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MAIN TEXT

Impact of concomitant aortic valve replacement in patients with mild-to-moderate aortic valve regurgitation undergoing left ventricular assist device implantation: EUROMACS analysis

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Abstract

Introduction: Left ventricular assist device (LVAD) therapy may lead to an aortic regurgitation, limiting left ventricular unloading and causing adverse events. Whether concomitant aortic valve replacement may improve outcomes in patients with preoperative mild-to-moderate aortic regurgitation remains unclear.

Methods: A retrospective propensity score-matched analysis of adult patients with preoperative mild-to-moderate aortic regurgitation undergoing durable LVAD implantation between 01/01/2011 and 30/11/2021 was performed. Patients undergoing concomitant valve surgery other than biological aortic valve

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replacement were excluded, resulting in 77 with concomitant biological aortic valve replacement and 385 without.

Results: Following 1:1 propensity score matching, two groups of 55 patients with and without biological aortic valve replacement were obtained, (mean age 59 ± 11 years, 92% male, 59.1% HeartWare). Aortic regurgitation was mild in 72.7% and 76.4% and moderate in 27.3% and 23.6% in non-replacement and replacement cohorts respectively. The 30-day survival was 89.1% vs. 85.5% ($p = 0.59$), 1-year survival 69.1% vs. 56.4% ($p = 0.19$), and 2-year survival 61.8% vs. 47.3% ($p = 0.10$) in the non-replacement and replacement groups, respectively. After a mean follow-up of 1.2 years, non-replacement patients had a higher incidence of pump thrombosis (11 [20%] vs. 3 [5.5%], $p = 0.022$) and fewer major bleedings (2 [3.6%] vs. 11 [20%], $p = 0.008$).

Conclusion: Compared with those treated conservatively, patients with mild-to-moderate aortic regurgitation undergoing concomitant aortic valve replacement during LVAD implantation have a similar survival up to 2 years on support. Patients with concomitant valve replacement had a higher risk of bleeding complications but fewer pump thromboses.

KEYWORDS

advanced heart failure, aortic regurgitation, EUROMACS, LVAD

1 | INTRODUCTION

Aortic regurgitation (AR) is a common complication after continuous-flow left ventricular assist device (LVAD) implantation, occurring in 25%–30% of patients within the first year on pump support.[1] The flow generated by the LVAD itself is the primary cause of worsening of pre-existing AR or the development of de novo regurgitation on support. In patients with an unloaded left ventricle (LV) on LVAD and a lack of contractility, the LV pressure during systole fails to exceed the aortic pressure, keeping the aortic valve mostly closed.[2] This mechanism eventually leads to degeneration of the aortic leaflets and dilation of the aortic root, impairing proper leaflet coaptation.[3] The regurgitant aortic valve creates a shortcut in the circulation, limiting LV unloading and reducing the cardiac output, which can potentially lead to persistent heart failure (HF) despite ongoing LVAD support.[4]

Concomitant biological aortic valve replacement (AVR) is recommended during LVAD implantation for patients with more than mild AR.[5,6] Current guidelines are mostly based on expert opinion, and data comparing treatment strategies among patients with preoperative AR undergoing LVAD implantation are limited.[7,8] On the one hand, the presence of significant AR on LVAD support has been associated with a poorer prognosis; However, additional AVR introduces the risks of complications and may impact early postoperative survival, particularly in patients with impaired hemodynamics (e.g., cardiogenic shock).[9,10] Despite the fact that preoperative AR leads to the development of significant AR after LVAD implantation, studies addressing whether AVR has an impact in this subset of patients are lacking.[10]

Therefore, we conducted the current analysis to assess the impact of concomitant biological AVR as compared with conservative treatment among patients with mild-to-moderate AR undergoing LVAD implantation with contemporary continuous-flow pumps.

2 | METHODS

2.1 | Study design

The presented study is a propensity score matched observational retrospective analysis of the EUROMACS dataset, aiming to evaluate the impact of concomitant AVR in patients with preoperative mild-to-moderate AR undergoing LVAD implantation (Figure 1).

The complications, as defined in the EUROMACS database according to the INTERMACS (Interagency Registry of Mechanically Assisted Circulatory Support)

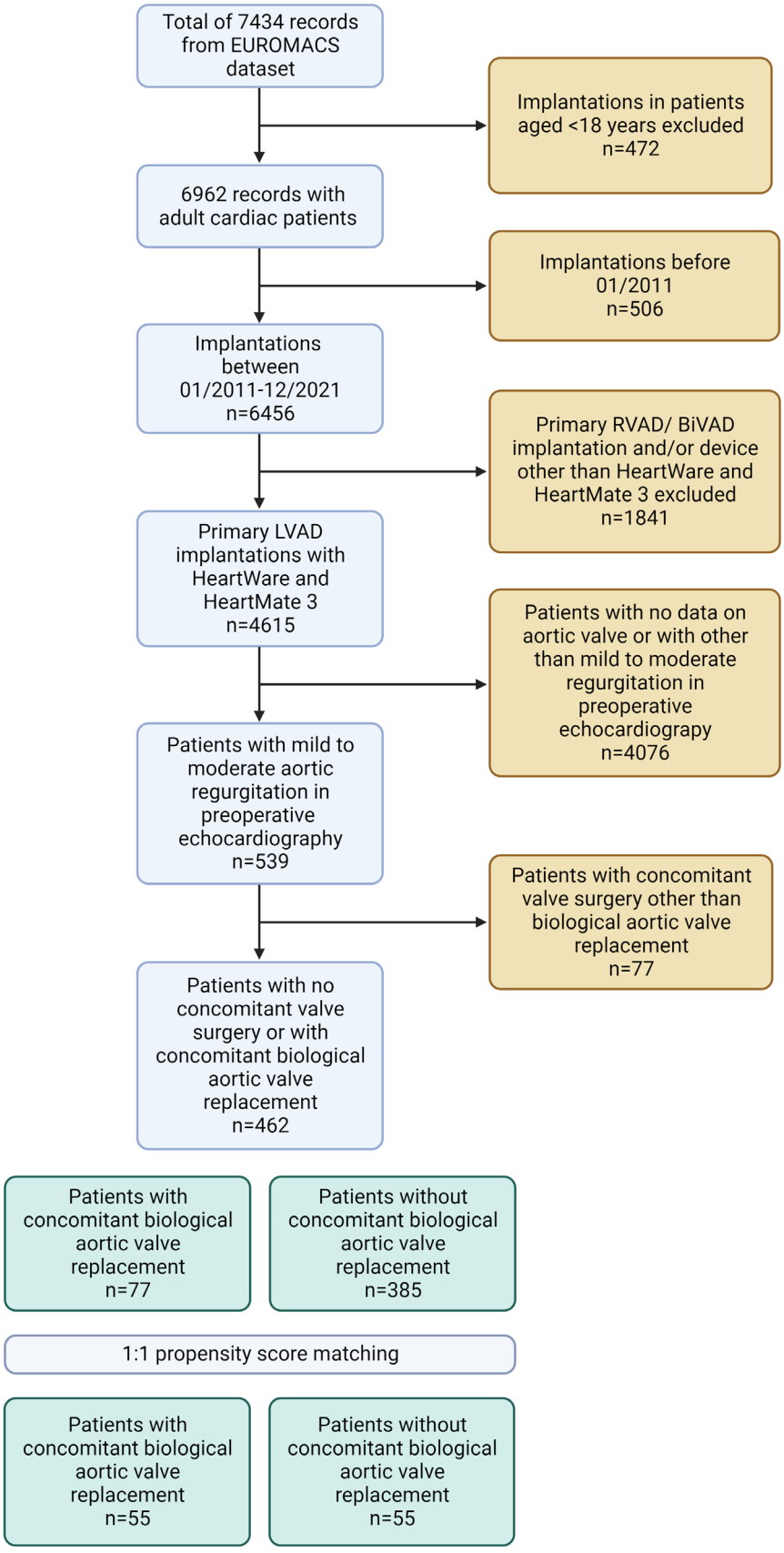

FIGURE 1 Flow chart. BiVAD, biventricular assist device; LVAD, left ventricular assist device; RVAD, right ventricular assist device.

definitions, were recorded and followed up. For this analysis, only adult patients who underwent primary LVAD implantation with a contemporary continuous-flow pump (HeartWare HVAD, HW; Medtronic, Minneapolis, MN, USA; HeartMate 3, HM3; Abbott, Chicago, IL, USA) between 01/01/2011 and 31/12/2021 with preoperative

mild-to-moderate AR were considered. Patients were excluded if treated with concomitant mitral, tricuspid and/or pulmonary valve surgery, or if undergoing AV repair or replacement with a mechanical valve (i.e., only bioprosthetic AVR was considered).

2.2 | Patient selection

Following in−/exclusion criteria for patient selection were applied:

Inclusion criteria	Exclusion criteria
• Adult patients (≥18 years) • Date of surgery between 01/2011 and 12/2021 • In order to eliminate the potential impact of the device model, only continuous-flow centrifugal VADs were included in the analysis: HeartWare HVAD (HW; Medtronic, Minneapolis, MN, USA) and HeartMate 3 (HM3; Abbott, Chicago, IL, USA) • To eliminate the potential impact of device configuration, only patients undergoing primary LVAD implantation were included in the analysis • Patients with echocardiographic data on preoperative AR • Patients without concomitant valve surgery other than biological AVR	• Patients <18 years of age • Surgery before 01/2011 • Patients with a device type other than HeartWare HVAD or HeartMate 3 • Patients who underwent primary right ventricular (RVAD), biventricular assist device (BiVAD), and total artificial heart (TAH) implantation • Patients with no echocardiographic data on preoperative AR • Patients, who underwent concomitant valve surgery other than biological AVR

2.3 | Study end points

The primary end point was survival of up to 3 years on LVAD support (demonstrated in Kaplan–Meier estimates). Due to a small number of patients at risk, a 2-year benchmark for survival and adverse event analysis was applied. Secondary end points were the incidences of adverse events during the early postoperative period and the subsequent follow-up and included bleeding complications, neurological dysfunction, right heart failure, device-related infections, and device thromboses.

Heart transplant and weaning from LVAD support are considered end point events by the EUROMACS registry, so no survival and complication data are collected beyond these events. For the survival analysis, patients after heart transplant or weaning were not censored, but also not followed up.

2.4 | Ethics statement

The patients' written consent was obtained in order to allow data utilization for the EUROMACS registry and research purposes. The data from the EUROMACS database are presented in pseudo-anonymized form. The study was approved by EUROMACS research board and by the institutional ethics committee of the German Heart Centre Charité (EA4/003/12).

2.5 | Echocardiographic parameters

The preoperative assessment of AR in the EUROMACS database is based on a classification system that includes the following categories: none, trivial, mild, moderate, and severe. The categorization and assessment of AR severity were not standardized and might differ between participating institutions.

According to the European Association of Cardiothoracic Surgery (EACTS) Expert consensus article, patients with intraoperative moderate or severe AR should undergo a concomitant aortic valve surgery during LVAD implantation.[6] The fact, that some patients in our cohort underwent no concomitant AV surgery despite significant regurgitation, can be explained by the discrepancy in pre- and intraoperative echocardiographic measurements. At the same time, it is important to note that the degree of AR can potentially worsen after the initiation of LVAD support, which will also require a concomitant AV surgery.[6]

2.6 | Statistical analysis

For baseline characteristics, continuous variables are summarized as mean and standard deviation (SD), or as median and interquartile range [25th quartile, 75th quartile] in the case of non-normal data. For categorical variables, numbers and percentages are reported. Normality was assessed with Kolmogorov–Smirnov test. Categorical variables were compared with Chi-square or Fisher's test, while continuous variables were compared with Student *t* test or Mann–Whitney test, when opportune.

To account for imbalances in the study groups, a propensity score was calculated by logistic regression. Variables including demographics, the severity of cardiogenic shock, organ dysfunction, and risk-modifying end-organ parameters that impact long-term survival were used for propensity score matching. And 1:1 propensity score matching was performed using the nearest neighbor algorithm without replacement and a caliper width of 0.2 standard deviations of the logit of the propensity score. The balance of covariates was considered

satisfactory for a standardized mean difference (SMD) of 0.1 and is presented graphically (Figure S1).[11] Kaplan–Meier survival curves and log-rank p-values were used to evaluate and visually represent long-term outcomes. Cox regression analyses were performed to compare outcomes between patients with and without AVR. Results are presented as hazard ratios (HR) and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

Competing risk analyses were used to evaluate the incidence of adverse events with explant due to all-cause death, weaning or, heart transplantation as competing outcomes. In the case of recurrent adverse events, the first event in a patient was analyzed. Subdistribution hazard ratios (SHRs) were calculated using clustered Fine–Gray models.

The difference in continuous variables between patient groups was analyzed using the exact Wilcoxon signed-rank test, and the McNemar test was used for categorical variables. The relative risk of complications on support was calculated. Results were presented as risk d ratios (RR) with corresponding 95% CIs.

R version 4.0.2 [R development Core team (2020). R: A Language and Environment for Statistical Computing] was used for statistical analysis.

3 | RESULTS

3.1 | Patient characteristics

Of 7434 patients in the EUROMACS registry who underwent LVAD implantation with a contemporary continuous-flow pump between 01/01/2011 and 31/12/2021, 539 with preoperative mild-to-moderate AR were considered. Seventy-seven patients undergoing concomitant valve surgery other than biological AVR were excluded, resulting in a final population of 462 patients, 77 of whom underwent concomitant biological AVR. In 385 patients, the surgery did not involve the native aortic valve (Figure 1).

Propensity score matching was performed with the 1:1 nearest neighbor method, resulting in 55 patients in each group (Figure 1). The mean age in the matched cohorts was 61 [IQR 54–66] years, 101 (92%) patients were male, 67 (61%) were on inotropic support prior to surgery, and 30 (27.3%) were on temporary mechanical circulatory support (Table 1). Baseline characteristics were well-balanced between the groups, apart from body mass index, which was slightly higher among patients undergoing conservative valve treatment (27.6 (SD: 4.5) vs. 25.8 (SD: 4.5), $p=0.033$). Eighty-two (74.5%) patients had mild and 28 (25.5%) had moderate AR. The proportion of AR between the matched groups was similar: 72.7% and 27.3% in the non-AVR and 76.4% and 23.6% in the AVR group for mild and moderate AR, respectively ($p=0.66$) (Table 1). LVAD device models were similar between the cohorts: HVAD 58.2% and HM3 41.8% and 60.0% vs. 40% for the non-AVR and AVR groups, respectively ($p=0.846$). In 67 (61%) patients, LVAD implantation was performed as a bridge-to-transplantation strategy, while 39 (35.5%) patients underwent the surgery as destination therapy; in 4 (3.5%) patients, an LVAD was implanted as an emergency rescue approach (Table 2).

3.2 | Postoperative outcomes

Immediate postoperative outcomes are presented in Table 2. In the matched cohorts, AVR patients —compared with the conservatively treated group— exhibited a longer duration of surgery (202 [IQR 160–255] min vs. 305 [IQR 243–388] min, $p<0.001$), a longer time on cardiopulmonary bypass (82 [IQR 61–112] min vs. 147 [116–185] min, $p<0.001$), and a longer period of peri-operative invasive ventilation (26 [IQR 12–121] hours vs. 93 [IQR 22–576] hours, $p=0.033$), ICU stay (7 [IQR 5–19] days vs. 14 [IQR 7–38] days, $p=0.019$) and stepdown care (16 [IQR 25–27] days vs. 23 [IQR 13–33] days, $p=0.015$). No difference was observed between the groups concerning postoperative reintubation and dialysis.

3.3 | Survival

The Kaplan–Meier analysis of survival in the unmatched cohorts showed a significantly better survival for the non-AVR group up to 3 years after implantation. Conversely, survival in the matched cohorts was similar throughout the whole follow-up period (Table 3, Figure 2).

In particular, 30-day survival was 89.1% vs. 85.5% ($p=0.59$), 1-year survival 69.1% vs. 56.4% ($p=0.19$), and 2-year survival 61.8% vs. 47.3% ($p=0.10$) in the non-AVR and the AVR group, respectively. There was no significant difference in the cumulative incidence of death between the groups [SHR 1.4 (0.71–2.35), $p=0.21$], AVR vs. non-AVR, respectively. Cox regression analysis demonstrated that concomitant AVR was not a predictor of 2-year mortality (HR 1.47, $p=0.181$ [CI 0.84–0.2.58]) (Table 3).

There was no significant difference in the cumulative incidence of heart transplantations [SHR 1.1 (0.41–2.99), $p=0.84$] and LVAD weaning [SHR 2.64 (0.54–13), $p=0.23$] between the AVR and non-AVR group, respectively (Table 3). Cumulative incidence functions for competing outcomes (death, heart transplantation, weaning from support) in matched cohorts are shown in Figure 3.

TABLE 1 Baseline data before and after propensity score matching.

	Unmatched population								Matched population							
	Overall ($n=462$)		LVAD alone ($n=385$)		LVAD+AVR ($n=77$)				Overall ($n=110$)		LVAD alone ($n=55$)		LVAD+AVR ($n=55$)			
Baseline features	***n***	**%**	***n***	**%**	***n***	**%**	***SMDs***	***p*-value**	***n***	**%**	***n***	**%**	***n***	**%**	***SMDs***	***p*-value**
Age, years, mean (SD)	59 (52–65)		60 (51–66)		58 (52–65)		0.05	0.73	61 (54–66)		63 (53–67)		59 (55–66)		−0.07	0.7
Gender, male	404	87.4	335	87	69	89.6	0.09	0.53	101	91.8	51	92.7	50	90.9	0.007	0.73
BMI, kg/m^2, mean (SD)	25.6 (23.0–28.5)		25.7 (23.0–28.4)		25.1 (22.8–29.3)		0.06	0.91	26.2 (23.5–29.4)		27.6 (24.7–30.0)		24.9 (22.7–28.4)		−0.42	0.033
BSA, m^2, mean (SD)	1.94 (1.80–2.11)		1.93 (1.80–2.10)		2.01 (1.86–2.14)		0.26	0.026	2.01 (1.87–2.12)		2.03 (1.89–2.11)		2.00 (1.86–2.14)		−0.19	0.37
INTERMACS patient profile							−0.55	0.01							−0.24	0.44
1	53	11.5	39	10.1	14	18.2			17	15.5	9	16.4	8	14.5		
2	110	23.8	90	23.4	20	26			25	22.7	11	20	14	25.5		
3	114	24.7	91	23.6	23	29.9			36	32.7	18	32.7	18	32.7		
4 to 7	179	38.7	162	42.1	17	22.1			32	29.1	17	30.9	15	27.3		
Missing	6	1.3	3	0.8	3	3.9			0	–	0	–	0	–		
Primary diagnosis							−0.15	0.17							−0.03	0.04
Dilated myopathy: ischemic	210	45.5	176	45.7	34	44.2			56	50.9	29	52.7	27	49.1		
Dilated myopathy: idiopathic	93	20.1	69	17.9	24	31.2			29	26.4	10	18.2	19	34.5		
Dilated myopathy: viral	48	10.4	45	11.7	3	3.9			10	9.1	8	14.5	2	3.6		
Dilated myopathy: familial	10	2.2	9	2.3	1	1.3			2	1.8	1	1.8	1	1.8		
Dilated myopathy: other	57	12.3	52	13.5	5	6.5			7	6.4	6	10.9	1	1.8		
Congenital heart disease	8	1.7	7	1.8	1	1.3			1	0.9	0	–	1	1.8		
Hypertrophic cardiomyopathy	7	1.5	5	1.3	2	2.6			1	0.9	0	–	1	1.8		
Restrictive cardiomyopathy	7	1.5	5	1.3	2	2.6			3	2.7	1	1.8	2	3.6		
Valvular cardiomyopathy	7	1.5	6	1.6	1	1.3			1	0.9	0	–	1	1.8		
Missing	15	3.2	11	2.9	4	5.2			0	–	0	–	0	–		
Preoperative inotropes	226	48.9	177	46	49	63.6	0.29	0.022	67	60.9	31	56.4	36	65.5	0.18	0.33
Previous cardiac surgery	79	17.1	69	17.9	10	13	−0.16	0.26	19	17.3	11	20	8	14.5	−0.13	0.45
IABP	26	5.6	20	5.2	6	7.8	0.07	0.28	9	8.2	4	7.3	5	9.1	0.07	0.49
ECMO	43	9.3	33	8.6	10	13	0.11	0.3	13	11.8	6	10.9	7	12.7	0.06	0.79
Other VAD	35	7.6	28	7.3	7	9.1	0.04	0.71	8	7.3	6	10.9	2	3.6	−0.27	0.14
Device brand							−0.17	0.587							−0.14	0.846

TABLE 1 (Continued)

	Unmatched population								Matched population							
	Overall (*n* = 462)		LVAD alone (*n* = 385)		LVAD+AVR (*n* = 77)				Overall (*n* = 110)		LVAD alone (*n* = 55)		LVAD+AVR (*n* = 55)			
Baseline features	***n***	**%**	***n***	**%**	***n***	**%**	***SMDs***	***p*-value**	***n***	**%**	***n***	**%**	***n***	**%**	***SMDs***	***p*-value**
HW	251	54.3	207	53.8	44	57.1			65	59.1	32	58.2	33	60		
HM3	211	45.7	178	46.2	33	42.9			45	40.9	23	41.8	22	40		
LVEF, %, mean (SD)	20 (15–24)		19 (15–23)		20 (14–25)		−0.568	0.605	20 (15–25)		20 (15–21)		20 (14–25)		0.084	0.676
Aortic regurgitation							−0.153	0.005							−0.068	0.662
Mild	347	75.1	299	77.7	48	62.3			82	74.5	40	72.7	42	76.4		
Moderate	115	24.9	86	22.3	29	37.7			28	25.5	15	27.3	13	23.6		
Missing	0	–	0	–	0	–			0	–	0	–	0	–		
Mitral regurgitation							0.289	0.025							0.155	0.467
None	21	4.5	18	4.7	3	3.9			9	8.2	7	12.7	2	3.6		
Trivial	26	5.6	20	5.2	6	7.8			8	7.3	3	5.5	5	9.1		
Mild	135	29.2	102	26.5	33	42.9			45	40.9	21	38.2	24	43.6		
Moderate	159	34.4	140	36.4	19	24.7			31	28.2	16	29.1	15	27.3		
Severe	102	22.1	90	23.4	12	15.6			17	15.5	8	14.5	9	16.4		
Missing	19	4.1	15	3.9	4	5.2			0	–	0	–	0	–		
Tricuspid regurgitation							0.303	0.142							0.106	0.335
None	23	5	17	4.4	6	7.8			7	6.4	5	9.1	2	3.6		
Trivial	42	9.1	34	8.8	8	10.4			14	12.7	9	16.4	5	9.1		
Mild	177	38.3	140	36.4	37	48.1			45	40.9	18	32.7	27	49.1		
Moderate	145	31.4	125	32.5	20	26			32	29.1	16	29.1	16	29.1		
Severe	63	13.6	57	14.8	6	7.8			12	10.9	7	12.7	5	9.1		
Missing	12	2.6	12	3.1	0	–			0	–	0	–	0	–		
Invasive hemodynamics, mean (SD)																
sPAP, mmHg	51 (17)		51 (18)		51 (17)		0.01	0.99	51 (18)		53 (21)		49 (14)		−0.24	0.36
dPAP, mmHg	25 (10)		25 (10)		25 (10)		−0.03	0.98	25 (11)		27 (12)		24 (10)		−0.26	0.301
RAP, mmHg	10 (6–15)		11 (6–15)		9 (4–13)		1.87	0.06	9 (5–13)		11 (6–14)		8 (5–12)		−0.32	0.2
PCWP, mmHg	23 (8)		23 (8)		23 (8)		0.24	0.87	22 (8)		23 (9)		21 (8)		−0.22	0.42
PVR, dynes/sec/cm^{-5}	220 (143–331)		215 (143–328)		253 (142–377)		−0.73	0.43	220 (140–328)		217 (126–321)		252 (145–344)		0.42	0.14

(Continues)

TABLE 1 (Continued)

	Unmatched population							Matched population						
	Overall (*n* = 462)		LVAD alone (*n* = 385)		LVAD+AVR (*n* = 77)			Overall (*n* = 110)		LVAD alone (*n* = 55)		LVAD+AVR (*n* = 55)		
Baseline features	***n***	**%**	***n***	**%**	***n***	**%**	***SMDs***	***p*-value**	***n***	**%**	***n***	**%**	***n***	**%**	***SMDs***	***p*-value**
CI, L/min/m^2	1.9 (1.6–2.1)		1.9 (1.6–2.1)		2.0 (1.7–2.3)		−0.19	0.06	2.0 (1.7–2.2)		1.99 (1.5–2.2)		1.99 (1.74–2.46)		0.23	0.37
CO, L/min	3.6 (3.0–4.3)		3.5 (3.0–4.1)		4.0 (3.4–5.0)		−0.67	0.005	4.0 (3.2–4.5)		3.9 (3.1–4.4)		4.0 (3.4–4.7)		0.28	0.28

Abbreviations: AVR, aortic valve replacement; BMI, body mass index; BSA, body surface area; CI, cardiac index; CO, cardiac output; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; s/dPAP, systolic/diastolic pulmonary artery pressure; SD, standard deviation; SMDs, standardized mean differences; VAD, ventricular assist device.

3.4 | Complications on follow-up

The median follow-up was similar in both groups (1.2 [IQR 0.3–3.0] years for non-AVR and 1.3 [0.4–2.7] for AVR), resulting in 1750 and 1717 cumulative patient-months, respectively.

Patients in the non-AVR cohort demonstrated a significantly higher incidence of overall pump thrombosis (11 [20%] vs. 3 [5.5%], $p = 0.022$). At the same time, AVR patients experienced a two fold higher incidence of major bleeding requiring surgical revision (2 [3.6%] vs. 11 [20%], $p = 0.008$) (Tables 3 and S1). Cox regression analysis showed concomitant AVR as predictor of pump thrombosis (HR 0.12, $p = 0.046$ [CI 0.02–0.96]) and major bleeding (HR 4.58, $p = 0.051$ [CI 0.99–21.2]) (Table 3).

There was no statistically significant difference in the incidence of other major adverse events and complications (device-related infections, device malfunction, neurological dysfunction, etc.) during the follow-up (Table 3).

3.5 | Subgroup analysis

An additional subgroup analysis of matched patients with regard to the device type implanted was performed (Table S2). Patients receiving HW device have demonstrated a trend toward a higher incidence of pump thrombosis and right heart failure (12.3% vs. 2.2%, $p = 0.057$ and 20.0% vs. 6.7% $p = 0.052$), (Figure 4). Moreover, patients on HW have demonstrated a lower 2-year survival (44.6% vs. 68.9, $p = 0.015$ for HW vs. HM3 resp.).

4 | DISCUSSION

This is the largest analysis evaluating the impact of biological AVR among LVAD patients with preoperative mild-to-moderate AR. The main findings of our investigation can be summarized as follows:

- The impact of biological AVR on the postoperative mortality of patients with preoperative mild-to-moderate AR undergoing LVAD implantation appears to be neutral. This finding appears to remain consistent over the longer term follow-up.
- Concomitant AVR is associated with longer procedural, cardiopulmonary bypass, intubation times, and overall ICU stay, with no impact on reintubation, and dialysis.
- Concomitant AVR is associated with a higher occurrence of major bleeding and a lower occurrence of pump thrombosis. The difference in major bleeding complications is significant over the follow-up period

TABLE 2 Early postoperative course and outcomes.

	Unmatched population							Matched population						
	Overall (*n* = 462)		LVAD alone (*n* = 385)		LVAD+AVR (*n* = 77)			Overall (*n* = 110)		LVAD alone (*n* = 55)		LVAD+AVR (*n* = 55)		
	n	%	*n*	%	*n*	%	*p*-value	*n*	%	*n*	%	*n*	%	*p*-value
Inflow location							0.023							0.32
LV	446	96.5	374	97.1	72	93.5		109	99.1	55	100	54	98.2	
LA	1	0.2	0	–	1	1.3		1	0.9	0	–	1	1.8	
Missing	15	3.2	11	2.9	4	5.2		0	–	0	–	0	–	
Outflow location							0.08							0.15
Ascending	422	91.3	349	90.6	73	94.8		108	98.2	53	96.4	55	100	
Descending	23	5	23	6	0	–		2	1.8	2	3.6	0	–	
Other	1	0.2	1	0.3	0	–		0	–	0	–	0	–	
Missing	15	3.2	11	2.9	4	5.2		0	–	0	–	0	–	
Concomitant procedures														
ASD/PFO closure	26	5.6	19	4.9	7	9.1	0.8	9	8.2	3	5.5	6	10.9	0.76
CABG	6	1.3	1	0.3	5	6.5		4	3.6	1	1.8	3	5.5	0.58
CPB time, min, mean (SD)	90 (62–127)		82 (58–113)		144 (112–187)		0.001	114 (80–154)		82 (61–112)		147 (116–185)		0.001
Implant time, min, mean (SD)	232 (175–330)		217 (168–308)		289 (242–385)		0.001	245 (198–360)		202 (160–255)		305 (243–388)		0.001
ICU stay, days, mean (SD)	10 (10–25)		9 (5–23)		14 (7–33)		0.011	11 (5–28)		7 (5–19)		14 (7–38)		0.019
Stepdown care stay, days, mean (SD)	17 (7–28)		16 (7–27)		21 (4–32)		0.10	20 (8–30)		16 (25–27)		23 (13–33)		0.015
Ventilation, hours, mean (SD)	32 (14–165)		28 (13–124)		68 (22–564)		0.01	48 (13–256)		26 (12–121)		93 (22–576)		0.033
Reoperation for bleeding within 48 h	30	6.5	21	5.5	9	11.7	0.48	7	6.4	1	1.8	6	10.9	0.85
Reoperation for bleeding after 48 h	28	6.1	20	5.2	8	10.4	0.66	7	6.4	0	–	7	12.7	0.18
Dialysis	17	3.7	12	3.1	5	6.5	0.08	5	4.5	1	1.8	4	7.3	0.14
Reintubation	16	3.5	12	3.1	4	5.2	0.24	4	3.6	1	1.8	3	5.5	0.27
30-day mortality	49	10.6	36	9.4	13	16.9	0.05	14	12.7	6	10.9	8	14.5	0.59
Current device strategy							0.44							0.98
BTT	298	64.5	247	64.2	51	66.2		67	60.9	33	60	34	61.8	
DT	128	27.7	105	2.3	23	29.9		39	35.5	20	36.4	19	34.5	
BTR	11	2.4	11	2.9	0	–		0	–	0	–	0	–	
Rescue	24	5.2	21	5.5	3	3.9		4	3.6	2	3.6	2	3.6	

Abbreviations: ASD, atrial septal defect; AVR, aortic valve replacement; BTR, bridge to recovery; BTT, bridge to transplantation; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DT, destination therapy; HM3, HeartMate III; HW, HeartWare; ICU, intensive care unit; LA, left atrium; LV, left ventricle; LVAD, left ventricular assist device; PFO, patent foramen ovale; SD, standard deviation.

but occurs mainly during the early postoperative course of the index hospitalization.

AR is both a significant comorbidity and a complication in advanced HF patients treated with a durable LVAD. It results in the recirculation of regurgitant blood volume and a reduction in cardiac output, which can impair patients' hemodynamics and lead to persistent HF despite LVAD support. Even if pre- and intraoperative echocardiography remains crucial for an assessment of AV function,

a precise evaluation of AR severity remains challenging due to its strong dependency on the surrounding hemodynamic boundaries, particularly on afterload.[12,13] This is of great relevance in the setting of LVAD candidacy, as mechanical LV unloading may significantly modify the hemodynamic forces driving AR, and accordingly, its severity.

The lack of data on the impact of concomitant AV procedures, especially in patients with a milder degree of AR, gives rise to management uncertainty and an ongoing discussion within the VAD society.

According to the latest International Society of Heart and Lung Transplantation (ISHLT) guidelines, AR that is greater than mild should be addressed at the time of LVAD implant. AVR using a biologic valve should be performed, if necessary (class of recommendation: I, level of evidence: C).[5] Additionally, different aortic valve closure techniques might be considered in selected patients with more than mild AR (class of recommendation: IIb, level of evidence: C).[5] The EACTS expert consensus article suggests concomitant biological AVR in more than mild AR (class of recommendation: IIa, level of evidence: B) or use of a central coaptation stitch (class of recommendation: IIb, level of evidence: B).[6] Aortic valve closure, however, is not recommended (class of recommendation: III, level of evidence: C).[6] This discrepancy highlights the lack of evidence regarding the optimal technique and timing to address AR in LVAD patients. No specific recommendations are available on how to address mild AR. This issue is of particular concern, as in the INTERMACS registry preoperative mild AR was associated with a progression to moderate or more severe AR following LVAD implantation which, in turn, was associated with increased long-term mortality.[10]

Our study demonstrated that patients with preoperative mild-to-moderate AR who underwent concomitant biological AVR during LVAD implantation had similar survival rates compared with those without AVR. Despite non-significant outcomes, a slightly better outcomes among patients in the non-replacement group can be observed in long-term follow-up. The difference in survival might become more apparent in a larger sample size.

Patients undergoing a concomitant AVR suffered a significantly higher rates of major surgical bleeding complications occurring during the early postoperative period (Table S1). It is important to underline that concomitant

TABLE 3 Cox regression analysis for 2-year outcomes with LVAD+AVR as reference.

	HR	*p*-value	CI 95%
Mortality	1.47	0.181	0.84–2.58
Heart transplantation	0.88	0.852	0.24–3.29
Weaning	5.27	0.129	0.62–45.16
Major infection	0.98	0.941	0.559–1.75
Device malfunction	1.62	0.294	0.66–3.96
Pump thrombosis	0.12	0.046	0.02–0.96
Neurological dysfunction	1.42	0.377	0.65–3.10
Hemorragic stroke	1.71	0.463	0.41–7.18
Ischemic stroke	1.26	0.699	0.39–4.15
Major bleeding requiring surgery	4.59	0.051	0.99–21.24
Right heart failure	0.66	0.417	0.24–1.81

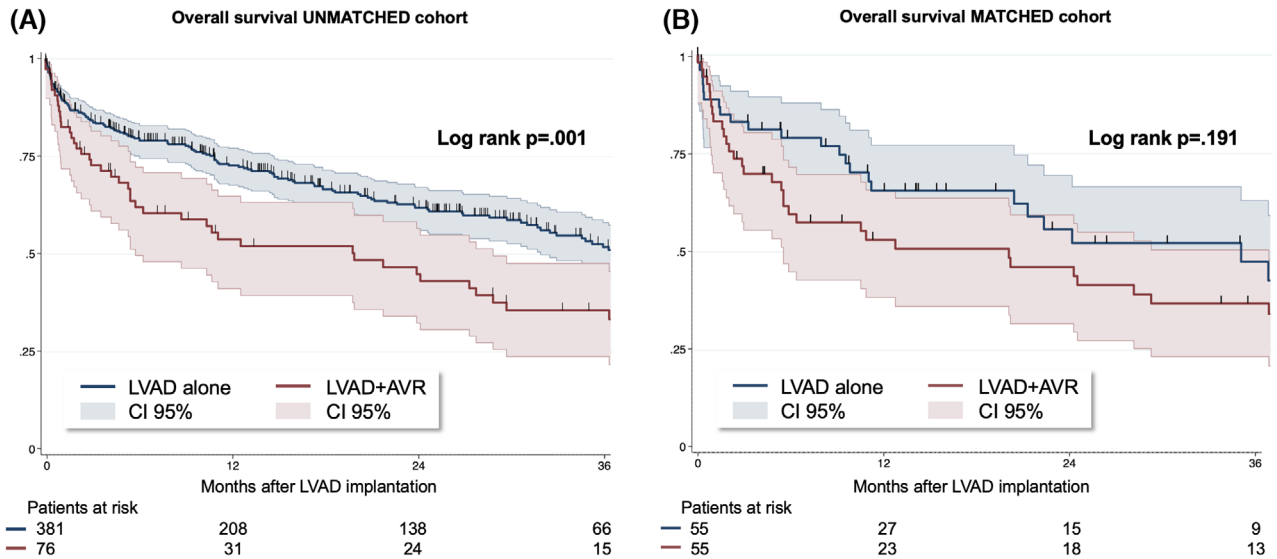

FIGURE 2 Kaplan–Meier estimates for survival in unmatched (A) and matched (B) cohorts. AVR, aortic valve replacement; LVAD, left ventricular assist device.

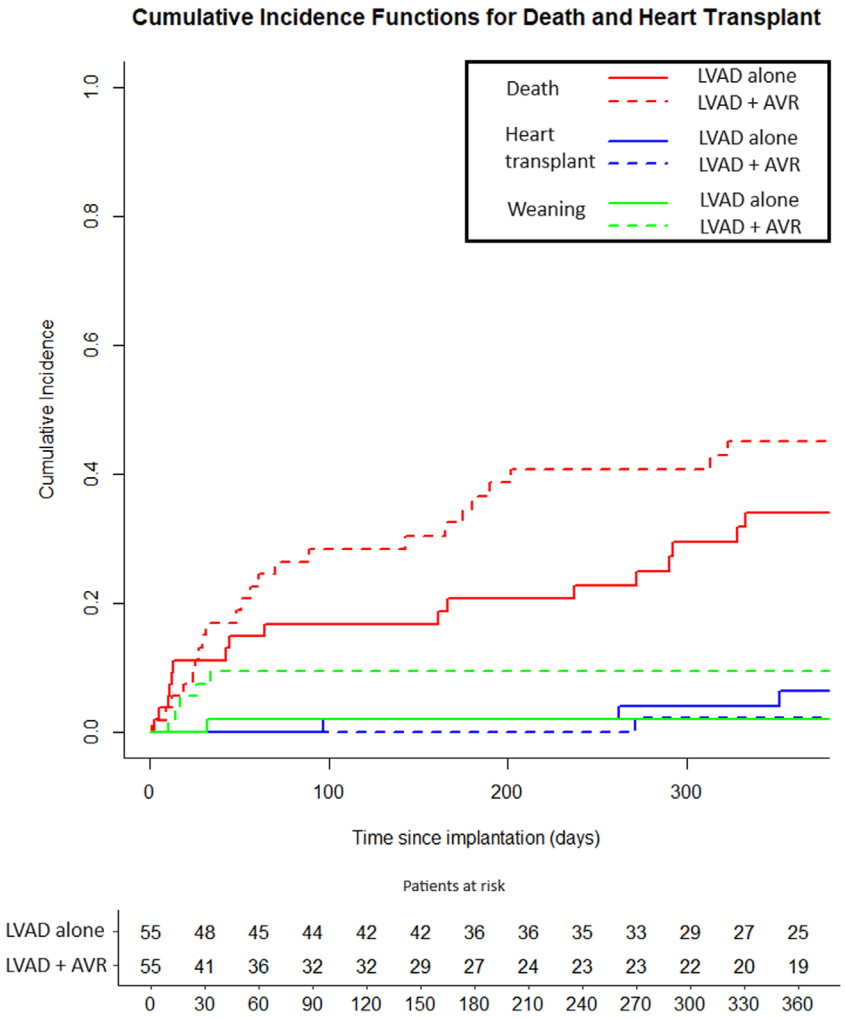

FIGURE 3 Cumulative incidence functions for competing outcomes (death, heart transplantation, weaning from support) in matched cohorts. AVR, aortic valve replacement; LVAD, left ventricular assist device.

AVR requires cardioplegia and cardiopulmonary bypass initiation, which can negatively impact outcomes, particularly in patients in a critical preoperative state or in cardiogenic shock. Additionally, patients who underwent AVR in our cohort had an increased risk of postoperative bleeding, likely due to the high-dose anticoagulation required for CPB establishment and the aortotomy line as an additional potential bleeding site. Therefore, careful attention should be paid to anticoagulation and bleeding management in the postoperative care of patients undergoing LVAD implantation with concomitant AVR.[8]

4.1 | Thromboembolic events

The decreased excursion of the leaflets secondary to LVAD unloading potentially leads to blood stasis and thrombus formation in the aortic root.[14] We observed a higher incidence of pump thrombosis among patients with unaddressed AR, which manifested mainly in the early postoperative course. This finding apparently contrasts with previous data suggesting a higher incidence of thromboembolic complications, especially aortic root thrombosis in LVAD patients undergoing AVR.[15] The subgroup analysis of patients in the matched cohort revealed a numerically higher incidence of pump thromboses in patients treated with HW (12.3% for HW vs. 2.2% for HM3 $p=0.057$), which is in the line with previous data and might explain our observations.[16] However, the results are beyond the burden of statistical significance (Table S2). The question of whether these observations remain of clinical significance among patients treated exclusively with HMIII is yet to be answered. It is important to underline that we observed no statistically significant difference in antiplatelet and anticoagulation medication at discharge in patients with and without AVR (Table S3).

4.2 | Alternative approaches for concomitant AR management

We excluded patients who underwent concomitant AV repair; therefore, we cannot elaborate on whether this approach may have different peri-operative and long-term

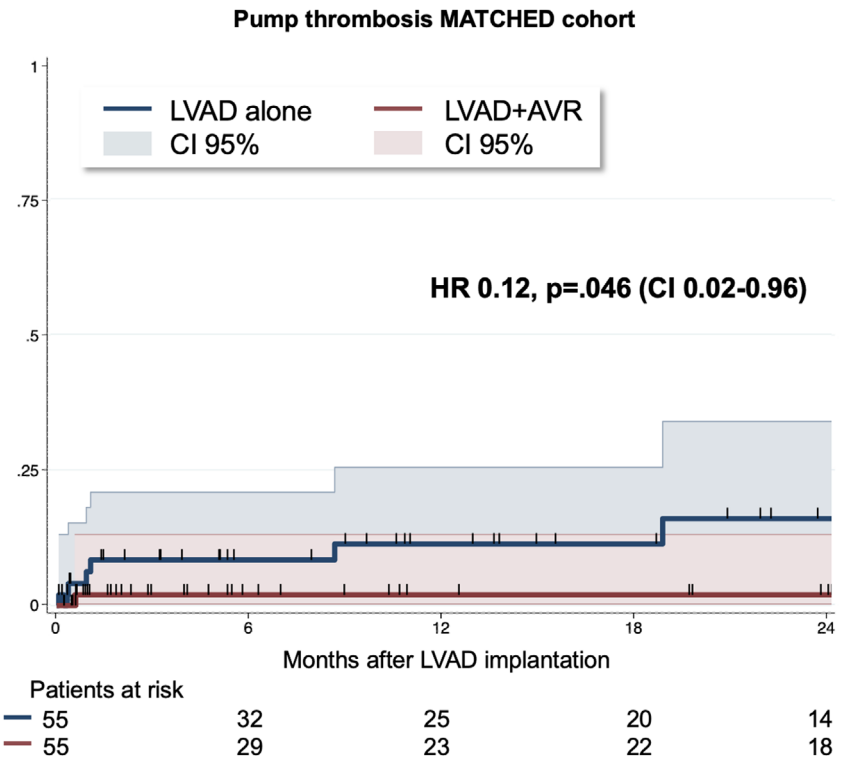

FIGURE 4 Kaplan–Meier estimates for incidence of pump thrombosis (A) and major bleeding (B) in matched cohorts. AVR, aortic valve replacement; LVAD, left ventricular assist device.

outcomes. Aortic valve repair is an alternative to valve replacement, typically involving the application of central or commissural stitches to achieve leaflet fusion or sufficient leaflet coaptation and reduce the degree of AR.[17] While this approach is less time-consuming and preserves the native valve, LVAD patients who undergo aortic valve repair have been shown to have a higher risk of thromboembolic complications and pump thrombosis.[17]

Aortic valve closure, whether performed concomitantly during LVAD implantation or percutaneously at a later stage, is considered a bailout option for patients ineligible for alternative approaches to address AR.[7] It is, therefore, rarely performed. After complete valve closure, patients have significantly higher mortality compared with those who undergo AV replacement or repair.[7] Aortic valve closure is not recommended in LVAD patients with relevant AR, especially as any significant device malfunction can lead to immediate cardiac arrest as patients on LVAD cannot generate their own cardiac output.[6,7]

4.3 | Transcatheter aortic valve implantation

In recent years, transcatheter aortic valve implantation (TAVI) has been increasingly applied to treat AR in patients on LVAD support.[18] This approach avoids surgical AVR in previously operated patients on anticoagulation, which is especially important as the outflow graft anastomosis to the ascending aorta lies in direct proximity to the standard aortotomy incision lines and has to be freed from adhesions.[12] However, TAVI in the context of LVAD is not suitable for every patient. An enlarged aortic annulus and absence of calcifications can impede the secure anchoring of the TAVI prosthesis and can even lead to its migration.[12] In this context, special implantation techniques including pre-stenting of the aorta and using or valve-in-valve approach can be performed.[18]

4.4 | Limitations

The results of the present investigation should be interpreted in light of several limitations. First, this is a propensity-matched analysis of clinical practice data. Despite having adjusted for many variables, we cannot exclude an impact of unmeasured confounding factors, and randomized studies to definitively assess the impact of AVR in patients with preoperative AR are warranted. Second, preoperative AR was assessed according to clinical practice. While we cannot exclude variations in AR assessment between participating institutions, this is reflective of real-world practice. Third, post-LVAD AR degrees and AR long-term trajectories were not available; therefore, we are unable to elaborate on the impact of AVR on these surrogate outcomes, previously associated with adverse long-term outcomes in mechanically unloaded patients. The missing data on AR progression and its impact on non-AVR patients represents an important limitation, which should be considered in future studies.

Fourth, we cannot exclude type II errors due to the study sample size. With the limits of post hoc power analysis, based on the study sample size we estimated a power of 57.8% to assess a significant difference in 5-year mortality between the groups. While suboptimal, this study represents the largest propensity-matched comparison of alternative management strategies among LVAD patients with preoperative mild-to-moderate AR.

5 | CONCLUSION

Patients with mild-to-moderate AR who undergo concomitant biological AVR during LVAD implantation exhibit similar survival rates compared with those in whom the aortic valve is left untreated. Patients with concomitant AVR have a higher risk of bleeding complications in the early postoperative period but are less likely to develop pump thrombosis. Further investigations are needed to compare different approaches to AR therapy in LVAD patients. These studies would provide valuable insights into the optimal management strategy for AR in the context of LVAD therapy.

AUTHOR CONTRIBUTIONS

Gregorio Gliozzi: data curation, methodology, visualization, writing – original draft, writing – review and editing; **Gaik Nersesian:** data curation, methodology, visualization, writing – original draft, writing – review and editing; **Guglielmo Gallone:** methodology, writing – original draft, writing – review and editing; **Felix Schönrath:** writing – review and editing, supervision; **Ivan Netuka:** writing – review and editing; **Daniel Zimpfer:** writing – review and editing; **Theo de By:** data curation, writing – review and editing; **Gloria Faerber**: writing – review and editing; **Antonio Spitaleri**: writing – review and editing; **Igor Vendramin**: writing – review and editing; **Jan Gummert:** writing – review and editing; **Volkmar Falk**: writing – review and editing; **Bart Meyns:** writing – review and editing; **Mauro Rinaldi:** writing – review and editing; **Evgenij Potapov:** writing – original draft, writing – review and editing, supervision; **Antonio Loforte:** writing – original draft, writing – review and editing, supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no relevant conflicts of interests within the submitted work.

DATA AVAILABILITY STATEMENT

The data analyzed in the study were provided by the EUROMACS database of the EACTS and cannot be provided to a third party without the permission of EUROMACS.

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SUPPORTING INFORMATION

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

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