The HeartWare Ventricular Assist Device (HVAD): A Single Institutional 10-Year Experience

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Abstract

Objectives The aim of this study was to analyze our 10-year experience with the HVAD in a real-world scenario in a high-volume German heart center.

Methods We retrospectively analyzed outcomes of adults (≥18 years) with terminal heart failure (HF), who underwent HVAD implantation for durable LVAD therapy in our center between October 2009 and March 2020. Primary and secondary end points were all-cause death after implantation and LVAD-associated complications, respectively. We focused the distinct analyses on risk profiles at the time of implantation and implant strategies, i.e., bridge-to-transplant (BTT) or destination therapy (DT).

Results A total of 510 patients were included, with 229 and 281 individuals in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 1 (45%) and 2 to 4, respectively. Median follow-up was 26 months (IQR: 5–54 months). Overall survival at 1, 3, and 5 years after HVAD implantation was 66% (95% CI; 61.7–70%), 49.4% (95% CI; 44.9–53.8%), and 37.4% (95% CI; 32.8–42%), not censored for LVAD exchange, LVAD explantation, or heart transplantation. INTERMACS level 1 and peri-operative temporary right heart assistance were independent risk factors for survival. Survival was best in BTT patients undergoing heart transplantation at any time during follow-up. The INTERMACS level at time of HVAD implantation did not affect survival after heart transplantation. Freedom from the combined end point of any device-associated severe complication and death was 44.5% (95% CI; 40–48.8%) at 1-year after implantation.

Conclusion The HVAD is a reliable pump for durable mechanical circulatory support even in high-risk patients. Still, heart transplantation outperforms durable MCS therapy for a superior long-term survival.

Keywords
- left ventricular assist device
- heart transplantation
- survival
- complications
- HeartWare ventricular assist device

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Introduction

Left ventricular assist devices (LVADs) have become a treatment option in advanced heart failure (HF) with improving outcomes during the last two decades.[1,2] The success of the modern LVADs is attributed to tremendous technical advances addressing size, biocompatibility, durability, and effectiveness.[2] Modern third and fourth-generation LVADs are relatively small intrapericardially implantable, continuous-flow (CF) centrifugal pumps.[3–5]

The Heartware ventricular assist device (HVAD) (Medtronic, United States) has been the first relevant CF centrifugal pump LVAD. It has been CE mark and FDA approved in 2008 and 2012 for the bridge-to-transplant (BTT) indication, respectively.[2,3] The published results after HVAD implantation show relatively good survival rates of up to >80% at 1 year. Such data are derived from clinical trials with certain inclusion and exclusion criteria and may thus not reflect a "real-world" scenario.[3,5–9]

This study was meant to report the "real-world" long-term clinical experience and outcome with the HVAD in a high-volume German heart center.

Materials and Methods

Patients and Study Design

All patients who received a HVAD as their first durable mechanical circulatory support (MCS) device were eligible for this retrospective analysis. Excluded were patients ≦18 years, adults with transposition of the great arteries, patients undergoing isolated RVAD implantation, or concomitant biventricular assist device implantation (►**Fig. 1**). This single-center study (reference no. 2020–627) was approved by the institutional ethics committee of the Ruhr-University Bochum in Bad Oeynhausen, Germany. We performed a retrospective analysis of our prospectively maintained institutional MCS database. The severity of HF and adverse events were classified according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions.[6,9] Routine laboratory and surgical data were collected from the hospitals electronic patient database as indicated. Clinical follow-up was closed in April 2020. Cardiac surgery, anti-coagulation management and anti-infective therapy were performed in a routine fashion.[10] Eligibility for heart transplantation has been evaluated and discussed routinely in a multi-disciplinary transplant board in all transplant candidates. High urgency (HU) status listing requests were applied to and in accordance with the business rules of the Eurotransplant foundation criteria for patients on durable MCS (Box B criteria, see below).

End Points

The primary end point was defined as death after HVAD implantation due to all causes. Analyzing the MCS-related complications during follow-up, secondary end points were pump infection, cerebrovascular accident (ischemic insult and bleeding; CVA), pump thrombosis, right heart failure (RHF), device malfunction, ventricular tachycardia (VT), and gastrointestinal bleeding (GIB). Patients undergoing HVAD explantation, HVAD exchange, or heart transplantation were censored at the time of intervention. Based on the EUROMACS registry protocol, we summarized individual causes of death as indicated. We delineated 10 dominant causes of death designated as sepsis, multiorgan failure (MOF), CVA, cardiopulmonary failure, GIB, lung disease, RHF, device malfunction, unknown cause and others.[2,11]

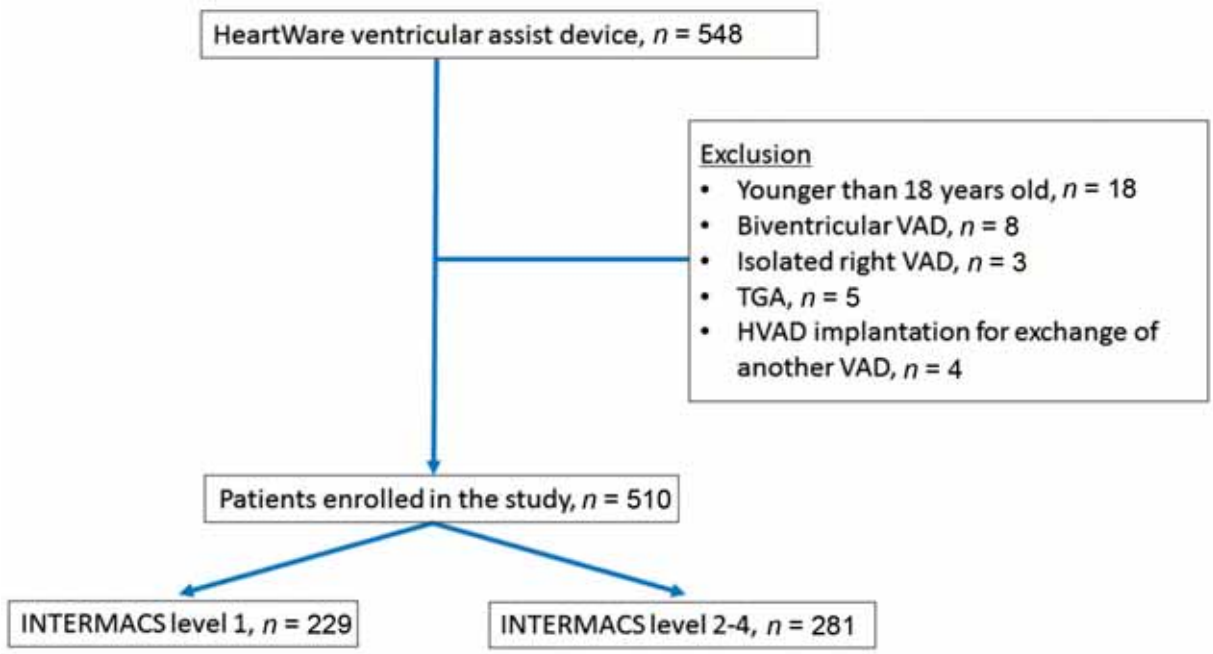


Fig. 1 Patient selection. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; TGA, transposition of the great arteries; VAD, ventricular assist device.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD) or as median +25th-75th percentile interquartile range for continuous variables, and frequency and percentage for categorical variables, as indicated. Univariate comparisons were performed with Student's paired or unpaired *t*-test for continuous normally distributed data. The Mann-Whitney U test was used for comparisons of non-parametric continuous data and Fisher's exact test for categorical data. Data for survival and freedom from adverse events were analyzed using the Kaplan-Meier method; comparisons between groups were made using the log-rank test. The predictors for peri-procedural and long-term mortality was evaluated by multivariate Cox regression analysis, and the results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Age at HVAD implantation, body mass index (BMI), body surface area, diabetes mellitus, peripheral artery disease, prior cardiac surgery, the temporary RVAD use, CVA, prior cardiac arrest, laboratory values at implantation, prior temporary MCS use, as well as INTERMACS level 1 versus 2 to 4 were chosen as candidate covariates. These covariates were included via stepwise regression analysis using a probability for stepwise entry of 0.05. Differences were considered statistically significant at values of probability of less than 0.05. All statistical analyses were performed using the R software.

Results

Baseline Demographics and Echocardiographic Characteristics

A total of 607 HVADs were implanted into 548 patients during the study period and 510 patients were included in the analyses, because they received implantation of an HVAD as a primary LVAD; 38 patients were excluded (►**Fig. 1**). ►**Table 1** depicts baseline characteristics of the final study population. Patient mean age was 54.6 ± 12.1 years and 82.7% were males. At the time of HVAD implantation, a large proportion of patients ($n = 229$) was in INTERMACS level 1, while fewer patients were in INTERMACS levels 2, 3 and 4, i.e., $n = 150$, $n = 115$, and $n = 16$, respectively. The latter three groups were collectively considered for the subsequent analyses. No patient was implanted in INTERMACS levels greater than level 4. Common comorbidities and pre-implant HF treatments are outlined in ►**Table 1**. The most common etiology of HF was ischemic cardiomyopathy (ICM; $n = 266$, 52%) (►**Table 1**). The implantation strategy was BTT in 427 patients (84%) and destination therapy (DT) in 83 cases (16%). Baseline characteristics differed only slightly between INTERMCS level 1-patients and INTERMACS levels 2 to 4 patients and between BTT and DT patients (►**Table 1**).

Peri-procedural Characteristics

INTERMACS level 1-patients and BTT-patients were preoperatively more frequently supported by temporary MCS-devices when compared with INTERMACS level 2 to 4-patients and DT patients, respectively (►**Table 2**). Additional procedures are listed in ►**Table 2**. Additional procedures were more frequently performed in INTERMACS level 2 to 4 patients when compared with INTERMACS level 1 patients. Need for pre-surgical mechanical ventilation and post-surgical ventilation times, as well as ICU stays was more frequent and longer in patients implanted in INTERMACS level 1 when compared with patients in INTERMACS levels 2 to 4. Hospital stays were comparable. Temporary RVADs were more frequently used in INTERMACS level 1 patients when compared with INTERMACS levels 2 to 4 patients (40.6 vs. 20.6%, $p \leq 0.001$), while the time interval of temporary RVAD support was comparable [median 17 days (IQR; 12–33 days) in INTERMACS level 1 vs. 23 days (IQR; 3–35 days) in INTERMACS levels 2–4, $p = 0.485$] (►**Table 2**).

Survival after HVAD Implantation

The median follow-up in this study was 26 months (IQR; 5–54 months). The 3-months overall survival rate after HVAD implantation was significantly worse in the INTERMACS level 1 group when compared with INTERMACS levels 2 to 4 patients (75.3 vs. 87.8%, $p < 0.001$). There was no 3-months survival difference comparing BTT and DT patients (►**Table 2**). Overall survival rates at 1, 3, and 5 years after HVAD implantation were 66% (95% CI; 61.7–70%), 49.4% (95% CI; 44.9–53.8%), and 37.4% (95% CI; 32.8–42%), not censored for LVAD exchange, LVAD explantation, or heart transplantation (►**Fig. 2A**). Overall median survival was 35 months (95% CI; 26–43 months). Survival was best in BTT patients undergoing heart transplantation at any time during follow-up (►**Fig. 2B**), i.e., 1-, 3- and 5-year survival in BTT HVAD patients undergoing heart transplantation at any time during follow-up was 92.8% (95% CI; 86.7–96.2%), 83.1% (95% CI; 75.3–88.6%), and 77.6% (95% CI; 69.0–84.1%), respectively. There was no significant survival difference in BTT HVAD patients undergoing heart transplantation at any time during follow-up when comparing INTERMACS level 1 and INTERMACS levels 2 to 4 patients ($p > 0.05$; ►**Fig. 2B**). Importantly, only a minority of BTT-HVAD patients (30%) could be transplanted. HVAD patients not undergoing heart transplantation during follow-up, i.e., BTT ($n = 301$) and all DT patients ($n = 83$), had a strikingly poorer prognosis (►**Fig. 2B**), i.e., 1-, 3- and 5-year survival rates of 56.8% (95% CI; 51.6–61.6%), 37.2% (95% CI; 32.2–42.3%), and 20.7% (95% CI; 16.0–25.9%), respectively. There was no significant survival difference in these HVAD patients not undergoing heart transplantation during follow-up when comparing INTERMACS level 1 and INTERMACS levels 2 to 4 patients ($p > 0.05$; ►**Fig. 2B**).

The most common causes of death were MOF and sepsis, followed by cerebrovascular accidents (►**Table 3**). Multivariate analyses revealed that age at implantation, [HR 1.053 (95% CI; 1.028–1.079), $p < 0.001$], BMI [HR 1.045 (95% CI; 1.002–1.090), $p = 0.042$], need for temporary RVAD support [HR 3.110 (95% CI; 1.978–4.890), $p < 0.001$], and INTERMACS level 1, [HR 2.114, (95% CI; 1.300–3.437), $p = 0.0025$] at the time of HVAD implantation remained as independent predictors of 3-months mortality. Age at implantation [HR 1.05 (95% CI; 1.03–1.06), $p < 0.001$], need for temporary RVAD

Table 1 Baseline characteristics of the study cohort

	All cohort ($n = 510$)	INTERMAC 1 ($n = 229$)	INTERMACS 2–4 ($n = 281$)	*p*-Value	BTT ($n = 427$)	DT ($n = 83$)	*p*-Value
Age at implantation, mean ± SD (years)	54.6 ± 12.1	52.0 ± 10.9	56.7 ± 12.6	<0.001	51.9 ± 11.0	68.1 ± 7.7	<0.001
Male gender, *n*/*N*	422/510	183/229	239/281	0.157	354/427	68/83	0.87
Body surface area, mean ± SD (m^2)	2.0 ± 0.23	2.0 ± 0.24	2.0 ± 0.22	0.009	1.98 ± 0.24	1.95 ± 0.19	0.24
Body mass index, mean ± SD (kg/m^2)	25.9 ± 5.1	26.5 ± 5.4	25.4 ± 4.8	0.016	25.9 ± 5.2	25.6 ± 4.5	0.53
Pathology							
Ischemic cardiomyopathy	266 (52)	125 (54)	141 (50)	0.33	221 (52)	45 (54)	0.72
Dilated cardiomyopathy	155 (30)	64 (28)	91 (32)	0.33	126 (30)	29 (35)	0.3
Myocarditis	57 (11)	25 ((11)	32 (11)	1	56 (13)	1 (1.2)	<0.001
Others	32 (6)	15 (7)	17 (6)	0.856	24 (5.6)	8 (9.6)	0.211
Diabetes mellitus	142 (28)	53 (23)	89 (32)	0.037	116 (27)	26 (31)	0.42
Peripheral vascular disease	47 (9)	17 (7)	30 (11)	0.22	35 (8.2)	12 (14)	0.095
Chronic obstructive lung disease	55 (11)	21 (9)	34 (12)	0.32	46 (11)	9 (11)	1
History of ischemic stroke	61 (12)	18 (8)	43 (15)	0.013	53 (12)	8 (9.6)	0.58
History of bleeding stroke	5 (1)	3 (1)	2 (0.71)	0.66	4 (9.4)	1 (1.2)	0.59
Previous cardiac resynchronization therapy	168 (33)	54 (24)	114 (41)	<0.001	128 (30)	40 (48)	0.002
Previous implanted cardioverter defibrillator	337 (66)	118 (52)	219 (78)	<0.001	267 (63)	70 (84)	<0.001
Previous cardiac surgery	121 (24)	52 (23)	69 (25)	0.68	96 (22)	25 (30)	0.16
History of smoking	226 (44)	91 (40)	135 (48)	0.073	202 (47)	24 (29)	0.0017
History of alcohol use	42 (8)	18 (8)	24 (8.5)	0.87	39 (8.2)	3 (3.6)	0.125
History of drug abuse	21 (4)	8 (3)	13 (4.6)	0.66	19 (4.4)	2 (2.4)	0.552
Medication							
Angiotensin-converting enzyme inhibitor	145 (28)	37 (16)	108 (38)	<0.001	122 (29)	23 (28)	1
Angiotensin receptor blocker	201 (39)	44 (19)	157 (56)	<0.001	166 (39)	35 (42)	0.624
Acetylsalicylic acid	112 (22)	53 (23)	59 (21)	0.59	98 (23)	14 (17)	0.25
β-blocker	273 (54)	89 (39)	184 (65)	<0.001	222 (52)	51 (61)	0.12
Amiodaron	281 (55)	135 (59)	146 (52)	0.128	227 (53)	54 (65)	0.054
INTERMACS	1.84 ± 0.88	1	2.52 ± 0.60	<0.001	1.76 ± 0.86	2.27 ± 0.87	<0.001
INTERMACS level 1	229 (45)	229 (100)	*		210 (49)	19 (18)	
INTERMACS level 2	150 (29)	*	150 (53)		123 (29)	27 (33)	
INTERMACS level 3	115 (23)	*	115 (41)		82 (19)	33 (40)	
INTERMACS level 4	16 (6)	*	16 (5.7)		12 (2.8)	4 (4.8)	

(*Continued*)

Table 1 (*Continued*)

BTT	427 (84)	210 (92)	217 (77)	<0.001	*	*	*
DT	83 (16)	19 (8)	64 (23)	<0.001	*	*	*
Laboratory							
Creatinine, mg/dL	1.58 ± 0.90	1.63 ± 1.1	1.55 ± 0.74	0.31	1.58 ± 0.92	1.58 ± 0.77	0.99
Glomerular filtration rate, mL/min/1.73 m^2	47 ± 24	48 ± 26	46 ± 23	0.41	48 ± 25	43 ± 23	0.071
Blood urea nitrogen, mg/dL	74.0 ± 47.9	74.7 ± 48.4	73.3 ± 47.5	0.76	73.5 ± 48.7	76.3 ± 43.5	0.63
Hemoglobin, g/dL	11.1 ± 7.65	10.4 ± 1.8	11.8 ± 10.2	0.038	11.2 ± 8.29	10.8 ± 1.65	0.64
Total bilirubin, mg/dL	1.95 ± 2.04	2.45 ± 2.58	1.51 ± 1.26	<0.001	1.99 ± 2.13	1.74 ± 1.48	0.32
C-reactive protein, mg/dL	6.77 ± 7.4	10.5 ± 8.6	3.64 ± 4.3	<0.001	7.0 ± 7.5	5.37 ± 6.6	0.07
Aspartate transaminase, IU/L	310 ± 1,218	525 ± 1,708	132 ± 479	<0.001	338 ± 1,305	160 ± 537	0.24
Alanine aminotransferase, IU/L	244 ± 788	365 ± 1069	142 ± 403	0.0018	264 ± 840	134 ± 376	0.19

Abbreviations: BTT, bridge-to-transplant; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.
Note: *n* represents the number of patients (%) if not otherwise specified.

support [HR 2.22 (95% CI; 1.66–2.98), $p < 0.001$], and INTERMACS level 1 [HR 1.55, (95% CI; 1.16–2.07), $p < 0.001$] at the time of HVAD implantation remained as independent predictors of long-term mortality.

Time Course of LVAD Complications

During follow-up, the most common complications on HVAD support included pump infection, VT, GIB, embolic stroke, ICB, right HF, and pump thrombosis (►**Fig. 3**). Device malfunction occurred very seldom. Freedom from any device-associated severe complication and death was 44.5% (95% CI; 40–48.8%) at 1-year after implantation. Freedom from major complications with ongoing HVAD support did not generally differ between INTERMACS level 1-patients and INTERMACS levels 2 to 4 patients, except for ischemic stroke, which occurred more frequently in INTERMACS level-1 patients (►**Fig. 3**). Pump infections ($p < 0.05$) and pump thromboses ($p < 0.05$) occurred less frequently in DT patients when compared with BTT patients (►**Fig. 4**). The fractions of INTERMACS level 1 patients were 49% and 23% in BTT and DT patients, respectively. All other incidences of major complications did not differ significantly between BTT and DT patients. During follow-up, 58 patients developed new or recurrent RHF that required intensified medical therapy or urgent heart transplantation. Peri-operative need for temporary RVAD support was a strong and independent risk factor for reoccurrence of RHF [HR 2.632, (95% CI; 1.554–4.459), $p < 0.001$].

Outcome after Heart Transplantation

Only 126 BTT HVAD patients underwent heart transplantation during follow-up. One, 3 and 5-year survival after heart transplantation of HVAD patients was 79.4% (95% CI; 71.0–85.6%), 73.1% (95% CI; 63.8–80.3%), and 68.9% (95% CI; 58.9–77.0%), respectively. According to Kaplan-Meier analysis, the survival rate after HTx was not significantly different between patients implanted with the HVAD in INTERMACS level 1 ($n = 54$) or INTERMACS levels 2 to 4 ($n = 72$) ($p = 0.62$; ►**Fig. 5A**). Of those 126 patients, 104 patients (82.5%) required urgent HTx (HU status) because of life-threatening LVAD-associated complications and were thus prioritized on the waiting list, while the minority of 22 patients (17. 5%) were transplanted in regular "T" status. Survival of HVAD patients after HTx did not significantly differ between HU and T-status patients ($p = 0.57$; ►**Fig. 5B**).

The reasons for HU-status listing in the 104 patients were $n = 35$ for pump infection, $n = 16$ for cerebrovascular accidents (ischemic insults and/or bleeding), $n = 12$ repeated pump thrombosis, $n = 17$ RHF, $n = 2$ device malfunction, $n = 9$ therapy-refractory ventricular arrhythmia, $n = 7$ GIB and $n = 6$ others.

Discussion

Several studies have been published demonstrating favorable outcomes in durable MCS therapy, using the intrapericardially implantable HVAD.[3,12–16] Large registry data on patient outcome after centrifugal flow pump implantation is

Table 2 Perioperative data of the study cohort

	All cohort ($n = 510$)	INTERMAC 1 ($n = 229$)	INTERMACS 2–4 ($n = 281$)	*p*-Value	BTT ($n = 427$)	DT ($n = 83$)	*p*-Value
Prior MCS use							
Prior ECMO	132 (26)	132 (58)	0 (0)	<0.001	120 (28)	12 (14)	0.0092
Prior IABP use	105 (21)	103 (45)	2 (0.7)[a]	<0.001	99 (23)	6 (7.2)	<0.001
Prior Impella use	22 (4.3)	22 (10)	0	<0.001	19 (4.4)	3 (3.6)	1
Prior intubation	101 (20)	96 (42)	5 (1.8)	<0.001	91 (21)	10 (12)	0.13
Prior cardiac arrest	39 (7.6)	35 (15)	4 (1.4)	<0.001	37 (8.7)	2 (2.4)	0.067
Prior temporary MCS time use	[a]	7 (IQR; 3–14.25)	[a]	[a]	7 (IQR; 3–14)	8.5 (IQR; 7–14.75)	0.157
Additional procedures							
Coronary artery bypass grafting	25 (4.9)	8 (3.5)	17 (6)	0.142	25 (5.9)	0 (0)	0.021
Ventricular septal defect closure	1 (0.2)	1 (0.4)	0 (0)	0.45	1 (0.2)	0 (0)	1
Ablation	2 (0.4)	0 (0)	2 (0.7)	0.5	1 (0.2)	1 (1.2)	0.3
Aortic valve replacement	48 (9.4)	13 (5.7)	35 (12)	0.0095	33 (7.7)	15 (18)	0.0065
Mitral valve replacement (biological valve)	8 (1.6)	2 (0.9)	6 (2)	0.31	5 (1.2)	3 (3.6)	0.13
Tricuspid valve repair	69 (14)	21 (9.2)	48 (17)	0.0094	55 (13)	14 (17)	0.38
Temporary RVAD implantation	151 (30)	93 (41)	58 (21)	<0.001	132 (31)	19 (23)	0.151
Temporary RVAD use time, days	21 (IQR; 12.5–34)	17 (IQR;12–33)	23 (IQR; 13–35)	0.485	20.5 (IQR; 12–35)	22 (IQR;13.5–23.5)	0.371
Intensive care unit							
Ventilation time, hours	96 (IQR; 19–563)	248 (IQR; 64–776)	31 (IQR; 16–274)	<0.001	92 (IQR; 18–557)	114 (IQR; 25–615)	0.186
Intensive care unit stay, days	21 (IQR; 8–54)	33 (IQR; 14–62.5)	13 (IQR;6–43)	<0.001	21 (IQR; 8–53.5)	20 (IQR; 7–56)	0.991
Hospital stay, days	24 (IQR; 15–40)	24 (IQR; 14–44)	23.5 (IQR; 17–40)	0.783	23 (IQR; 15–40)	25.5 (IQR; 16.8–42.5)	0.541
Medication at discharge							
Angiotensin-converting enzyme inhibitor	170 (33)	61 (27)	109 (39)	0.0046	144 (34)	26 (31)	0.71
Angiotensin receptor blocker	32 (6)	10 (4.4)	22 (7.8)	0.14	166 (39)	35 (42)	0.62
Acetylsalicylic acid	303 (59)	128 (56)	175 (62)	0.148	263 (62)	40 (48)	0.028
β-blocker	278 (55)	118 (52)	160 (57)	0.25	238 (56)	40 (48)	0.23
Amiodaron	199 (39)	84 (37)	115 (41)	0.36	172 (40)	27	0.22

(*Continued*)

Table 2 (*Continued*)

Laboratory at discharge							
Creatinine, mg/dL	1.2 ± 0.69	1.1 ± 0.60	1.2 ± 0.75	0.73	1.1 ± 0.7	1.2 ± 0.58	0.28
Blood urea nitrogen, mg/dL	50.1 ± 33.1	48.8 ± 32.6	51.2 ± 33.4	0.46	48.8 ± 32.8	57.6 ± 33.4	0.046
Hemoglobin, g/dL	10.4 ± 1.43	10.3 ± 1.42	10.5 ± 1.44	0.38	10.4 ± 1.41	10.4 ± 1.53	0.8
Total bilirubin, mg/dL	2.07 ± 4.33	2.76 ± 5.29	1.51 ± 3.27	0.0029	2.10 ± 4.46	1.89 ± 3.59	0.71
C-reactive protein, mg/dL	5.22 ± 6.20	5.91 ± 6.97	4.68 ± 5.46	0.039	5.19 ± 6.15	5.44 ± 6.48	0.76
Aspartate transaminase, IU/L	281 ± 2078	460 ± 2773	138 ± 1263	0.11	338 ± 1305	161 ± 538	0.24
Alanine aminotransferase, IU/L	73 ± 316	97 ± 321	53 ± 311	0.16	264 ± 840	134 ± 376	0.19
3-mo survival rate, 95% Cis	0.821 (0.785–0.852)	0.753 (0.692–0.804)	0.878 (0.833–0.911)	<0.001	0.837 (0.798–0.869)	0.746 (0.638–0.827)	0.051

Abbreviations: BTT, bridge-to-transplant; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; RVAD, right ventricular assist device.

[a]IABP was explanted preoperatively.

Note: *n* represents the number of patients (%) if not otherwise specified.

at hand,[6,7,17] but do not distinctively analyze the clinical outcome after HVAD implantation. Registry and post-market trial data have to be interpreted with care. They may not necessarily represent a "real-world" scenario, also considering center-specific differences in patient selection and implant strategies. Center size, experience, and the presence or absence of a transplant program come into play, particularly in high-risk patients.[8,11]

The latest INTERMACS registry report attests overall survival rates after sole LVAD implantation of 84% after 1 year.[6] The EUROMACS data show a lower 1-year survival of only 69%.[7] The Northern American experience may differ from the European because of deviant heart transplantation policies and donor organ volumes. The EUROMACS data and our current report are well in line with a recently published smaller-sized German single-center experience with the HVAD, in which the 1-year overall survival after HVAD implantation was 69.7%.[18] The authors discussed that the relatively poorer outcome may owe to the fact that they implanted a relatively high number of high-risk patient. Our current findings underline this latter notion, showing a significantly higher mortality rate in INTERMACS level 1 patients. Our patient cohort recruited nearly half of high-risk patients. Further indicating that our "real-world" patient collective has been at particular high risk, the rate of concomitantly implanted temporary RVADs of nearly 30% is comparably high.[19] The relatively high number of temporary RVAD implants may very well be discussed, but there is no established and generally accepted clear-cut marker for the prediction of post-LVAD implant RV performance and the indication for RVAD implantation.[11,20,21] We might be relatively liberal in using mechanical RV support, but we could show that concomitant implantation of a temporary RVAD is a negative predictor for survival after HVAD implantation. We conclude that our patient collective has been at particularly high risk. Eventually, many of our HVAD patients were already way down the road of HF at the time of implantation, presenting with biventricular failure. Of note, perioperative RHF is an accepted indicator for a negative outcome after LVAD implantation.[22]

Considering the inferior survival of INTERMACS level 1 patients after HVAD implantation, it may be discussed whether more restrictive patient selection in general may help to improve outcomes. Such considerations have to be balanced to the otherwise fatal course of these patients not undergoing durable MCS implantation. We feel that early patient referral represents the only reasonable measure to improve outcomes. HF patients need to be repetitively evaluated early on during the course of HF by a multidisciplinary team, consisting of HF-dedicated cardiac surgeons, cardiologists, VAD-coordinators, psychologists, etc.[11] Interventional measures, e.g., the MitraClip, may be considered, however, not as an alternative but rather as a palliative bridge to durable MCS therapy, buying time, and life quality.[2,23,24] In fact, survival per se is only one end point after durable MCS implantation. Early implantation of any durable MCS device has to be carefully evaluated also in view of

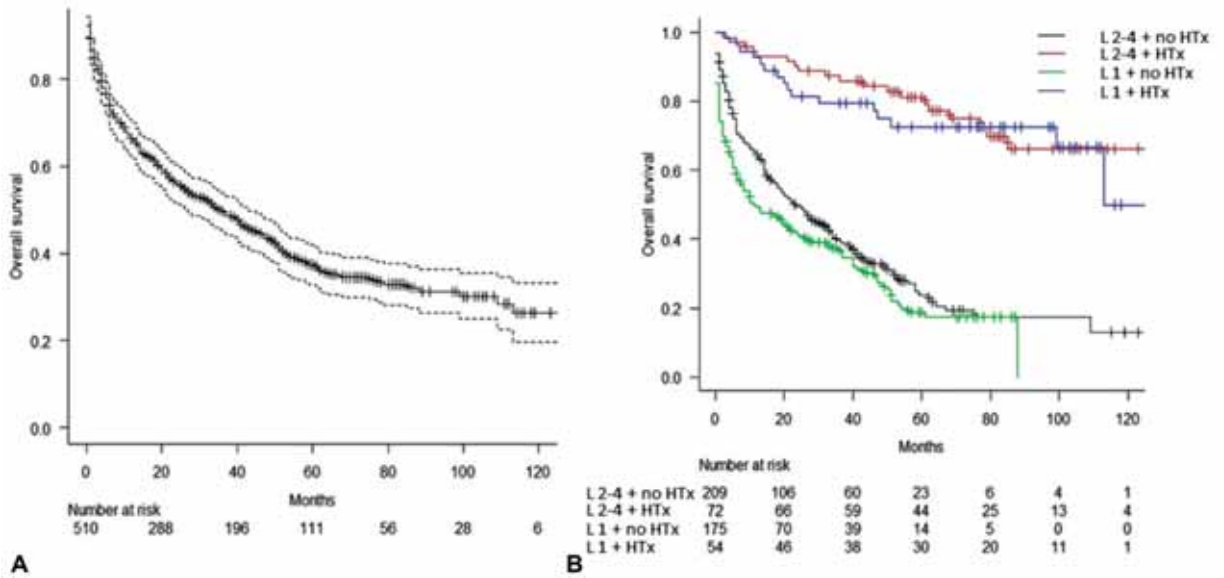


Fig. 2 Survival after HVAD implantation. (**A**) Kaplan-Meier overall survival estimate and 95% confidence interval in the entire study cohort censored for all-causes of death. (**B**) Kaplan-Meier survival estimates in transplanted (*blue and red curves*) and non-transplanted (*green and black curves*) HVAD patients of Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 1 *(blue and green curves*) and levels 2–4 (*red and black curves*).

Table 3 Causes of the death in the study cohort

	3 months	1 year	3 years	5 years
Multiorgan failure	44 (45.3%)	67 (39.0%)	87 (34.8%)	93 (30.5%)
Sepsis	29 (29.9%)	47 (27.3%)	57 (22.8%)	65 (21.3%)
Cerebrovascular accident	12 (12.4%)	29 (16.9%)	48 (19.2%)	59 (19.3%)
Others	12 (12.4%)	29 (16.9%)	58 (23.3%)	88 (28.9%)
All	97 (100%)	172 (100%)	250 (100%)	305 (100%)

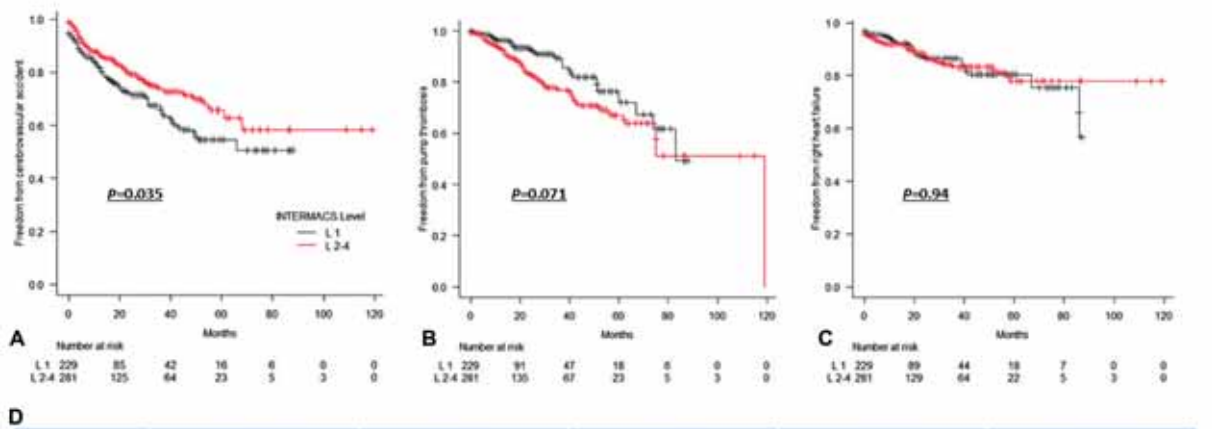
Note: *n* represents the number of patients (%).

device-related complications, which may dramatically limit life quality.

The latest INTERMACS report documents that combined major event of first infection, bleeding, device malfunction, stroke or death occurs in approximately 70% of all implanted LVAD patients within the first year.[6] Despite the high risk, the rates of major complications were comparably low in our study groups.[1–4] They were in general not relevantly different between 1 year surviving high-risk and INTERMACS levels 2 to 4 patients, except for CBA. This reflects the higher risk in INTERMACS level 1 patients.[18] Likewise, BTT patients consisted of 49% INTERMACS level 1 patients and showed more frequently pump infections and pump thromboses when compared with DT patients. Generally, the incidence of adverse events after HVAD implantation is highest early post implant with lower long-term rates.[25] Several studies on the outcome after HVAD implantation pointed out that vigorous patient surveillance is key to reduce complication rates.[20,26,27] However, interpreting data on complication rates across different studies is difficult because of differently censored data and definitions.

The ENDURANCE trial showed a lower rate of pump replacements owing to pump thromboses in the HVAD cohort when compared with control individuals treated with the former standard of care LVAD, the Heartmate II.[4] Incidences of pump thromboses may be reduced, e.g., by intensified blood pressure control (our unpublished data), but it remains a dramatic complication in HVAD patients and the treatment is risky. As in the MOMENTUM 3 trial, we had no event of pump thrombosis in our patients implanted with the Heartmate 3, the latest commercially available CF centrifugal pump LVAD.[5] In this matter, we found a grand advantage of the Heartmate 3 over the HVAD in a short-term matched pair analysis.[10] Short-term survival did not differ between the two devices. It remains elusive whether preferring the more recent device for durable MCS therapy is justified long-term.

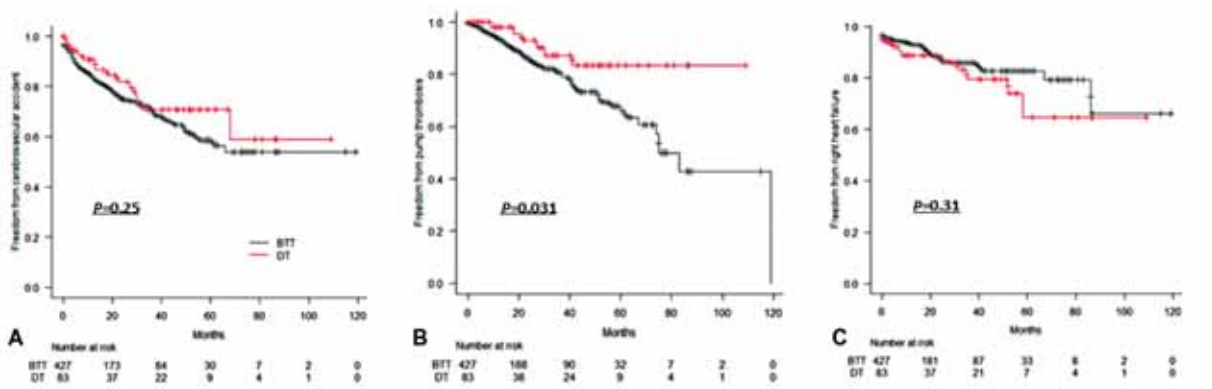
We feel that the major finding of our present study is to demonstrate that heart transplantation represents the most powerful means to warrant long-term survival, independent of the risk at HVAD implantation. The International Society for Heart and Lung Transplantation (ISHLT) registry demonstrates a median survival after heart transplantation



D

	0-3 months		0-1 years		0-3 years		0-5 years		0-7 years	
VAD-complications	INTERMACS 1	INTERMACS2-4	INTERMACS 1	INTERMACS2-4	INTERMACS 1	INTERMACS2-4	INTERMACS 1	INTERMACS2-4	INTERMACS 1	INTERMACS2-4
Pump infection	0.5 %	0.4 %	2.8 %	2.4 %	10.0 %	11.7 %	12.3 %	24.4 %	29.6 %	24.4 %
VT/VF	9.4 %	4.8 %	11.8 %	9.6 %	12.8 %	20.7 %	22.2 %	29.5 %	27.1 %	34.2 %
GI-bleeding	5.3 %	8.2 %	8.2 %	12.9 %	16.1 %	17.6 %	22.2 %	19.2 %	22.2 %	25.4 %
CVA	9.1 %	5.4 %	18.5 %	13.7 %	35.3 %	26.2 %	45.4 %	34.3 %	49.3 %	41.7 %
Pump thrombosis	2.1 %	2.6 %	7.2 %	12.5 %	17.2 %	26.3 %	21.8 %	27.7 %	27.4 %	37.1 %
Right heart failure	4.5 %	5.4 %	7.6 %	8.1 %	13.6 %	16.8 %	19.5 %	22.1 %	24.6 %	22.1 %
Device malfunction	0.6 %	0 %	0.6 %	0 %	2.3 %	1.7 %	2.3 %	1.7 %	2.3 %	1.7 %

Fig. 3 Freedom from the first ventricular assist device (VAD)-associated complications differentiated between Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 1 (*black curves*) and levels 2–4 (*red curves*) at the time of HVAD implantation. (**A**) Kaplan-Meier estimate for freedom from a cerebrovascular accident (CVA). (**B**) Kaplan-Meier estimate for freedom from a pump thrombosis. (**C**) Kaplan-Meier estimate for freedom from a right heart failure. (**D**) Cumulative incidences of VAD-associated complications. GI, gastro-intestinal; VT/VF, ventricular tachycardia or ventricular fibrillation with implanted cardioverter defibrillator shock.



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	0-3 months		0-1 years		0-3 years		0-5 years		0-7 years	
VAD-complications	BTT	DT	BTT	DT	BTT	DT	BTT	DT	BTT	DT
Pump infection	0.5 %	0 %	3.0 %	0 %	13.4 %	0 %	23.9 %	0 %	33.5 %	0 %
VT/VF	6.9 %	6.5 %	10.2 %	13.5 %	18.2 %	16.1 %	27.4 %	24.5 %	29.1 %	35.3 %
GI-bleeding	7.8 %	2.7 %	11.5 %	8.2 %	17.6 %	11.1 %	21.6 %	11.1 %	21.6 %	26.9 %
CVA	7.7 %	5.7 %	17 %	9.3 %	30.2 %	29.2 %	41.5 %	29.2 %	46.1 %	41 %
Pump thrombosis	1.5 %	0 %	6.4 %	2 %	19.4 %	12.8 %	34.4 %	16.6 %	57.2 %	16.6 %
Right heart failure	4.8 %	6.2 %	7.2 %	11.4 %	14.3 %	20.4 %	17.3 %	35.3 %	20.7 %	35.3 %
Device malfunction	0.3 %	0 %	0.3 %	0 %	0.2 %	5.9 %	1.2 %	5.9 %	1.2 %	5.9 %

Fig. 4 Freedom from the first ventricular assist device (VAD)-associated complications differentiated between the bridge-to-transplant (BTT; *black curves*) and destination therapy (DT; *red curves*) implant strategies at the time of HVAD implantation. (**A**) Kaplan-Meier estimate for freedom from a cerebrovascular accident (CVA). (**B**) Kaplan-Meier estimate for freedom from a pump thrombosis. (**C**) Kaplan-Meier estimate for freedom from a right heart failure. (**D**) Cumulative incidences of VAD-associated complications. VT/VF, ventricular tachycardia or ventricular fibrillation with implanted cardioverter defibrillator shock; GI, gastrointestinal.

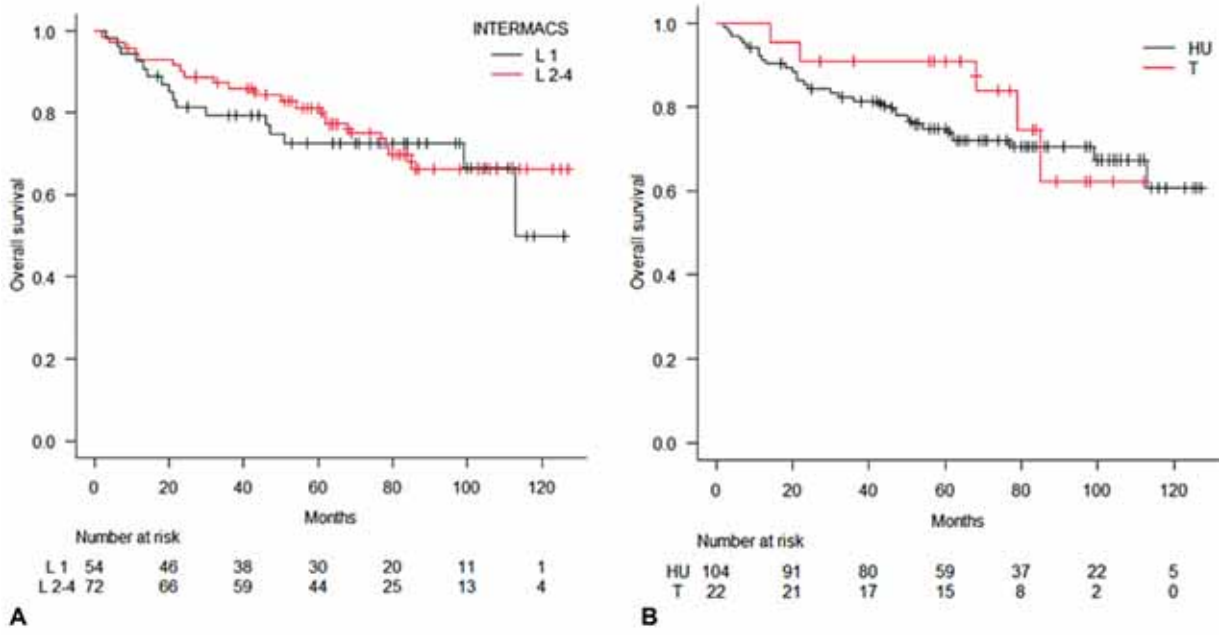

Fig. 5 Survival after heart transplantation of BTT-HVAD patients. (**A**) Survival after heart transplantation of BTT-HVAD patients in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 1 (*black curve*) and levels 2 to 4 (*red curve*) at the time of HVAD implantation. (**B**) Survival after heart transplantation of BTT-HVAD patients with Eurotransplant high-urgency (HU) listing-status (*black curve*) and regular transplantable (T) listing-status (*red curve*) at the time of transplantation.

of approximately 11 years, clearly outperforming durable MCS therapy.[28] The dramatic organ shortage in Germany forces physicians to use the alternative of durable MCS, while this is rather an exception in countries with large donor organ pools, e.g., Spain.[29] The indication for durable MCS implantation has to be particularly discussed in patients with contraindications against subsequent heart transplantation. Complication rates and their impact on life quality should be predominantly evaluated in these patients rather than survival per se. Of note, durable MCS may be implanted as a bridge-to-candidacy, but the chances to receive a heart transplant remains fairly low, at least in the current German situation. Our retrospective study design does not allow to reliably differentially analyze the bridge-to-candidacy and DT indication for HVAD implantation in our patient cohort.

In conclusion, this report on long-term "real-world" experience with the HVAD expands on previous findings demonstrating that this pump is reliable for the treatment of terminal HF patients, even in high-risk patients. The BTT indication appears to be vital for long-term survival. The indication for durable MCS implantation must be evaluated balancing the chances of receiving a heart transplant and life quality with ongoing LVAD support.

Authors' Contribution

T.G. did the conceptualization of the study, data retrieval, data analyses, and revision of the manuscript. S.V.R. contributed toward data analysis, writing, and revision of the manuscript. H.F. did the data retrieval, writing, and revision of the manuscript. M.-A.D. contributed toward data analysis, writing, and revision of the manuscript. M. R.C. worked upon data retrieval, data analysis, and revision of the manuscript. K.H.-M. did the data analysis and revised the manuscript. J.F.G. Conceptualized the study and revised the manuscript. M.M. contributed toward the conceptualization of the study, data retrieval, data analyses, writing and revision of the manuscript. R.S. did the conceptualization of the study, data retrieval, data analyses, writing and revision of the manuscript.

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Conflict of Interest

None declared.

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