by the Niguarda Ca' Granda Hospital Institutional Ethical Committee, following the STROBE statement (http://www.strobe-statement.org/), and the good clinical practise. We compared the clinical characteristics and 1-year outcome of 213 consecutive patients with advanced HF managed either with LVAD or with HTx from January 2006 to February 2012 in our hospital: 49 patients underwent continuous-flow LVAD implantation and 164 received HTx. LVAD indication was reported to be BTT in 22 cases, bridge-to-candidacy (BTC) in 15 cases, and DT in 12 cases. All BTT patients were on the transplant waiting list at our centre. In the considered time frame (January 2006–February 2013) 11 (22 %) patients that were supported by LVAD were subsequently transplanted, with an average time of support of 14 ± 7 months, thus they are only accounted as part of the LVAD group. Within the HTx group, 2 re-transplantations and 1 heart–kidney combined transplantation were included. LVAD patients were censored at the time of HTx or explant due to recovery ($n = 1$) in the survival analysis. Follow-up data were available for all patients, and were analysed until the end of February 2013, when all the patients have at least a one-year follow-up. 2-year survival was also analysed. In the survival analysis, patients were censored at 2-years, or at the last visit (when follow-up were shorter than 2 years), or at the time of death, or (for LVAD patients) at the time of HTx. Cumulative days of follow-up were 21,509 In the LVAD patients ($n = 49$), and 100,493 in the HTx patients.

Characteristics and experience of the Centre are reported as supplementary methods online.

Postoperative patient care of patient who underwent HTx

Detailed enlisting criteria and donor and recipient monitoring have been previously described [18–22]. Pharmacological treatment and general management of transplanted patients were in accordance with the recommendations of the currently available ISHLT guidelines for the care of heart transplant recipients [23]. Brief details on donor procurement, surgical technique and post-transplant follow-up are provided in the online Supplemental material.

Device description and postoperative patient care of patient who has undergone LVAD

Four different continuous-flow LVADs were used since 2006: 6 (12 %) Micromed DeBakey LVAD (Micromed Technology Inc., TX, USA), 8 (16 %) Berlin Heart Incor

(Berlin Heart AG, Germany), 33 (67 %) HeartMate II (HMII, Thoratec, CA, USA) and 2 (4 %) HeartWare HVAD (HeartWare, Australia). Brief details on surgical technique, device description, anticoagulation treatment and follow-up of patients under LVAD are provided in the online Supplemental material.

Statistical analysis

See statistical analysis description in supplemental methods online.

Results

Baseline characteristics

From January 2006 to February 2012, a total of 213 consecutive patients with advanced HF underwent either continuous-flow LVAD ($n = 49$) implant or HTx ($n = 164$) at our hospital. The clinical features of the overall study population are summarized in Table 1 (see also supplemental results online). After matching procedure, the clinical characteristics were well-balanced between the two groups, allowing to better compare the net effect of LVAD ($n = 39$) vs. HTx ($n = 39$) treatment (Table 2) in patients with actually refractory HF. The two groups still differed for mean pulmonary artery pressure (mPAP). Increased mPAP represents an important risk factor and a potential contraindication to HTx, whereas it is not a contraindication to LVAD treatment, thus justifying a larger proportion of patients with increased mPAP in the LVAD group, despite accurate matching between the two groups.

LVAD vs. HTx strategy and 1-year outcome

After a 1-year follow-up, a total of 41 deaths occurred: 12 among LVAD patients (0.33 per patient-year) vs. 29 among HTx patients (0.21 per patient-year). Main cause of death was multiorgan failure in LVAD patients ($n = 4$; 33.3 %) and early graft failure in HTx patients ($n = 15$; 51.7 %). The other causes of death in the two groups are listed in Table 3. Kaplan–Meier survival curves estimated one-year survival of 75.5 % in the LVAD vs. 82.3 % in HTx, which was not statistically significantly different. Hazard ratio (HR) for death was 1.46; 95 % confidence interval (CI) 0.74–2.86; $p = 0.27$ for LVAD vs. HTx (Fig. 1a). In matched LVAD vs HTx patient groups, the estimated 1-year survival was almost identical: 76.9 % in LVAD patients vs. 79.5 % in HTx recipients (HR 1.15; 95 % CI 0.44–2.98, $p = 0.78$; Fig. 1b; online Table 3). Four patients (8 %) in the LVAD group underwent HTx within the first year after implant, and 3 out of 4 (75 %) survived at least one year after HTx. Only one patient (2 %) recovered after 7 months of LVAD support [this patient had a recent diagnosis of acute refractory HF exacerbated by atrial tachycardia that needed extracorporeal membrane oxygenator (ECMO) and then LVAD], and one patient (2 %) underwent device replacement in the first year after implant due to device malfunction (after 5 months, Berlin Incor).

LVAD vs. HTx strategy and 2-year outcome

After a median follow-up of 24 month (interquartile 15–24 months), with 180 (85 %) patients with a complete 2-year follow-up, a total of 48 deaths occurred: 14 among LVAD patients (0.24/patient-year) vs. 34 among HTx patients (0.13/patient-year). The causes of deaths after the first year of follow-up in the LVAD group ($n = 2$) were bleeding ($n = 1$) and cancer ($n = 1$); whereas in the HTx group ($n = 5$) were infection ($n = 1$), sudden death ($n = 1$), antibody-mediated rejection ($n = 1$), cancer ($n = 1$), and graft failure ($n = 1$). Kaplan–Meier survival curves estimated 2-year survival of 71.4 % in the LVAD vs. 79.3 % in HTx, which was not statistically significantly different. HR for death was 1.56; 95 % CI 0.84–2.92; $p = 0.16$ for LVAD vs. HTx (Fig. 2a). Kaplan–Meier survival curves estimated 2-year survival between matched groups of LVAD patients (71.8 %) and HTx patients (76.9 %) were not statistically significant different with an HR of 1.35; 95 % CI 0.56–3.28, $p = 0.50$ (Fig. 2b).

BTT vs. HTx strategy and mid-term outcome

As further analysis, we compared the outcome of patients on list for HTx, who received a LVAD as BTT ($n = 22$, 45 % out of patients receiving a LVAD) vs. HTx patients. Kaplan–Meier survival curves estimating 1-year survival of BTT vs. HTx showed a non-statistically significant advantage of BTT (95.5 vs. 82.3 %; HR 0.24, 95 % CI 0.32–1.73, $p = 0.16$), confirmed at 2-year follow-up (90.9 vs. 79.3 %; HR 0.43, 95 % CI 0.10–1.80, $p = 0.25$) (Fig. 3). See further results as supplemental results online.

LVAD vs. HTx receiving marginal donors and mid-term outcome

In our HTx series, the median age of hearts donors was 45 years (Q1–Q3: 32–55 years), that means about 10 years older than mean donor age reported in the ISHLT registry (2006–2010) [24]. Acceptance of so-called "marginal" donors is often dictated by patient worsening while awaiting HTx. Thus, to better understand the effectiveness of two different approaches (extended criteria for donor acceptance or LVAD implantation), we compared survival in LVAD patients vs. recipients of donors of at least 60 years

Table 1 Clinical characteristics of 213 patients with advanced heart failure

	HTx	LVAD	*p*
N	164	49	
Age (year)	51 (38–59)	54 (48–63)	0.007
Patients ≥50 years, *n* (%)	91 (55)	34 (69)	0.10
Female, *n* (%)	52 (32)	5 (10)	0.003
Diabetes, *n* (%)	11 (7)	8 (16)	0.05
Insulin dependent diabetes, *n* (%)	7 (4)	0 (0)	0.36
Hospitalized, *n* (%)	82 (50)	49 (100)	<0.0001
Previous sternotomy, *n* (%)	30 (18)	0 (0)	0.0003
Ischemic cause of HF, *n* (%)	42 (26)	17 (35)	0.27
INTERMACS scale 1–3, *n* (%)	46 (28)	45 (92)	<0.0001
ICD, *n* (%)	128 (78)	37 (76)	0.70
Hemodynamic values			
RAP (mmHg)	4 (2–8)	7 (4–11)	0.02
mPAP (mmHg)	24 ± 10	37 ± 11	<0.0001
PCWP (mmHg)	17 ± 9	27 ± 9	<0.0001
CI (L/min/m^2)	1.8 ± 0.5	1.7 ± 0.4	0.49
Echocardiographic parameters			
LVEF (%)	24 (20–30)	22 (19–26)	0.051
LV EDD (mm)	65.0 (55.5–72.0)	70.5 (65.0–76.5)	0.003
TAPSE (mm)	14.4 ± 3.2	15.4 ± 2.3	0.12
RV diameter (4 chamber view) (mm)	37.6 ± 9.2	36.8 ± 11.0	0.73
Laboratory values			
Creatinine (mg/dl)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.71
Bilirubin (mg/dl)	0.9 (0.6–1.5)	1.1 (0.6–1.5)	0.69
AST (UI/L)	26 (19–38)	23 (18–43)	0.49
Hemoglobin (g/dl)	13.0 (11.8–14.4)	12.3 (11.4–13.4)	0.01
Hematocrit (%)	39.5 (35.2–43.5)	37.7 (34.4–40.4)	0.04
WBC (×10^9/L)	8.6 (7.1–10.4)	7.9 (6.3–12.1)	0.52
Platelets (×10^9/L)	234 (187–291)	243 (178–325)	0.39
INR	1.40 (1.09–2.23)	1.17 (1.09–1.59)	0.07
MELD-UNOS-modified	14 (10–18)	12 (9–16)	0.08
Concomitant medication or intervention during the hospitalization			
i.v. inotropic agent *n* (%)	81 (49)	48 (98)	<0.0001
IABP, *n* (%)	7 (4)	8 (16)	0.008
ECMO, *n* (%)	7 (4)	2 (4)	1
Short-term LVAD	1 (1)	0 (0)	1

HTx heart transplantation, *LVAD* left ventricular assist device, *HF* heart failure, *INTERMACS* Interagency Registry for Mechanically Assisted Circulatory Support, *ICD* implantable cardioverter-defibrillator, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure, *CI* cardiac index, *LVEF* left ventricular ejection fraction, *LVEDD* left ventricular end-diastolic diameter, *TAPSE* tricuspid annular plane systolic excursion, *RV* right ventricle, *AST* aspartate transaminase, *WBC* white blood count, *INR* international normalized ratio, *IABP* intra-aortic balloon pump, *ECMO* extra-corporeal membrane oxygenation. *MELD UNOS-modified* model for end-stage liver disease united network for organ sharing-modified

of age (HTx ≥ 60) ($n = 24$; see Supplemental Table 2 for comparisons of clinical characteristics). Kaplan–Meier survival curves estimating one-year survival of LVAD vs. HTx ≥ 60 showed a non-statistically significant advantage of LVAD strategy (75.5 vs. 58.3 %; HR 0.54, 95 % CI 0.23–1.23, $p = 0.14$), confirmed at 2-year follow-up (71.4 vs. 54.2 %; HR 0.58, 95 % CI 0.27–1.29, $p = 0.18$) (Fig. 4).

Perioperative outcome and predictors of death in LVAD patients

Peri-operative mortality at 30 day was 8 (16.3 %) vs. 18 (11.0 %), $p = 0.32$ in LVAD vs. HTx patients, mainly due to multiple organ failure and early graft failure, respectively. Peri-operative mortality between matched groups of LVAD and HTx patients were identical (6/39, 15.4 %). We further observed that 30-days mortality showed a non-statistically significant advantage of LVAD strategy ($n = 8/49$; 16.3 %) vs. HTx ≥ 60 ($n = 7/24$; 29.2 %, $p = 0.23$). Next, we investigated the factors associated with perioperative mortality in LVAD group. We identified only age [relative risk (RR) 1.10 95 % CI 1.01–1.20; $p = 0.031$] and preoperative bilirubin levels (RR 1.61 95 % CI 1.06–2.45; $p = 0.024$) as factors associated with increased mortality at Cox univariate analysis in the LVAD group, whereas age was the only variable with a significant RR for 90-day mortality (RR 1.09 95 % CI 1.01–1.18; $p = 0.026$). Among the LVAD patients the right ventricular failure (RVF) occurred in 25 patients (51.0 %) and in 1 case a RV assist device (RVAD) was implanted, nevertheless the patient died 1 day after the LVAD implantation. We used the following definition of RVF: the postoperative need for RVAD, and/or inotropes for ≥14 days, and/or nitric oxide (NO) inhalation for ≥48 h.

In-hospital stay and 1-year re-hospitalisation in LVAD and HTx patients

Considering the complete follow-up period of the first year after LVAD implant or HTx, we observed a longer pre-surgical hospital stay [median 20 days; interquartile (Q1–Q3: 9–35 vs. 1; 1–22; $p < 0.0001$)], and a longer post-surgical hospital stay (median 46 days; Q1–Q3: 30–65 vs. 24; 18–35; $p < 0.0001$) in LVAD vs. HTx recipients.

The percentage of patients that had at least one hospitalization during the first year after surgery was higher in LVAD vs HTx group ($n = 33$, 67.3 % vs. $n = 54$; 32.9 %, respectively, $p < 0.0001$). Total hospital readmissions were approximately, 3-fold higher in the LVAD group (1.45 patient/year) compared with HTx group

Table 2 Clinical characteristics of 78 matched patients with advanced heart failure treated with LVAD ($n = 39$) or HTx ($n = 39$)

	HTx	LVAD	*p*
N	39	39	
Age (year)	51 (43–60)	51 (46–61)	0.32
Patients ≥50 years-*n* (%)	23 (60)	23 (60)	1
Female, *n* (%)	5 (13)	5 (13)	1
Diabetes, *n* (%)	1 (3)	7 (18)	0.06
Insulin dependent diabetes, *n* (%)	0 (0)	0 (0)	1
Hospitalized, *n* (%)	39 (100)	39 (100)	1
Previous sternotomy, *n* (%)	0 (0)	0 (0)	1
Ischemic cause of HF, *n* (%)	14 (36)	14 (36)	1
INTERMACS scale 1-3, *n* (%)	36 (92)	36 (92)	1
ICD, *n* (%)	31 (79)	28 (72)	0.60
Hemodynamic values			
RAP (mmHg)	4 (3–7)	7 (4–11)	0.10
mPAP (mmHg)	28 ± 10	37 ± 10	0.004
PCWP (mmHg)	21 ± 8	28 ± 9	0.003
CI (L/min/m^2)	1.7 (1.5–2.0)	1.7 (1.5–1.9)	0.92
Echocardiographic parameters			
LVEF (%)	23 (19–25)	23 (20-26)	0.86
LV EDD (mm)	65.5 (58.5–75.5)	70.0 (65.0–75.5)	0.16
TAPSE (mm)	14.1 ± 3.4	15.6 ± 2.5	0.10
RV diameter (4 chamber view) (mm)	41.3 ± 8.3	36.3 ± 11.7	0.14
Laboratory values			
Creatinine (mg/dl)	1.0 (0.8–1.4)	1.1 (0.9–1.3)	0.62
Bilirubin (mg/dl)	1.1 (0.7–1.8)	1.1 (0.6–1.5)	0.44
AST (UI/L)	27 (20–40)	21 (16–36)	0.12
Hemoglobin (g/dl)	12.8 ± 1.8	12.4 ± 1.6	0.30
Hematocrit (%)	35.8 (30.4–41.4)	38.0 (34.8–40.6)	0.26
WBC ($\times 10^9$/L)	10.1 (6.6–13.4)	8.9 (6.9–12.3)	0.85
Platelets ($\times 10^9$/L)	219 (130–302)	273 (197–340)	0.07
INR	1.27 (1.10–2.12)	1.15 (1.10–1.57)	0.21
MELD-UNOS-modified	13 (10–19)	11 (9–15)	0.14
Concomitant medication or intervention during the hospitalization			
i.v. inotropic agent, *n* (%)	38 (97)	38 (97)	1
IABP, *n* (%)	6 (15)	8 (21)	0.77
ECMO, *n* (%)	2 (5)	1 (5)	1
Short-term LVAD	1 (3)	0 (0)	1

HTx Heart transplantation, *LVAD* left ventricular assist device, *HF* heart failure, *INTERMACS* Interagency Registry for Mechanically Assisted Circulatory Support, *ICD* implantable cardioverter-defibrillator, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure, *CI* cardiac index, *LVEF* left ventricular ejection fraction, *LVEDD* left ventricular end-diastolic diameter, *TAPSE* tricuspid annular plane systolic excursion, *RV* right ventricle, *AST* aspartate transaminase, *WBC* white blood count, *INR* international normalized ratio, *IABP* intra-aortic balloon pump, *ECMO* extra-corporeal membrane oxygenation. *MELD UNOS-modified* model for end-stage liver disease united network for organ sharing-modified

(0.51 patient/year), and in both groups the main cause of readmission was infection (see Table 3 for details). Nevertheless, major complications were relatively infrequently in both groups, and 23 % of readmissions in the LVAD group were for monitoring and treating patients with INR significantly below the target range or for identifying the reasons for unspecific symptoms, such as fatigue and dyspnoea. Among patients who experienced at least one readmission, the LVAD group had a longer length of stay in hospital in the first year after discharge compared with HTx group (median 22 days; Q1–Q3: 11–44 vs. 13; 6–21; $p = 0.02$). Also considering the matched groups of LVAD and HTx patients, the percentage of patients that had at least one hospitalization during the first year after surgery was higher in the LVAD group compared with HTx group (respectively, $n = 25$; 64.1 % vs. $n = 12$; 30.8 %; $p = 0.006$). Total hospital readmissions were still approximately, 3-fold higher in the LVAD group (1.52 patient/year) compared with HTx group (0.46 patient/year) (see online Table 2 for causes of readmission).

LVAD vs. HTx strategy and follow-up beyond 2 years

After a median follow-up of 958 days (interquartile 409–1642 days) or 2.6 years (1.1–4.5 years), a total of 53 deaths occurred: 17 among LVAD patients (0.24/patient-year) vs. 36 among HTx patients (0.07/patient-year). The total days of follow-up of individual HTX were 195,782 whereas for the LVAD patients were 25,231. Considering all these data, Kaplan–Meier survival curves estimated a survival of 65.3 % in the LVAD vs. 78.0 % in HTx, which was statistically different: HR for death was 2.02; 95 % CI 1.12–3.64; $p = 0.02$ for LVAD vs. HTx (see online Fig. 3). Kaplan–Meier survival curves estimated survival between matched groups of LVAD patients (64.1 %) and HTx patients (74.4 %) were not statistically significant different with an HR of 1.90; 95 % CI 0.82–4.41, $p = 0.13$ (see online Fig. 4). Nevertheless, the estimation of Kaplan–Meier survival curves for the LVAD group is limited after 2 years of follow-up because the number at risk in LVAD group is too low. A separation of the curves os survival probably can be suppose in particular after 3 years after LVAD implantation, although a longer follow-up with a larger number of LVAD patients is needed.

Twelve patients (24.5 %) in the LVAD group underwent HTx within the end of the follow-up (end of February 2013), and 10 out of 12 (83.3 %) survived at least 1 year after HTx. Only 1 (8.3 %) out 12 LVAD patients died in the peri-operative period after HTx (1 day after HTx).

Table 3 Causes of death and rehospitalization in patients treated with heart transplantation

	HTx		LVAD	
	Follow-up 50, 673 days		Follow-up 13,326 days	
	Events	Events/pt-y	Events	Events/pt-y
Death	29	0.21	12	0.33
Graft failure/multiorgan failure	15	0.11	4	0.11
Fatal bleeding	4	0.03	1	0.03
Infection	4	0.03	3	0.08
Sudden death	3	0.02	0	0
Acute graft rejection	2	0.01	–	–
Stroke				
Ischemic	0	0	1	0.03
Hemorrhagic	1	0.01	1	0.03
Neoplastic complications	0	0	1	0.03
Intestinal ischemia	0	0	1	0.03
Rehospitalization	71	0.51	53	1.45
Infection	19	0.14	13	0.36
LVAD-related infection	–	–	9	0.25
Acute graft rejection	18	0.13	–	–
Stroke				
Ischemic	1	0.01	1	0.03
Hemorrhagic	0	0	0	0
Other neurological complications	2	0.01	4	0.11
Neoplastic complications	2	0.02	1	0.03
Vascular complications	4	0.03	0	0
Renal failure	2	0.01	0	0
Surgical operations	2	0.01	1	0.03
ICD or PM implantation	2	0.01	3	0.08
Bleeding	2	0.01	5	0.14
Requiring PBRC	0	0	2	0.05
Out of range INR	0	0	6	0.16
Monitoring	4	0.03	6	0.16
Reported fatigue/dyspnoea	1	0.01	6	0.16
CAV	5	0.04	–	–
RV failure	1	0.01	2	0.05
Arrhythmia	1	0.01	5	0.14
Ventricular arrhythmia	0	0	4	0.11
Pericardial effusion	5	0.04	0	0
Pump thrombosis	–	–	0	0
Pump replacement	–	–	1	0.03
Other	2	0.01	3	0.08

pt-y patient/year, *HTx* heart transplantation, *LVAD* left ventricular assist device, *HF* heart failure, *ICD* implantable cardioverter-defibrillator, *PM* pacemaker, *PBRC* packed blood red cells, *INR* international normalized ratio, *CAV* cardiac allograft vasculopathy, *RV* right ventricle. Causes of fatal bleeding in the HTX group were: 2 lung hemorrhagia at day 1 and 2 after HTx, 1 ascending aortic rupture at day 4 after HTx, and 1 untreatable bleeding in the mediastinum at day 17 after HTx. Causes of fatal bleeding in the LVAD group was 1 gastric hemorraghia

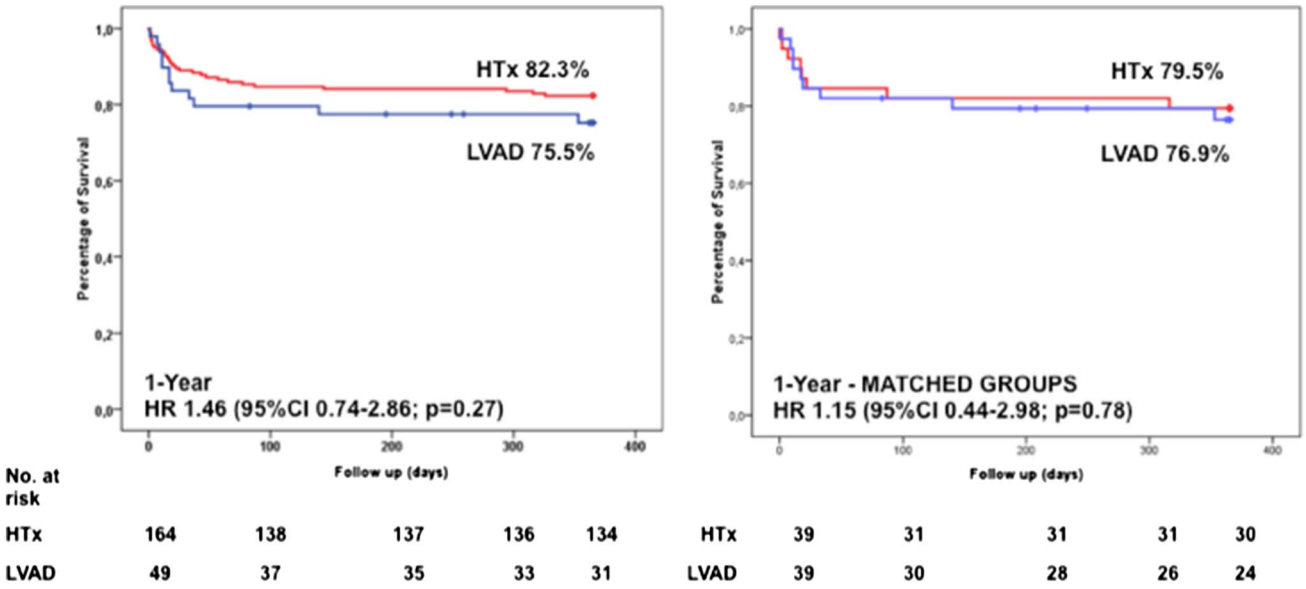
Discussion

In this Italian series, we found that the mid-term survival of patients with advanced HF treated with LVAD was not statistically different compared with those treated by HTx. Peri-operative mortality was similar, although patients treated with LVAD had worse preoperative conditions. Subanalysis of LVAD vs. HTx groups matched for relevant clinical characteristics further support this finding. The present study represents the largest direct comparison of continuous-flow LVAD vs. HTx in a population of consecutive patients with advanced HF. Collection and analysis of the data were not coordinated by any commercial sponsor, as in other published cohorts [5, 9, 11, 17]. Moreover, the proportion of patients remaining at least one year on LVAD despite BTT indication is remarkably high comparing with US series [6]. Finally, patients treated with LVAD as BTT indication showed a non-significant better outcome than HTx up to 2 years of follow-up.

The 75.5 % survival rate at 1 year and 71.4 % survival rate at 2 years of patients treated with LVAD is near to US data from selected populations in clinical trials. Miller et al. [6] reported a 68 % survival rate at 1 year in 133 patients implanted with an HMII LVAD as BTT (time period 2005–2006). Only 52 % of these patients were still on support after 1 year, whereas in our cohort just as few as 8 % of all LVAD patients were transplanted within the first postoperative year. In a recent trial, Slaughter et al. [9] reported a 73 % survival rate at 1 year in 281 patients implanted with a HMII LVAD for DT (time period 2007–2009). In a US registry, enrolling 169 patients treated with HMII LVAD as BTT, the survival rate at 1 year reached 85 % with 34 % receiving HTx within 1 year [13].

The use and the spread of LVAD across Europe is patchy and limited compared with US, although the new recommendations of the European Guidelines concerning LVAD as an effective therapeutical option for advanced HF will promote the diffusion of these devices [1]. European data are needed to clearly understand the impact of this therapy on the management of advanced HF patients and its interaction with HTx in terms of candidacy, bridging, and prioritization for organ allocation policies. Three main factors must be considered: reduction of suitable heart donors, aging of donors (on average, about 10 years older than in the ISHLT registry in our series) and increasing number of patients remaining on the waiting list for longer periods of time. The present analysis underlines that LVAD strategy has at least a mid-term efficacy that is not inferior to HTx, allowing hemodynamic stabilization, with a relatively low rate of serious adverse events.

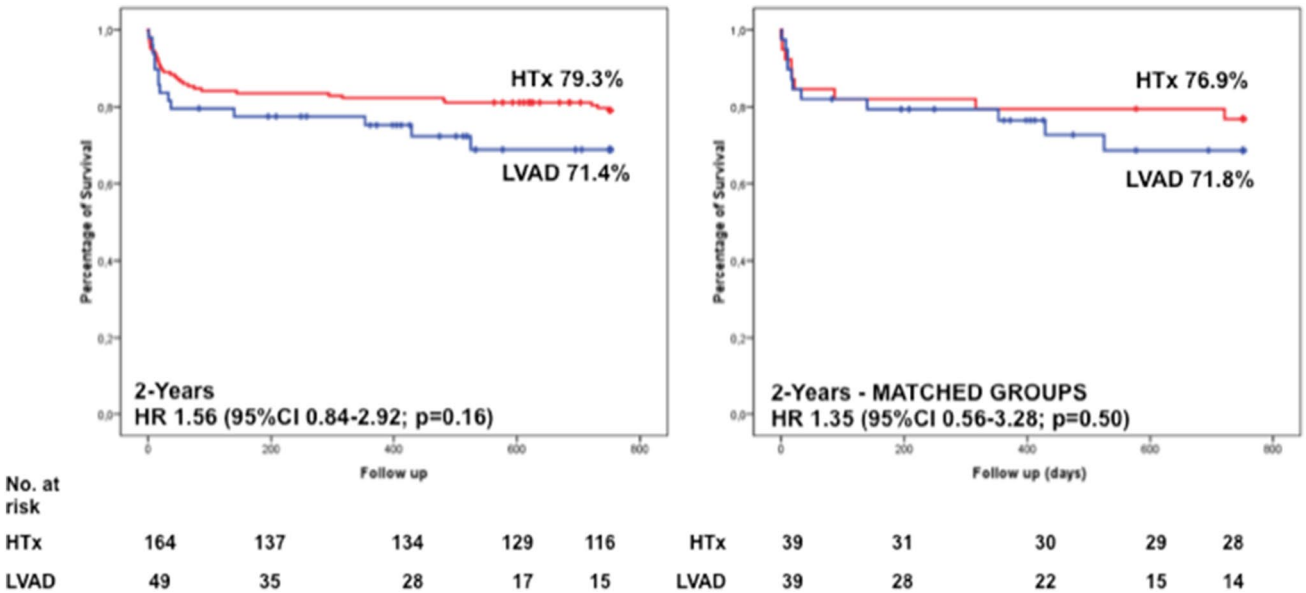
We observed that current post-transplant survival in our series is lower than that reported in the ISHLT Registry and in US data (87.3 % survival at 1 year in the OPTN/



No. at risk					
HTx	164	138	137	136	134
LVAD	49	37	35	33	31

HTx	39	31	31	31	30
LVAD	39	30	28	26	24

Fig. 1 Kaplan–Meier estimates of 1-year survival of the 213 consecutive patients with advanced heart failure. **a** 164 were treated with heart transplantation (HTx) vs. 49 with left ventricular assist device (LVAD) and **b** matched groups of LVAD patients ($n = 39$) and HTx patients ($n = 39$). Hazard ratio (HR) and 95 % confidence interval (CI) are referred for LVAD vs. HTx



No. at risk					
HTx	164	137	134	129	116
LVAD	49	35	28	17	15

HTx	39	31	30	29	28
LVAD	39	28	22	15	14

Fig. 2 Kaplan–Meier estimates of 2-year survival of the 213 consecutive patients with advanced heart failure. **a** 164 were treated with heart transplantation (HTx) vs. 49 with left ventricular assist device (LVAD) and **b** matched groups of LVAD patients ($n = 39$) and HTx patients ($n = 39$). Hazard ratio (HR) and 95 % confidence interval [CI] are referred for LVAD vs. HTx

SRTR 2011 annual data report—http://srtr.transplant.hrsa.gov/annual_reports) but it is in line with national Italian data [Centro Nazionale Trapianti (CNT) 2000–2009 HTx report: 83.8 ± 0.7 % survival at 1 year, available at http://www.trapianti.salute.gov.it/], and not statistically superior compared with LVAD strategy at our centre. In fact, while the 1-year survival rate from 1992 to 1998 was 87.5 % at our centre, [19] it is currently (2006-2011) 82.3 %. 2-year HTx survival rate of our series of 79.3 % is similar to those of other European series, as the Scandinavian experience [25]. Increasing age of heart donors represents an identified concern for early mortality [25]. At our center, mean donor age increased constantly over years, from 25 years at the beginning of our experience to 37 years by the 1990s and

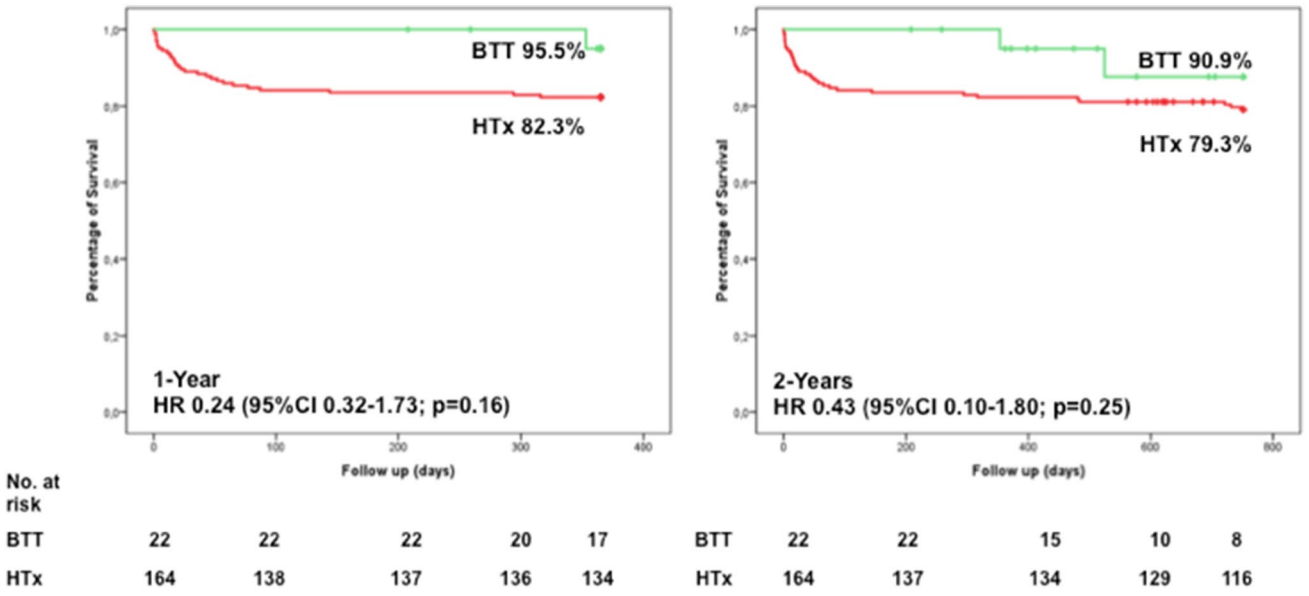


Fig. 3 Kaplan–Meier estimates of 1 (**a**) and 2-year (**b**) survival of 22 patients treated with LVAD as bridge-to-transplantation (BTT) indication vs. 164 patients treated with heart transplantation (HTx). Hazard ratio (HR) and 95 % confidence interval (CI) are referred for LVAD vs. HTx

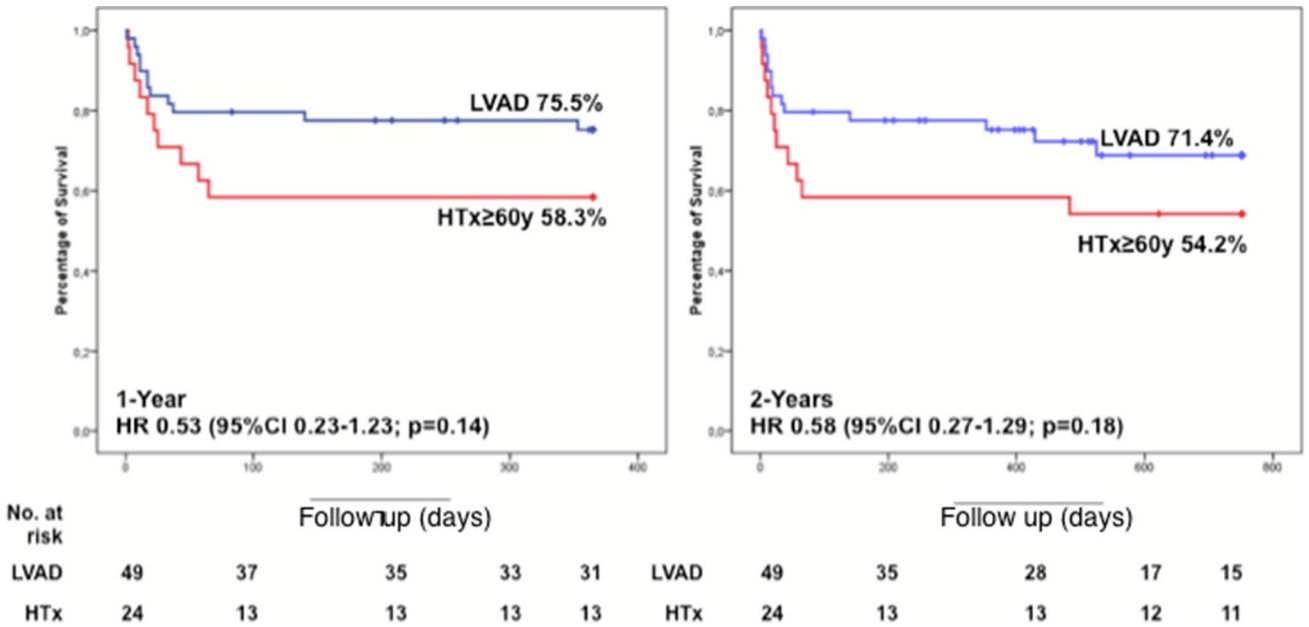


Fig. 4 Kaplan–Meier estimates of 1 (**a**) and 2-year (**b**) survival of 49 patients treated with LVAD vs. 24 recipients of donor hearts of at least 60 years of age (HTx ≥ 60). Hazard ratio (HR) and 95 % confidence interval (CI)

reached 45 years in the most recent cohort [3]. This trend is confirmed in other European experiences (http://www.eurotransplant.org). Previous analysis from our centre reported 30 days mortality significantly higher in patients transplanted with older donors (≥60-year-old): 32 % compared with 10 % among patients transplanted with younger donors (<60 years) [3]. Similarly, our subanalysis comparing older donors (≥60-year-old) vs. LVAD implanted patients showed a non-significant benefit of LVAD strategy, at least at 2-year follow-up.

Peri-operative mortality related to LVAD implant (16.3 %) appeared higher than in most recent US experiences (ranging from 18.7 % by Miller [6] to 4 % by more recent registries with BTT indication [13]), although considering only BTT indication, we had no peri-operative mortality. Patients with a BTT indication had also lower

peri-operative mortality than patients with a BTC/DT indication in our series (0 vs. 27 %, respectively). Patient's age and peri-operative bilirubin resulted significantly associated with an increased peri-operative mortality risk in LVAD group in our series, [26] but the limited number of patients and of events limit the generalization of this finding. Peri-operative RVF remains an important issue after LVAD implantation also in our series, nevertheless an accurate study of the RV function for a selection of suitable patients for LVAD with RV strain analysis and dobutamine stress echocardiography and with hemodynamic indexes derived by RHC can limited the number of severe RVF [27–30]. Pre-operative IABP and levosimendan have been generally used to reduce the incidence of RVF in our centre, although we did not have the support of randomized trial [31, 32].

We reported a longer hospital stay and a higher rate of readmissions in patients treated with LVAD with respect to HTx. The postoperative hospital stay after a LVAD implant (median 46 days) in our cohort was longer compared with previous reports (for instance Slaughter) [5] that reported a median length of 27 days, while the number of re-hospitalization was lower (1.56 vs. 2.64 patient-year) [5]. This could be related with a strict patient monitoring and training. Some recent experiences reported hospitalization rates after LVAD implant similar to ours [33, 34].

Although LVAD implies an intermediate priority for donor heart allocation in our area, our HTx candidates supported with LVAD de facto undergo transplantation almost exclusively in case of emerging complications or difficult patient adaptation to LVAD, making the distinction DT and BTT strategy not so clear. For this reason, we pooled together survival data on LVAD independently of initial indication, nevertheless we showed in subanalysis that patients on list at the time of LVAD implantation had a very good prognosis at 2 years, despite few of them received HTx. The choice of the right time for implantation of LVAD has been discussed for each candidate by a multidisciplinary team composed by HF specialists, cardiac surgeons and anaesthesiologists. In line with current guidelines, recurrent hospitalizations for worsening HF, actual or anamnestic need for inotropic support within the past 6 months, and worsening organ function identified candidates for LVAD implantation [7, 35]. Furthermore, several risk scores for evaluating the risk of death of patients with HF are generally tested to assess the potential benefit by a LVAD or HTx [36–39]. Another factor influencing indication was the presence of pulmonary hypertension poorly responsive to vasodilators in an otherwise good HTx candidate.

In a small series Williams et al. [16] compared HTx ($n = 13$) vs. LVAD ($n = 29$) strategy in HTx-eligible patients, and their results in terms of survival were close to ours. In fact, one-year outcomes were similar whether they received an allograft or LVAD for BTT, and HTx outcome was not adversely affected by prior LVAD implantation. It should be noted that in Williams' cohort, all 13 transplanted patients had previously received a LVAD [16]. In our study, we preferred to analyse post-LVAD survival up to HTx, and post-HTx survival in patients not previously treated with LVAD, to compare the net results of each of these therapies.

Study limitations

Caution should be used when interpreting the present findings, since this is not a randomized study. Thus, the comparison between the two groups can be methodologically debatable. However, this study represents the largest cohort of consecutive patients treated either with LVAD or HTx. Lack of significant differences concerning survival between LVAD and HTx could be attributable to inadequate power to assess this outcome; nevertheless at 1-year follow-up the survival curves of matched groups are overlapping suggesting that similar results would be expected even with a larger study population. Subanalysis of LVAD vs. HTx groups matched for relevant clinical characteristics further support similar outcome of LVAD or HTx treatment at mid-term follow-up. In a previous study, comparing mostly pulsatile-flow LVAD vs. HTx, a survival benefit of HTx was observed only after 3 years of follow-up [17]. We performed an exploratory analysis of the survival of LVAD and HTx patients beyond 2 years of follow-up, although the estimation of survival curves for the LVAD group is limited after 2 years of follow-up because the numbers at risk in LVAD group is too low. We observed a constant number of deaths each year after LVAD implantation, whereas we observed consistently that the mortality in the HTx group after 3 to 5 years from surgery is very low. Thus, a significant separation of the survival curves probably can be supposed in particular after 3 years after LVAD implantation, although a longer follow-up with a larger number of LVAD patients is needed. Speculatively, this could imply that in particular in LVAD BTT patients HTx should be performed within 2–3 years after LVAD implantation not to increase the number of LVAD patients who can die due to LVAD complications. Cost-effectiveness analysis were not estimated, and should be warranted, although it can be problematic comparing a valuable resource, either expensive, such as LVADs, with a priceless, such as donor hearts. We did not evaluate the quality of life and functional status improvement in LVAD vs. HTx-treated patients. However, the beneficial impact of LVAD on quality of life and functional status in patients with advanced HF have been documented [4], although patient-reported outcomes, such as health status, quality of life, and anxiety/depression should be further elucidated [40].

Conclusions

Despite worse preoperative conditions, at our center post-operative survival is not significantly lower after LVAD than after HTx, at least at 2-years after implant. Thus, LVAD therapy with continuous-flow devices represents a valid option, given the scarce number of donors for HTx also in Europe. Considering that the perioperative mortality of the patients transplanted without previous LVAD was 11 %, there was no increase of peri-operative mortality after HTx in LVAD patients (1 death out 12 LVAD patients that were transplanted 8.3 %) in our series. As further consideration, as annual mortality on HTx list is about 8–10 % plus 10–15 % of patients no more suitable for HTx annually among those on the list, it seems that among patients suitable both for LVAD (BTT indication) or HTx, the early treatment with LVAD as BTT appears a solution with a favorable risk/benefit profile. Timing for LVAD implantation and the interaction between LVAD and HTx, including organ allocation policies, should be continuously reassessed with the objective to improve overall survival in patients with advanced HF. Furthermore, based on our sub-analysis, LVAD treatment could be preferable than transplantation with marginal donors older than 60-year-old, although further studies are needed.

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Conflict of interest The authors declare that they have no conflict of interest.

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