

Survival following a concomitant aortic valve procedure during left ventricular assist device surgery: an ISHLT Mechanically Assisted Circulatory Support (IMACS) Registry analysis

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Aims

The aim of this study was to compare early- and late-term survival and causes of death between patients with and without a concomitant aortic valve (AoV) procedure during continuous-flow left ventricular assist device (LVAD) surgery.

Methods and results

All adult primary continuous-flow LVAD patients on the International Society of Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) Registry ($n = 15\,267$) were included in this analysis and stratified into patients submitted to a concomitant AoV procedure (AoV replacement or AoV repair) and patients without an AoV procedure. The primary outcome was early (≤ 90 days) survival post-LVAD surgery. Secondary outcomes were late survival (survival during the entire follow-up period) and conditional survival (in patients who survived the first 90 days post-LVAD surgery), and determinants. Patients who underwent concomitant AoV replacement ($n = 457$) had significantly reduced late survival compared with patients with AoV repair ($n = 328$) or without an AoV procedure ($n = 14\,482$) (56% vs. 61% and 62%, respectively; $P = 0.001$). After adjustment for other significant predictors, concomitant AoV replacement remained an independent predictor for early [hazard ratio (HR) 1.226, 95% confidence interval (CI) 1.037–1.449] and late (HR 1.477, 95% CI 1.154–1.890) mortality. However, patients undergoing AoV replacement or repair, in whom the presence of moderate-to-severe AoV regurgitation was diagnosed prior to LVAD implantation, had survival similar to patients not undergoing AoV interventions.

Conclusions

Concomitant AoV surgery in patients undergoing LVAD implantation is an independent predictor of mortality. Additional research is needed to determine the best AoV surgical strategy at the time of LVAD surgery.

Keywords

Left ventricular assist device • Aortic valve • Aortic valve replacement • Aortic valve repair • Survival

Introduction

In recent years, increasing numbers of patients have received a left ventricular assist device (LVAD) as treatment for end-stage heart failure (HF).¹ However, significant aortic valve (AoV) regurgitation

in patients with an LVAD causes a short circulation loop, in which blood is pumped into the aorta by the LVAD and flows directly back into the left ventricle.² This results in less unloading of the left ventricle and reduced systemic perfusion, indicated by an increased left ventricular end-diastolic diameter and higher

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levels of brain natriuretic peptide.³ Additionally, significant AoV regurgitation has been associated with increased mortality and higher hospitalization rates.^{3,4} Therefore, the performance of a concomitant AoV procedure in patients with moderate-to-severe AoV regurgitation at the time of LVAD surgery is recommended.⁵ Additionally, a concomitant AoV procedure at the time of LVAD surgery in patients with a mechanical AoV is also recommended⁵ because mechanical AoVs in LVAD patients are associated with increased risk for thromboembolic events.^{6,7} The decision to perform a concomitant AoV procedure can be based on additional perioperative (transoesophageal) echocardiographic images.

Concomitant AoV replacement with a bioprosthetic valve, AoV repair and the oversewing of the AoV are all considered as treatment strategies, with associated risks and benefits.⁸ However, conflicting results on the outcomes of concomitant AoV procedures have been reported and the contemporary data available on early and late survival outcomes in concomitant AoV procedures are limited.

The aim of this study was to compare early and late survival and causes of early and late death in patients with and without a concomitant AoV procedure during continuous-flow LVAD surgery in the International Society of Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) Registry.

Methods

The IMACS Registry is a multinational, multicentre database that collects prospective data and has been described previously.⁹ In short, the aim of the IMACS Registry is to enrol and monitor patients implanted with durable mechanical circulatory support devices, worldwide. The registry receives data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), the United Kingdom (UK) Registry and the Japanese Mechanically Assisted Circulatory Support (JMACS) Registry, as well as from individual hospitals worldwide.

All adult patients (aged ≥ 18 years) who underwent primary implantation of a continuous-flow LVAD from January 2013 to November 2017 were included in this analysis. Patients with a total artificial heart, isolated right ventricular assist device or with missing information on concomitant AoV procedures were excluded from this analysis (Supplementary material online, *Figure S1*). The endpoints for this analysis was all-cause mortality post-LVAD surgery, device explantation and heart transplantation. The primary outcome was early (≤ 90 days post-LVAD surgery) survival. Secondary outcomes were late (survival during the entire follow-up period) and conditional survival (in patients who survived the first 90 days post-LVAD surgery), causes of early and late death post-LVAD surgery, device explantation and heart transplantation. Causes of death were as defined earlier by the IMACS Registry because granular data on the causes of death were not available.⁹

Statistical analysis

Patient characteristics are presented as the mean \pm standard deviation or median and interquartile range (IQR), depending on the distribution of continuous data, and as counts and percentages for categorical data. One-way analysis of variance (ANOVA) or the Kruskal–Wallis test

were used to compare data for continuous variables, depending on the distribution of the data, and the chi-squared test was used to compare data for categorical variables. All LVAD patients included were stratified into those without a concomitant AoV procedure and those with AoV intervention (replacement or concomitant AoV repair) at LVAD implant. Additional data on which type of AoV repair technique was used were not available.

The probability of survival was analysed using the Kaplan–Meier method and compared using the log-rank test. A univariable Cox proportional hazard analysis was used to relate preoperative parameters, such as demographics, medication, echocardiographic, haemodynamic and laboratory characteristics with the study outcomes (Supplementary material online, *Tables S1* and *S2*). Variables with a *P*-value of <0.20 were entered in a multivariable Cox proportional hazard analysis in order to adjust the prediction of AoV procedures for confounders, applying the stepwise forward method, with a *P*-value of <0.05 as a model-entry criterion. Data were censored at heart transplantation or device explantation brought about by recovery. The competing outcomes methodology was used to estimate the probabilities of survival, mortality, heart transplantation or device explantation over time.

Several subanalyses were performed, including a survival analysis in patients with documented moderate-to-severe AoV regurgitation, a survival analysis stratified by INTERMACS class status, device destination and presence of AoV regurgitation, and a subanalysis excluding patients who proceeded to heart transplantation.

Missing data in the baseline variables were imputed using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used; otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations were performed and the pooled data were analysed. Variables with less than 40% missing data in the entire population were accepted for multiple imputation.¹⁰ The vast majority of variables had less than 5% missing data (Supplementary material online, *Table S3*). The imputed data were used only in the Cox proportional hazard analysis.

A two-tailed *P*-value of <0.05 was considered to indicate statistical significance. All analyses were performed using IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA).

The findings herein were reviewed and approved by the IMACS Steering Committee.

Results

In total, 15 267 LVAD patients were included in this analysis and were stratified into those without an AoV procedure ($n = 14\,482$, 94.9%), those undergoing AoV replacement ($n = 457$, 3.0%) and those undergoing AoV repair ($n = 328$, 2.1%). The median follow-up period was 13.2 months (IQR 5.5–25.6 months). The baseline characteristics are summarized in *Table 1*. Overall, the median patient age at LVAD surgery was 58 years, the majority of patients were men (79.3%) and the main aetiology of HF was non-ischaemic (61.5%). No AoV regurgitation prior to LVAD surgery was reported in 67.2% of patients without an AoV procedure, in 15.9% of patients with an AoV replacement and in 10.9% of patients with an AoV repair ($P < 0.001$). Patients with an AoV repair were significantly older compared with patients without an AoV procedure or with AoV replacement ($P < 0.001$), had a lower body mass index ($P < 0.001$), lower platelet count ($P = 0.001$), and received an LVAD more often as destination therapy ($P = 0.001$).

Table 1 Baseline and clinical characteristics of left ventricular assist device patients stratified by aortic valve procedure

	Overall population (n = 15 267)	No AoV procedure (n = 14 482)	AoV replacement (n = 457)	AoV repair (n = 328)	P-value
Demographics					
Age, years, median (IQR)	58.0 (49.0–66.0)	58.0 (48.0–66.0)	62.0 (53.0–69.0)	64.0 (57.0–69.0)	<0.001
Men, n (%)	12 093 (79.3%)	11 433 (79.1%)	396 (87.0%)	264 (80.5%)	<0.001
BSA, m ² , median (IQR)	2.04 (1.85–2.25)	2.04 (1.86–2.25)	1.99 (1.83–2.18)	1.96 (1.81–2.16)	<0.001
BMI, kg/m ² , median (IQR)	27.4 (23.8–32.0)	27.5 (23.9–32.1)	26.1 (22.8–30.4)	25.1 (22.8–29.4)	<0.001
Ischaemic aetiology, n (%)	5721 (38.5%)	5451 (38.6%)	147 (35.6%)	123 (39.5%)	0.437
Comorbidities, n (%)					
CVA	655 (4.4%)	621 (4.4%)	21 (4.8%)	13 (4.1%)	0.877
DM	1477 (9.9%)	1417 (10.0%)	37 (8.3%)	23 (7.0%)	0.105
Current smoker	866 (5.9%)	818 (5.9%)	29 (6.9%)	19 (5.8%)	0.693
Dialysis	444 (2.9%)	423 (2.9%)	16 (3.5%)	5 (1.5%)	0.246
Current ICD therapy	10 392 (78.1%)	9860 (78.1%)	279 (76.9%)	253 (81.9%)	0.393
History of CABG	2544 (19.0%)	2415 (19.1%)	68 (17.8%)	61 (19.4%)	0.814
Atrial fibrillation	1408 (21.9%)	1309 (21.6%)	58 (28.6%)	41 (22.8%)	0.058
NYHA class, n (%)					
I/II	174 (1.2%)	164 (1.2%)	7 (1.6%)	3 (1.0%)	0.761
III	2690 (19.2%)	2558 (19.3%)	79 (18.6%)	53 (17.0%)	
IV	11 151 (79.6%)	10 557 (79.5%)	339 (79.8%)	255 (82.0%)	
INTERMACS class, n (%)					
1	2373 (15.6%)	2269 (15.8%)	60 (13.3%)	44 (13.4%)	0.502
2	5173 (34.1%)	4887 (34.0%)	165 (36.5%)	121 (36.9%)	
3	5179 (34.1%)	4914 (34.1%)	156 (34.5%)	109 (33.2%)	
4	1968 (13.0%)	1873 (13.0%)	55 (12.2%)	40 (12.2%)	
5	315 (2.1%)	296 (2.1%)	9 (2.0%)	10 (3.0%)	
6	95 (0.6%)	86 (0.6%)	6 (1.3%)	3 (0.9%)	
7	68 (0.4%)	66 (0.5%)	1 (0.2%)	1 (0.3%)	
IABP prior to LVAD surgery, n (%)	4302 (28.9%)	4109 (29.1%)	105 (24.0%)	88 (26.8%)	0.049
ECMO prior to LVAD surgery, n (%)	891 (6.0%)	853 (6.0%)	18 (4.1%)	20 (6.1%)	0.238
Ventilator prior to LVAD surgery, n (%)	1934 (12.7%)	1845 (12.8%)	48 (10.5%)	41 (12.5%)	0.364
History of AoV replacement/repair	396 (3.0%)	282 (2.2%)	85 (22.3%)	29 (9.2%)	<0.001
Laboratory findings, median (IQR)					
Creatinine, mg/dL	1.20 (0.98–1.50)	1.20 (0.97–1.50)	1.27 (1.05–1.57)	1.20 (1.00–1.50)	0.003
BUN, mg/dL	25.0 (18.0–37.3)	25.0 (18.0–37.0)	29.0 (21.0–40.0)	26.0 (18.0–36.0)	<0.001
AST, U/L	29.0 (21.0–44.0)	29.0 (21.0–44.0)	30.0 (22.0–46.0)	30.0 (21.5–42.0)	0.226
ALT, U/L	29.0 (19.0–49.0)	29.0 (19.0–49.0)	28.5 (18.8–46.3)	29.0 (20.0–52.0)	0.782
LDH, U/L	279.0 (220.0–391.0)	279.0 (220.0–391.0)	289.5 (222.8–390.3)	276.5 (216.3–395.0)	0.753
Total bilirubin, mg/dL	1.0 (0.6–1.6)	1.0 (0.6–1.6)	1.1 (0.7–1.7)	1.1 (0.7–1.7)	0.010
WBC, ×10 ⁹ /L	7.9 (6.3–10.2)	7.9 (6.3–10.2)	7.8 (6.2–9.8)	7.5 (6.0–10.4)	0.167
Platelets, ×10 ⁹ /L	188.0 (142.0–242.0)	188.0 (142.0–242.0)	187.0 (132.0–232.0)	176.5 (131.3–226.0)	0.001
INR	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.3 (1.1–1.5)	1.2 (1.1–1.4)	<0.001
Albumin, g/dL	3.5 (3.0–3.8)	3.5 (3.0–3.8)	3.4 (3.0–3.8)	3.4 (3.0–3.8)	0.552
Haemoglobin, g/dL	11.3 (9.8–12.8)	11.3 (9.8–12.8)	11.2 (9.9–12.6)	11.2 (9.7–12.5)	0.539
Haemodynamics, median (IQR)					
RA pressure, mmHg	11.0 (7.0–16.0)	11.0 (7.0–16.0)	11.0 (7.0–17.0)	10.5 (7.0–15.0)	0.295
PCWP, mmHg	25.0 (19.0–31.0)	25.0 (19.0–31.0)	25.0 (20.0–31.0)	25.0 (19.0–32.0)	0.551
Systolic PAP, mmHg	50.0 (40.0–60.0)	50.0 (40.0–60.0)	51.0 (41.0–63.0)	50.0 (40.0–60.0)	0.012
Diastolic PAP, mmHg	25.0 (19.0–30.0)	25.0 (19.0–30.0)	25.0 (20.0–32.0)	24.0 (18.0–29.0)	0.026
Cardiac output, L/min	3.93 (3.14–4.80)	3.96 (3.15–4.80)	3.90 (3.20–4.71)	3.79 (3.00–4.55)	0.077
Echocardiographic data, n (%)					
LVEF					
≥40%	347 (8.5%)	327 (8.5%)	18 (14.4%)	2 (1.8%)	0.012
30–39%	484 (11.8%)	460 (11.9%)	12 (9.6%)	2 (10.7%)	
20–29%	3260 (79.7%)	3067 (79.6%)	95 (76.0%)	98 (87.5%)	
RVEF					
Normal	2941 (26.0%)	2790 (26.1%)	73 (22.4%)	78 (28.4%)	0.400
Mild	3272 (29.0%)	3086 (28.9%)	108 (33.1%)	78 (28.4%)	
Moderate	3473 (30.8%)	3283 (30.7%)	103 (31.6%)	87 (31.6%)	
Severe	1606 (14.2%)	1532 (14.3%)	42 (12.9%)	32 (11.6%)	
Mitral valve regurgitation					
None	1070 (7.6%)	1021 (7.6%)	32 (7.7%)	17 (5.4%)	0.067
Mild	4960 (35.2%)	4689 (35.1%)	164 (39.7%)	107 (34.3%)	
Moderate	4689 (33.3%)	4431 (33.2%)	138 (33.4%)	120 (38.5%)	
Severe	3368 (23.9%)	3221 (24.1%)	79 (19.1%)	68 (21.8%)	

Table 1 (Continued)

	Overall population (n = 15 267)	No AoV procedure (n = 14 482)	AoV replacement (n = 457)	AoV repair (n = 328)	P-value
Tricuspid valve regurgitation					
None	1257 (9.0%)	1210 (9.1%)	31 (7.5%)	16 (5.1%)	0.172
Mild	6865 (49.2%)	6491 (49.1%)	207 (49.8%)	167 (53.4%)	
Moderate	4197 (30.1%)	3969 (30.0%)	134 (32.2%)	94 (30.0%)	
Severe	1640 (11.7%)	1560 (11.8%)	44 (10.6%)	36 (11.5%)	
AoV regurgitation					
None	8426 (64.4%)	8330 (67.2%)	63 (15.9%)	33 (10.9%)	<0.001
Mild	4084 (31.2%)	3747 (30.2%)	182 (45.8%)	155 (51.3%)	
Moderate	492 (3.8%)	270 (2.2%)	119 (30.0%)	103 (34.1%)	
Severe	91 (0.7%)	47 (0.4%)	33 (8.3%)	11 (3.6%)	
LVEDD, mm, median (IQR)	68.0 (61.0–75.0)	68.0 (61.0–75.0)	69.0 (63.0–77.0)	68.0 (62.0–74.0)	0.009
Main LVAD strategy, n (%)					
BTT	4272 (28.0%)	4087 (28.2%)	116 (25.4%)	69 (21.0%)	0.001
BTC	4221 (27.7%)	4016 (27.7%)	126 (27.6%)	79 (24.1%)	
Destination therapy	6563 (43.0%)	6177 (42.7%)	206 (45.1%)	180 (54.9%)	
Rescue therapy	125 (0.8%)	122 (0.8%)	3 (0.7%)	0 (0%)	
Bridge to recovery	55 (0.4%)	51 (0.4%)	4 (0.9%)	0 (0%)	
Other	28 (0.2%)	26 (0.2%)	2 (0.4%)	0 (0%)	
Concomitant procedures, n (%)					
Congenital surgery	1030 (6.7%)	965 (6.7%)	39 (8.5%)	26 (7.9%)	0.201
Mitral valve surgery	538 (3.5%)	484 (3.3%)	26 (5.7%)	28 (8.5%)	<0.001
Tricuspid valve surgery	533 (3.5%)	486 (3.4%)	26 (5.7%)	21 (6.4%)	<0.001
Pulmonary valve surgery	8 (0.1%)	7 (0.007%)	1 (0.2%)	0 (0%)	0.268
RVAD surgery	99 (0.7%)	90 (0.7%)	8 (2.1%)	1 (0.3%)	0.005
Other concomitant surgery	2732 (17.9%)	2584 (17.8%)	85 (18.6%)	63 (19.2%)	0.754

ALT, alanine aminotransaminase; AoV, aortic valve; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; BTC, bridge to candidacy; BTT, bridge to transplant; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range; LDH, lactate dehydrogenase; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RVAD, right ventricular assist device; RVEF, right ventricular ejection fraction; WBC, white blood count.

Patients who received an AoV replacement were more often men ($P < 0.001$) and had a higher blood urea nitrogen level ($P < 0.001$) compared with patients without an AoV procedure or with an AoV repair. The baseline and clinical characteristics of 583 patients with documented moderate-to-severe AoV regurgitation at baseline are shown in Supplementary material online, Table S4.

Early, late and conditional survival

In the combined cohort of patients, the early survival rate (≤ 90 days post-LVAD surgery) was 90.3%, the late survival rate (up to 36 months post-LVAD surgery) was 62.1%, and the conditional survival rate (up to 36 months post-LVAD surgery in patients alive at 90 days post-LVAD surgery) was 68.8%. Early survival rates were 90.4% in patients without an AoV procedure, 85.1% in patients with an AoV replacement and 87.4% in patients with an AoV repair ($P < 0.001$) (Figure 1A). Although late survival rates differed significantly, at 62.4%, 55.5% and 60.9%, respectively ($P = 0.001$) (Figure 1B), the largest difference occurred in early survival post-LVAD surgery. No additional difference was observed in conditional survival rates (69.0%, 65.2% and 69.7%, respectively ($P = 0.268$) (Supplementary material online, Figure S2).

Patients without an AoV procedure stayed in the intensive care unit for a shorter period [median stay: 7 days (IQR 5–13 days)] compared with patients with an AoV replacement [median stay: 10 days (IQR 6–17 days)] and patients with an AoV repair [median

stay: 8 days (IQR 5–14 days)] ($P < 0.001$). Similarly, patients without an AoV procedure had a shorter hospital stay [median stay: 19 days (IQR 14–28 days)] compared with patients with an AoV replacement [median stay: 21 days (IQR 16–36 days)] and patients with an AoV repair [median stay: 20 days (IQR 14–30 days)] ($P < 0.001$). During the initial hospitalization, 843 (5.8%) patients without an AoV procedure, 44 (9.6%) patients with an AoV replacement and eight (2.4%) patients with an AoV repair died ($P < 0.001$).

The worst early and late survival rates were observed in patients who underwent mechanical AoV replacement procedures (82.7% and 50.6%, respectively), followed by those with biological AoV replacements (85.6% and 56.4%, respectively), and those submitted to AoV repair (87.4% and 60.9%, respectively), whereas patients without an AoV procedure demonstrated the best early and late survival rates (90.4% and 62.4%, respectively) ($P < 0.001$ and $P = 0.001$, respectively) (Supplementary material online, Figure S3). The baseline characteristics of patients in whom biological and mechanical AoV replacements, AoV repair and no AoV procedure were performed are shown in Supplementary material online, Table S5.

Patients with an AoV procedure and an INTERMACS class of 2 or 3 had significantly worse survival compared with patients without an AoV procedure, whereas no survival difference was observed in patients with an INTERMACS class of 1 or 4 and higher (Supplementary material online, Figure S4). Causes of death are shown in Supplementary material online, Table S6.

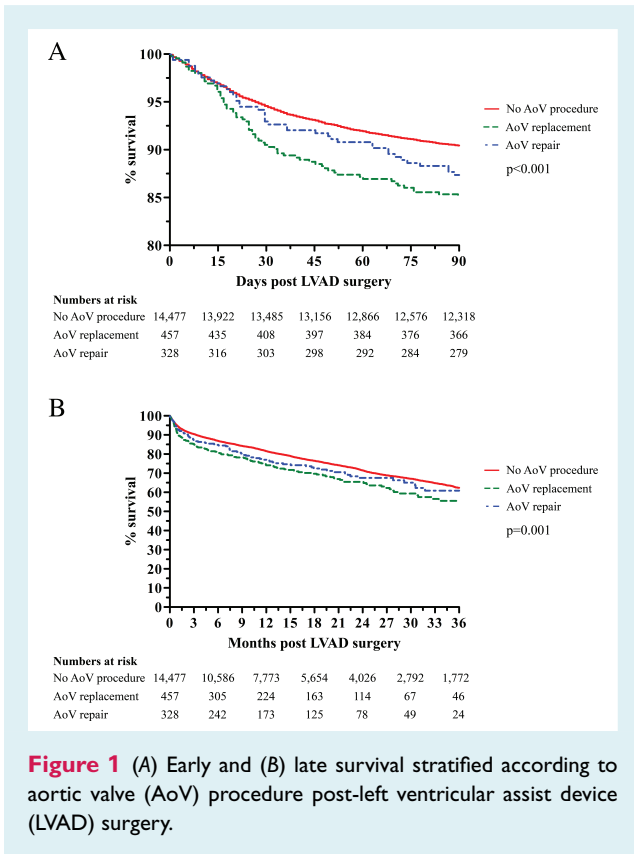


Figure 1 (A) Early and (B) late survival stratified according to aortic valve (AoV) procedure post-left ventricular assist device (LVAD) surgery.

Analyses of competing outcomes among the patient cohorts demonstrated that patients with an AoV replacement (29.0%) and patients with AoV repair (29.4%) less often underwent transplantation at 36 months post-LVAD surgery compared with patients without an AoV procedure (36.3%) (Supplementary material online, Figure S5).

In patients who did not proceed towards heart transplantation, patients without an AoV procedure had the best survival (Supplementary material online, Figure S6). No significant difference in early or medium-term survival was observed between patients who received the LVAD as a bridge to transplantation or as destination therapy, respectively (Supplementary material online, Figure S7).

Survival in patients with moderate-to-severe aortic valve regurgitation

No significant differences in early, late or conditional survival rates were observed among patients without an AoV procedure (89.4%, 58.5% and 65.4%, respectively), AoV replacement (90.6%, 57.5% and 63.5%, respectively) or AoV repair (86.7%, 61.3% and 70.8%, respectively) (Figure 2). Early, late and conditional survival rates in patients without an AoV procedure, stratified by AoV regurgitation at baseline, are shown in Supplementary material online, Figure S8. Rates of late survival in patients without an AoV procedure, with AoV replacement and with AoV repair, respectively, stratified by

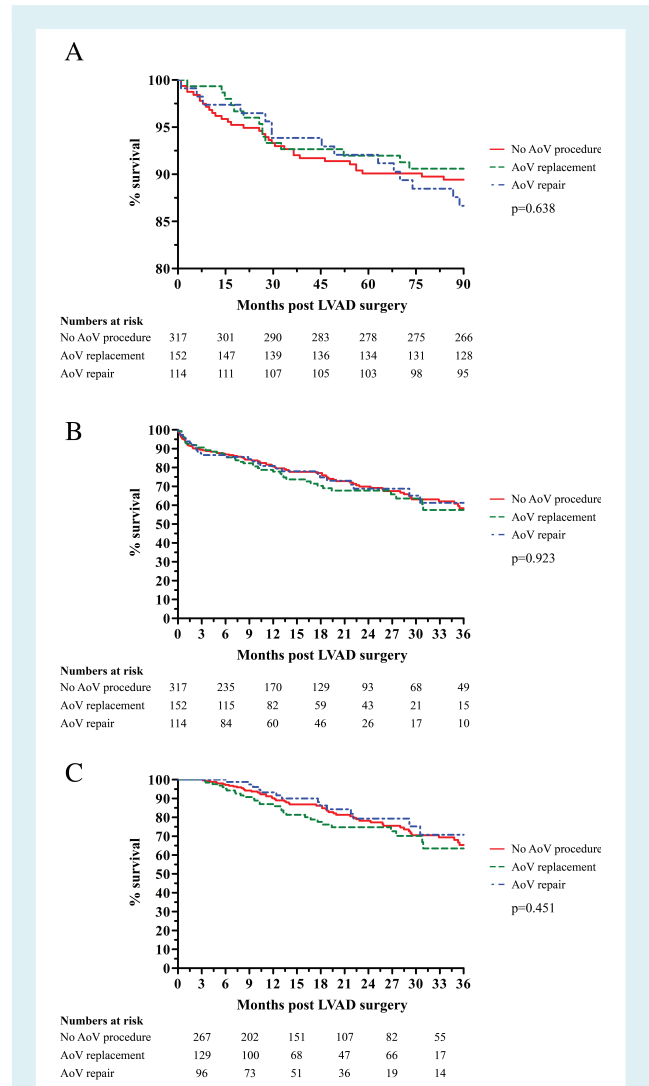


Figure 2 (A) Early, (B) late and (C) conditional survival in patients with moderate-to-severe aortic valve (AoV) regurgitation at baseline, stratified by no AoV procedure, AoV replacement and AoV repair post-left ventricular assist device (LVAD) surgery.

AoV regurgitation at baseline, are shown in Supplementary material online, Figure S9.

Causes of death

The causes of early and late death post-LVAD surgery are shown in Table 2 and Supplementary material online, Table S7. Multisystem organ failure was the most frequent cause of early death (27.7%), followed by circulatory failure (16.9%) and neurological events (15.9%). The most frequent cause of late death was neurological events (19.2%), followed by multisystem organ failure (17.5%) and circulatory failure (17.2%). The causes of death in patients surviving the first 90 days post-LVAD surgery are shown in Supplementary material online, Table S8.

Table 2 Causes of early death in left ventricular assist device (LVAD) patients post-LVAD surgery stratified by aortic valve procedure

	Overall population (n = 1452)	No AoV procedure (n = 1344)	AoV replacement (n = 67)	AoV repair (n = 41)
Multisystem organ failure	402 (27.7%)	368 (27.4%)	22 (32.8%)	12 (29.3%)
Circulatory failure	246 (16.9%)	230 (17.1%)	7 (10.4%)	9 (22.0%)
Neurological events	231 (15.9%)	220 (16.4%)	7 (10.4%)	4 (9.8%)
Withdrawal of support	161 (11.1%)	150 (11.2%)	6 (9.0%)	5 (12.2%)
Major infection	110 (7.6%)	101 (7.5%)	4 (6.0%)	5 (12.2%)
RV failure	80 (5.5%)	76 (5.7%)	3 (4.5%)	1 (2.4%)
Respiratory failure	72 (5.0%)	66 (4.9%)	4 (6.0%)	2 (4.9%)
Digestive/liver failure ^a	21 (1.4%)	21 (1.6%)	0 (0%)	0 (0%)
Device-related	10 (0.7%)	9 (0.7%)	1 (1.5%)	0 (0%)
Haematologic failure	8 (0.6%)	7 (0.5%)	1 (1.5%)	0 (0%)
Cancer	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Other	110 (7.6%)	95 (7.1%)	12 (17.9%)	3 (7.3%)

AoV, aortic valve; RV, right ventricular.

P-value for distribution between groups: 0.454.

^aIncluding hepatic dysfunction, renal dysfunction, pancreatitis.

Multivariable model

Independent risk factors for early mortality post-LVAD surgery after multivariable adjustment are shown in *Table 3*. Replacement of the AoV was significantly associated with an increased risk for early all-cause mortality, both unadjusted [hazard ratio (HR) 1.604, 95% confidence interval (CI) 1.255–2.05; $P < 0.001$] and adjusted (HR 1.477, 95% CI 1.154–1.890; $P = 0.002$) for other significant predictors, whereas AoV repair was not a significant predictor compared with no AoV procedure. Similarly, AoV replacement was a predictor for late all-cause mortality, both unadjusted (HR 1.360, 95% CI 1.152–1.605; $P < 0.001$) and adjusted (HR 1.226, 95% CI 1.037–1.449; $P = 0.017$) for other significant predictors (*Table 4*).

Discussion

This is the largest contemporary study to investigate outcomes after continuous-flow LVAD implantation with and without a concomitant AoV procedure. The main findings of this study refer to decreased survival, particularly early survival, in patients submitted to AoV replacement compared with patients without an AoV procedure, especially in patients with less than moderate-to-severe preoperative AoV regurgitation. Following adjustment for other significant predictors, AoV replacement remained an independent predictor for all-cause mortality. Furthermore, the main causes of early death included multiorgan failure, circulatory failure and neurological events.

Untreated significant AoV regurgitation can be very haemodynamically compromising as a result of the short circulation loop, whereas less severe AoV regurgitation may be less cumbersome. Surprisingly, in up to 15% of the present patients who underwent an AoV procedure, no AoV regurgitation was reported prior to LVAD surgery. In these patients, the decision to perform an AoV procedure may have been based on findings of significant AoV regurgitation in an additional perioperative (transoesophageal)

echocardiogram. Additionally, these patients may have undergone a concomitant AoV procedure in order to replace or oversew the AoV in the context of a pre-existing mechanical AoV, as is recommended.⁵ However, neither perioperative echocardiographic data nor data on the replacement of a mechanical AoV were collected in the IMACS database and therefore these hypotheses could not be tested. However, the present results indicate that AoV replacement is an independent predictor for mortality. In patients with preoperative moderate-to-severe AoV regurgitation, similar survival rates were observed in patients with and without a concomitant AoV procedure. These results suggest that patients with only mild preoperative AoV regurgitation who underwent concomitant AoV replacement had worse survival than patients without concomitant AoV replacement. These findings indicate that stringent criteria for a concomitant AoV procedure at the time of LVAD surgery may be warranted, especially in patients with only mild AoV regurgitation. Concomitant AoV procedures should be considered in patients with moderate-to-severe AoV regurgitation in view of the significant impact on effective LVAD circulation and potential risk for HF relapse or arrhythmias in long-term patient management.^{3,4} Additionally, less invasive procedures for the treatment of significant AoV regurgitation in LVAD patients have been suggested. The use of a transcatheter aortic valve replacement (TAVR) procedure to treat significant AoV regurgitation in patients already on LVAD support has been investigated in small studies, which have shown promising results.^{11–13} The concomitant use of a TAVR procedure with LVAD surgery could reduce circulatory bypass time, thereby reducing the risk for myocardial ischaemia, as shown in a recent case report.¹⁴ However, both experience with and evidence for this off-label use of the TAVR procedure are very limited, and this technique may have additional limitations with reference to the challenges associated with performing procedures of this type in LVAD patients. Additional trials to determine the optimal strategy for

Table 3 Multivariable predictors of early all-cause mortality in post-left ventricular assist device surgery patients stratified by aortic valve procedure

	Variable	HR	95% CI for HR		P-value
			Lower	Upper	
Univariable	No AoV procedure	Ref	Ref	Ref	Ref
	AoV replacement	1.604	1.255	2.050	<0.001
	AoV repair	1.331	0.976	1.816	0.071
Multivariable	No AoV procedure	Ref	Ref	Ref	Ref
	AoV replacement	1.477	1.154	1.890	0.002
	AoV repair	1.209	0.885	1.652	0.233
	Age	1.030	1.025	1.035	<0.001
	Sex (men vs. women)	0.817	0.718	0.930	0.002
	BMI	1.019	1.011	1.028	<0.001
	Creatinine	1.148	0.990	1.333	0.068
	BUN	1.007	1.005	1.010	<0.001
	AST	1.000	1.000	1.001	0.003
	Total bilirubin	1.197	1.127	1.272	<0.001
	Platelet	0.999	0.998	1.000	0.001
	Albumin	0.728	0.663	0.800	<0.001
	Haemoglobin	0.924	0.898	0.951	<0.001
	Mean RA pressure	1.011	1.004	1.019	0.004
	Pulmonary artery wedge pressure	0.990	0.983	0.996	0.002
	Moderate/severe tricuspid regurgitation	1.285	1.148	1.438	<0.001
	Moderate/severe mitral regurgitation	0.796	0.712	0.889	<0.001
	ECMO	1.612	1.345	1.932	<0.001
	LVAD strategy				
	BTT	Ref	Ref	Ref	Ref
	BTC	0.936	0.802	1.093	0.402
	DT	1.109	0.966	1.274	0.143
	Rescue therapy	2.233	1.147	4.347	0.018
Bridge to recovery	2.527	1.781	3.585	<0.001	
Other	1.325	0.423	4.152	0.629	

AoV, aortic valve; AST, aspartate transaminase; BMI, body mass index; BTC, bridge to candidacy; BTT, bridge to transplant; BUN, blood urea nitrogen; CI, confidence interval; DT, destination therapy; ECMO, extracorporeal membrane oxygenator; HR, hazard ratio; LVAD, left ventricular assist device; RA, right atrial.

the treatment of significant AoV regurgitation at the time of LVAD surgery are very much needed. The present results demonstrate that in patients with significant AoV regurgitation, survival rates are lower than in other patients undergoing LVAD implantation and are not influenced by concomitant AoV surgery.

Early and late survival

Previous studies investigating the association between survival and AoV procedures reported conflicting results, with some studies indicating worse survival,^{15–18} whereas others reported similar or better survival rates in patients with a concomitant AoV procedure.^{19–23} However, most of these reports referred to single-centre studies and were limited by lower numbers of patients undergoing a concomitant AoV procedure (only one study included more than 100 patients with an AoV procedure), and some reported only outcomes of multiple concomitant cardiac procedures combined. The largest study used the INTERMACS dataset and included 6721 adult LVAD patients, of whom 125 underwent concomitant AoV closure, 95 underwent AoV repair

and 85 underwent AoV replacement between June 2006 and December 2012.¹⁵ In the INTERMACS study, patients undergoing a concomitant AoV procedure had significantly lower 1-year survival rates (79% in patients undergoing AoV repair, 72% in patients undergoing AoV replacement and 64% in patients undergoing AoV closure) compared with patients without an AoV procedure (81%) ($P = 0.0003$). In comparison with the INTERMACS study,¹⁵ the current study reflects a more contemporary worldwide LVAD population and includes a much higher number of LVAD patients and a higher number of AoV procedures. The late survival rates in the present study were higher than in the INTERMACS study, which most probably reflects improvements in LVAD management and survival that have occurred over time. Similarly to the INTERMACS study,¹⁵ the present results demonstrate a lower survival rate in patients with an AoV procedure, although the lowest survival rates were recorded in patients with an AoV replacement in this study but in patients with an AoV closure in the INTERMACS study.

Only biological prostheses are recommended for concomitant AoV replacement, and a concomitant AoV procedure at the time

Table 4 Multivariable predictors of late all-cause mortality in post-left ventricular assist device surgery patients stratified by aortic valve procedure

	Variable	HR	95% CI for HR		P-value
			Lower	Upper	
Univariable	No AoV procedure	Ref	Ref	Ref	Ref
	AoV replacement	1.360	1.152	1.605	<0.001
	AoV repair	1.150	0.933	1.418	0.190
Multivariable	No AoV procedure	Ref	Ref	Ref	Ref
	AoV replacement	1.226	1.037	1.449	0.017
	AoV repair	1.052	0.853	1.298	0.635
	Age	1.024	1.021	1.028	<0.001
	BMI	1.016	1.011	1.022	<0.001
	Ischaemic aetiology	1.070	1.001	1.144	0.047
	INTERMACS class (1–3 vs. 4–7)	1.101	1.005	1.207	0.040
	Creatinine	1.111	1.014	1.217	0.024
	BUN	1.006	1.004	1.007	<0.001
	Total bilirubin	1.085	1.042	1.129	<0.001
	Platelet	0.999	0.999	1.000	0.016
	INR	1.062	0.995	1.134	0.070
	Albumin	0.872	0.822	0.924	<0.001
	Haemoglobin	0.938	0.922	0.954	<0.001
	Mean RA pressure	1.011	1.006	1.015	<0.001
	PAWP	0.992	0.988	0.996	<0.001
	Moderate/severe tricuspid regurgitation	1.144	1.068	1.226	<0.001
	Moderate/severe mitral regurgitation	0.845	0.790	0.904	<0.001
	IABP	1.074	1.000	1.154	0.050
	ECMO	1.354	1.185	1.546	<0.001
	LVAD strategy				
	BTT	Ref	Ref	Ref	Ref
	BTC	0.979	0.889	1.077	0.661
DT	1.145	1.050	1.248	0.002	
Rescue therapy	1.484	0.873	2.521	0.145	
Bridge to recovery	1.599	1.201	2.128	0.001	
Other	0.806	0.301	2.159	0.668	

AoV, aortic valve; BMI, body mass index; BTC, bridge to candidacy; BTT, bridge to transplant; BUN, blood urea nitrogen; CI, confidence interval; DT, destination therapy; ECMO, extra-corporeal membrane oxygenator; HR, hazard ratio; IABP, intra-aortic balloon pump; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanical Assisted Circulatory Support; LVAD, left ventricular assist device; PAWP, pulmonary artery wedge pressure; RA, right atrial.

of LVAD surgery is recommended in patients with a mechanical AoV.⁵ Despite these recommendations, a small number of patients still received a concomitant mechanical AoV during LVAD surgery. The present results clearly demonstrate that patients with a mechanical AoV have the worst survival and thereby support recommendations for the use of only biological prostheses in LVAD patients.

Multiple closure and repair techniques, each with their own risks and benefits, have been reported in LVAD patients.⁸ Variations in the operating techniques used may explain the variations in outcome after AoV repair observed between the INTERMACS and IMACS studies. However, this hypothesis could not be tested because neither database includes sufficient data to discriminate between different operating techniques. Additionally, the present results do not discriminate between AoV repair and closure, which may contribute to the observed variation. However, in patients in whom AoV closure was conducted, native ejection

from the heart is not possible, especially during catastrophic pump dysfunction. Catastrophic pump dysfunction, although rare, is a severe complication and represents the cause of death in 2% of all LVAD patients.¹ Additionally, oversewing of the AoV creates a blind pouch, which potentially increases the risk for thrombus formation on the AoV and hence raises the risk for thromboembolic events. Therefore, the decision to close the AoV should not be taken lightly.

Causes of death

In the present combined cohort of LVAD patients, the most common causes of early death were multisystem organ failure, circulatory failure and neurological events post-LVAD surgery, which reflect the findings of a previous report.²⁴ The lower survival in patients with an AoV replacement appears to be accompanied by an increase in multisystem organ failure, whereas patients

undergoing AoV repair more often died as a result of circulatory failure compared with patients without an AoV procedure. Surprisingly, fatal neurological events occurred frequently, and more often in patients without an AoV procedure, compared with patients with a concomitant AoV replacement or repair. It is possible that antithrombotic and antiplatelet therapy was introduced earlier in patients submitted to an AoV procedure compared with patients without an AoV procedure, and thereby prevented fatal neurological events. However, detailed information on the timing of the introduction of antithrombotic and antiplatelet therapy was lacking. Unfortunately, no granular data for more specification of the causes of early and late death were available in the IMACS database.

The most common causes of late death were neurological events, multiorgan failure and circulatory failure, which is in line with previous reports from the INTERMACS, EUROMACS and IMACS databases.^{1,24,25} Patients with an AoV replacement or repair died more often as a result of multisystem organ failure, and patients with an AoV repair died more often as a result of circulatory failure compared with patients without an AoV procedure.

Competing outcomes

In this cohort, LVAD patients with an AoV procedure were less often submitted to transplant in comparison with patients without an AoV procedure. As previously suggested, AoV regurgitation may be treated more aggressively in patients with an LVAD as destination therapy.¹⁵ However, the observed difference between those without an AoV procedure and those with AoV replacement is not fully explained by the difference in device strategy. Potentially, the significantly higher age of patients with an AoV replacement may have influenced the decision not to proceed towards transplantation after LVAD implantation.

Limitations

This study has some limitations. Firstly, as a result of its retrospective nature, this study lacks some data. Although multiple imputation was used to deal with the issue of missing data, this may have caused a minor bias. Additionally, some errors may have occurred during data entry. Secondly, in order to ensure data anonymization, LVAD brand information is not available in the research database. Therefore, brand-specific subanalyses could not be performed. Data on the presence and severity of AoV regurgitation were available for all patients; however, information on why surgeons elected to perform AoV replacement or repair, respectively, was not available. It is likely that such decisions varied among participating centres based on local experiences and preferences. Additionally, the degree of AoV regurgitation was graded by the local site and not by an independent core laboratory, and this may have caused some bias. Lastly, no discrimination between AoV repair and closure was made in the database.

Conclusions

This is the largest study to compare short- and long-term survival rates after concomitant AoV procedures in continuous-flow

LVAD patients with pre-existing AoV regurgitation. Concomitant AoV surgery is associated with lower survival rates compared with the absence of an AoV procedure. Particularly in patients with only mild preoperative AoV regurgitation, survival rates are negatively impacted by concomitant AoV replacement. These results suggest that the resolution of mild AoV regurgitation may not outweigh the risks associated with AoV surgery, whereas the resolution of moderate-to-severe AoV regurgitation may improve LVAD management. Therefore, additional research is urgently needed to determine the optimal strategy for the treatment of AoV regurgitation at the time of LVAD surgery.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

- Goldstein DJ, Meyns B, Xie R, Cowger J, Pettit S, Nakatani T, Netuka I, Shaw S, Yanase M, Kirklin JK. Third Annual Report from the ISHLT Mechanically Assisted Circulatory Support Registry: a comparison of centrifugal and axial continuous-flow left ventricular assist devices. *J Heart Lung Transplant* 2019;**38**:352–363.
- Bouabdallaoui N, El-Hamamsy I, Pham M, Giraldeau G, Parent MC, Carrier M, Rouleau JL, Ducharme A. Aortic regurgitation in patients with a left ventricular assist device: a contemporary review. *J Heart Lung Transplant* 2018;**37**:1289–1297.
- Truby LK, Garan AR, Givens RC, Wayda B, Takeda K, Yuzefpolskaya M, Colombo PC, Naka Y, Takayama H, Topkara VK. Aortic insufficiency during contemporary left ventricular assist device support: analysis of the INTERMACS registry. *JACC Heart Fail* 2018;**6**:951–960.
- Aggarwal A, Raghuvir R, Eryazici P, Macaluso G, Sharma P, Blair C, Tatoes AJ, Pappas PS, Bhat G. The development of aortic insufficiency in continuous-flow left ventricular assist device-supported patients. *Ann Thorac Surg* 2013;**95**:493–498.
- Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J; International Society for Heart and Lung Transplantation. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant* 2013;**32**:157–187.
- Ahn H, Granfeldt H, Hubbert L, Peterzen B. Long-term left ventricular support in patients with a mechanical aortic valve. *Scand Cardiovasc J* 2013;**47**:236–239.
- Mokashi SA, Schmitto JD, Lee LS, Rawn JD, Bolman RM 3rd, Shekar PS, Couper GS, Chen FY. Ventricular assist device in patients with prosthetic heart valves. *Artif Organs* 2010;**34**:1030–1034.
- Cowger J, Rao V, Massey T, Sun B, May-Newman K, Jorde U, Estep JD. Comprehensive review and suggested strategies for the detection and management of aortic insufficiency in patients with a continuous-flow left ventricular assist device. *J Heart Lung Transplant* 2015;**34**:149–157.
- Kirklin JK, Cantor R, Mohacsi P, Gummert J, de By T, Hannan MM, Kormos RL, Schueler S, Lund LH, Nakatani T, Taylor R, Lannon J. First annual IMACS report: a global International Society for Heart and Lung Transplantation registry for mechanical circulatory support. *J Heart Lung Transplant* 2016;**35**:407–412.

10. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Med Res Methodol* 2017;**17**:162.
11. Phan K, Haswell JM, Xu J, Assem Y, Mick SL, Kapadia SR, Cheung A, Ling FS, Yan TD, Tchanchaleishvili V. Percutaneous transcatheter interventions for aortic insufficiency in continuous-flow left ventricular assist device patients: a systematic review and meta-analysis. *ASAIO J* 2017;**63**:117–122.
12. Kar B, Prathipati P, Jumean M, Nathan SS, Gregoric ID. Management of aortic insufficiency using transcatheter aortic valve replacement in patients with left ventricular assist device support. *ASAIO J* 2019;**66**:e82–e86.
13. Yehya A, Rajagopal V, Meduri C, Kauten J, Brown M, Dean L, Webster J, Krishnamoorthy A, Hrobowski T, Dean D. Short-term results with transcatheter aortic valve replacement for treatment of left ventricular assist device patients with symptomatic aortic insufficiency. *J Heart Lung Transplant* 2019;**38**:920–926.
14. Murashita T, Joyce DL, Pochettino A, Stulak JM, Joyce LD. Concomitant valve-in-valve transcatheter aortic valve replacement and left ventricular assist device implantation. *Innovations* 2017;**12**:147–149.
15. Robertson JO, Naftel DC, Myers SL, Prasad S, Mertz GD, Itoh A, Pagani FD, Kirklin JK, Silvestry SC. Concomitant aortic valve procedures in patients undergoing implantation of continuous-flow left ventricular assist devices: an INTERMACS database analysis. *J Heart Lung Transplant* 2015;**34**:797–805.
16. McKellar SH, Deo S, Daly RC, Durham LA III, Joyce LD, Stulak JM, Park SJ. Durability of central aortic valve closure in patients with continuous flow left ventricular assist devices. *J Thorac Cardiovasc Surg* 2014;**147**:344–348.
17. John R, Naka Y, Park SJ, Sai-Sudhakar C, Salerno C, Sundareswaran KS, Farrar DJ, Milano CA. Impact of concurrent surgical valve procedures in patients receiving continuous-flow devices. *J Thorac Cardiovasc Surg* 2014;**147**:581–589; discussion 589.
18. Dranishnikov N, Stepanenko A, Potapov EV, Dandel M, Siniawski H, Mladenow A, Hubler M, Grauhan O, Weng Y, Krabatsch T, Hetzer R, Kukucka M. Simultaneous aortic valve replacement in left ventricular assist device recipients: single-center experience. *Int J Artif Organs* 2012;**35**:489–494.
19. Goda A, Takayama H, Pak SW, Uriel N, Mancini D, Naka Y, Jorde UP. Aortic valve procedures at the time of ventricular assist device placement. *Ann Thorac Surg* 2011;**91**:750–754.
20. Adamson RM, Dembitsky WP, Baradaran S, Chammas J, May-Newman K, Chillcott S, Stahovich M, McCalmont V, Ortiz K, Hoagland P, Jaski B. Aortic valve closure associated with HeartMate left ventricular device support: technical considerations and long-term results. *J Heart Lung Transplant* 2011;**30**:576–582.
21. Fukuhara S, Takeda K, Chiuzan C, Han J, Polanco AR, Yuzefpolskaya M, Mancini DM, Colombo PC, Topkara VK, Kurlansky PA, Takayama H, Naka Y. Concomitant aortic valve repair with continuous-flow left ventricular assist devices: results and implications. *J Thorac Cardiovasc Surg* 2016;**151**:201–209, 210.e1–2.
22. Pal JD, Klodell CT, John R, Pagani FD, Rogers JG, Farrar DJ, Milano CA; HeartMate II Clinical Investigators. Low operative mortality with implantation of a continuous-flow left ventricular assist device and impact of concurrent cardiac procedures. *Circulation* 2009;**120** (11 Suppl):S215–S219.
23. Fukuhara S, Ikegami H, Polanco AR, Song JJ, Han J, Takeda K, Kurlansky PA, Takayama H, Naka Y. Concomitant repair for mild aortic insufficiency and continuous-flow left ventricular assist devices. *Eur J Cardiothorac Surg* 2017;**52**:1062–1068.
24. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB, Naftel DC. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. *J Heart Lung Transplant* 2017;**36**:1080–1086.
25. de By T, Mohacsi P, Gahl B, Zittermann A, Krabatsch T, Gustafsson F, Leprince P, Meyns B, Netuka I, Caliskan K, Castedo E, Musumeci F, Vincentelli A, Hetzer R, Gummert J; EUROMACS Members. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report. *Eur J Cardiothorac Surg* 2018;**53**:309–316.