Clinical impact and 'natural' course of uncorrected tricuspid regurgitation after implantation of a left ventricular assist device: an analysis of the European Registry for Patients with Mechanical Circulatory Support (EUROMACS)

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ABSTRACT

Objectives

Data on the impact and course of uncorrected tricuspid regurgitation (TR) during left ventricular assist device (LVAD) implantation are scarce and inconsistent. This study explores the clinical impact and natural course of uncorrected TR in patients after LVAD implantation.

Methods

The European Registry for Patients with Mechanical Circulatory Support was used to identify adult patients with LVAD implants without concomitant tricuspid valve surgery. A mediation model was developed to assess the association of TR with 30-day mortality via other risk factors. Generalized mixed models were used to model the course of post-LVAD TR. Joint models were used to perform sensitivity analyses.

Results

A total of 2496 procedures were included (median age: 56 years; men: 83%). TR was not directly associated with higher 30-day mortality, but mediation analyses suggested an indirect association via preoperative elevated right atrial pressure and creatinine (P = 0.035) and bilirubin (P = 0.027) levels. Post-LVAD TR was also associated with increased late mortality [hazard ratio 1.16 (1.06–1.3); P = 0.001]. On average, uncorrected TR diminished after LVAD implantation. The probability of having moderate-to-severe TR immediately after an implant in patients with none-to-mild TR pre-LVAD was 10%; in patients with moderate-to-severe TR pre-LVAD, it was 35% and continued to decrease in patients with moderate-to-severe TR pre-LVAD, regardless of pre-LVAD right ventricular failure or pulmonary hypertension.

Conclusions

Uncorrected TR pre-LVAD and post-LVAD is associated with increased early and late mortality. Nevertheless, on average, TR diminishes progressively without intervention after an LVAD implant. Therefore, these data suggest that patient selection for concomitant tricuspid valve surgery should not be based solely on TR grade.

ABBREVIATIONS

CI	**Confidence interval**
EUROMACS	**European Registry** for Patients with Mechanical Circulatory Support
LVAD	**Left ventricular** assist device
RA	**Right atrium**
RV	**Right ventricular**
RVF	**Right ventricular** function
SEM	**Structural equation** model
TR	**Tricuspid regurgitation**

INTRODUCTION

Tricuspid regurgitation (TR) is common in patients with end-stage heart failure undergoing left ventricular assist device (LVAD) implant [1]. Most studies addressing TR after an LVAD implant focus on comparing patients with and without tricuspid valve surgery concomitant with an LVAD implant [2]. However, it is still unclear what the 'natural' course of post-LVAD TR is, and which patients will potentially benefit most from concomitant tricuspid valve surgery. TR has been reported to decrease after an LVAD implant [3–5], but it is not known whether this occurs in all patients uniformly or only in subgroups. Assessing the course and clinical impact of TR after LVAD is important, because it may provide a rationale to perform, or to refrain from performing, tricuspid valve surgery during LVAD implantation. Therefore, this study explores the evolution of TR after an LVAD implant in patients who did not undergo concomitant tricuspid valve surgery. Furthermore, we explored the impact of the preoperative and postoperative TR grade on early (30-day) and late mortality using the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database. We hypothesized that pre-LVAD TR is part of an interplay with other risk factors [e.g. right ventricular (RV) failure, pulmonary hypertension, renal and/or liver function] and that TR may be associated with 30-day mortality by increasing these risk factors. Therefore, we performed a mediation analysis. To account for the dynamic nature of TR after LVAD implantation and potential survival bias, the longitudinal evolution of TR was modelled and linked to survival under the joint modelling framework.

METHODS

Data source

EUROMACS is a registry of the European Association for Cardio- Thoracic Surgery. In this registry, all relevant clinical, echocardiographic haemodynamic and laboratory parameters of patients who require mechanical circulatory support have been collected prospectively since January 2011. Participating centres (Supplementary Material, Table S1) were allowed to enter

data before 2011 retrospectively. Detailed descriptions of the database and collection procedure were provided previously [6].

Patients

All patients operated between 2005 and 2018 were identified. Patients under 18 years of age, with no recorded pre-LVAD TR grade and with concomitant tricuspid valve surgery were excluded from analysis (Supplementary Material, Fig. S1). Additionally, we excluded patients with a planned durable RV assist device, biventricular assist device or total artificial heart implant. Patients were followed until death or the end of the study. Patients were censored at heart transplant or explant.

Outcome

The main outcomes that were assessed were 30-day mortality, late mortality (defined as death after 30 days) and TR grade (5-point system: none–trivial–mild–moderate–severe).

Statistical analyses

Continuous data are presented as mean (standard deviation) (Gaussian distribution) or median (interquartile range) (non-Gaussian distribution). Categorical data are presented as frequencies (percentage). Comparisons among continuous variables were made with the one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Continuous data outside 3 standard deviations were considered erroneous and removed (Supplementary Material, Table S2). Comparisons of categorical variables were made with the χ^2 test or with the Fisher's exact test, as appropriate. Due to multiple testing (34 tests), a Bonferroni correction was applied, considering $P = 0.0014$ as significantly different. Data with <50% missing values were imputed using multiple imputation (Supplementary Material, Text S1 and Tables S3 and S4).

Univariable and multivariable ordinal proportional odds regression models were used to explore determinants associated with TR at baseline. A forwards stepwise modelling strategy was applied in which all covariates with *P*-value <0.10 were entered into the multivariable model.

We hypothesized that the effect of TR on 30-day mortality was mediated by well-known risk factors. Therefore, mediation analysis with a structural equation model (SEM) was performed. The selected variables incorporated into the model included right atrial pressure, creatinine and bilirubin levels and the international normalized ratio (all were incorporated as continuous variables), and were based on previous literature [7–9]. Using SEM, one can compute direct and indirect associations (associations via other variables) on outcomes by specifying a pathway. The conceptual pathways are shown in Fig. 1. A comprehensive explanation of mediation analyses with SEM is provided in Supplementary Material, Text S1. Late mortality was calculated and visualized using the Kaplan–Meier method, and a log-rank test was performed to compare strata. Modified Clark's C, denoted as C*, was used to calculate completeness of follow-up [10].

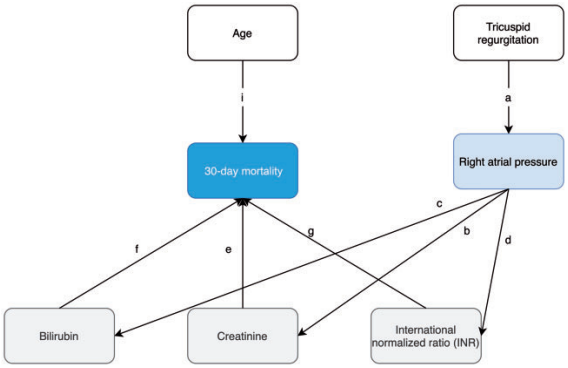


Figure 1: Path diagram of the structural equation model with table of regressions. Paths are indicated by labels a–h, which correspond to the labels in Table 3. Arrows denote the direction of the regression [e.g. tricuspid regurgitation predicts right atrial pressure (path a), which in term predicts creatinine level (path b)]. INR: internationalized normal ratio.

Evolution of tricuspid regurgitation

Logistic mixed models were used to assess longitudinal evolution of TR grade over time (Supplementary Material, Text S1). Subgroup analysis was done for patients with moderate-to-severe TR pre-LVAD. In these patients, separate models containing RV ejection fraction impairment, pulmonary hypertension, pre-LVAD mitral regurgitation, pre-LVAD rhythm, duration of cardiac diagnosis (time elapsed since first cardiac diagnosis) and pre-LVAD right atrium (RA) pressure were developed to investigate the association of these variables with the course of post- LVAD TR. All analyses were done in R (version 3.6.3) (R Project for Statistical Computing: https://www.r-project.org/).

Sensitivity analyses

It is possible that a portion of the dropout of patients is caused by deaths due to TR, resulting in informative censoring (survival bias). In this case, the dropout is not random, thus leading to bias in the mixed model results. Therefore, a sensitivity analysis was performed in which the dynamic longitudinal evolution of TR was inserted into a Cox model under the joint modelling framework. Modelling these entities together alleviates possible bias due to missing values that are missing not at random (i.e. survival bias). The other baseline covariates inserted in the Cox model were based on information from previously published articles; only the current value parameterization of TR was investigated [11, 12]. Several other sensitivity analyses were conducted to test the robustness of the model estimates. These analyses included: exclusion of patients with pre-LVAD extracorporeal membrane oxygenation and patients with postoperative durable RV assist device. Additionally, centre heterogeneity was accounted for in the random effects by performing a mixed model with patients nested in hospitals.

RESULTS

The database contained 3948 procedures. After applying the exclusion criteria, 2411 patients undergoing 2496 procedures were included (Supplementary Material, Fig. S1). In total, 1892 patients had recorded late follow-up (>30 days) with a median of 1.3 interquartile range (0.5–2.6) years, with a completeness of 85% (C*).

Baseline characteristics

Baseline characteristics stratified to TR grade are presented in Table 1. Nearly all the baseline characteristics differed significantly between patients with none-to-mild TR compared to those with moderate-to-severe TR, even after the Bonferroni correction. Seventy-three potential determinants were tested in univariable ordinal regression models, and 12 determinants remained significant in multivariable analyses. Among others, a higher TR grade at baseline was significantly associated with more peripheral oedema, other pulmonary and mitral valve dysfunction, higher RA pressure, more loop diuretics and worse right ventricular function (RVF) (Supplementary Material, Table S5).

Table 1: Baseline characteristics stratified to pre-left ventricular assist device TR grade

	None-to-mild TR	Moderate-to-severe TR	*P*-value
Demographics			
n	1690	806	
Age (years)	56.00 (47.00–62.00)	56.00 (46.00–62.00)	0.71
Male gender, *n* (%)	1416 (83.8)	657 (81.5)	0.17
Body surface area (m^2)	1.99 (1.83–2.12)	1.92 (1.78–2.08)	<0.001
White race, *n* (%)	1234 (86.3)	626 (86.2)	0.97
Ischaemic aetiology HF, *n* (%)	620 (43.3)	251 (35.2)	<0.001
≥2 Years since first diagnosis	811 (60.3)	494 (70.4)	<0.001
Destination therapy	294 (17.5)	128 (15.9)	0.36
Ascites	96 (8.5)	94 (16.9)	<0.001
Rhythm, *n* (%)			0.001
Sinus	796 (58.1)	341 (49.6)	
Atrial fibrillation	225 (16.4)	130 (18.9)	
Paced	28 (2.0)	28 (4.1)	
Other	322 (23.5)	189 (27.5)	
INTERMACS profile, *n* (%)			<0.001
1	238 (14.7)	79 (10.1)	
2	538 (33.3)	259 (33.2)	
3	457 (28.3)	205 (26.3)	
≥4	384 (23.7)	237 (30.4)	

Table 1: Baseline characteristics stratified to pre-left ventricular assist device TR grade (continued)

	None-to-mild TR	Moderate-to-severe TR	*P*-value
IABP, *n* (%)	173 (12.0)	58 (8.1)	0.008
ECMO, *n* (%)	183 (11.2)	50 (6.5)	<0.001
Ventilator (%)	224 (15.6)	52 (7.3)	<0.001
Medication, *n* (%)			
Loop diuretics	1060 (78.8)	588 (86.7)	<0.001
Use of ≥3 inotropes	182 (13.0)	93 (13.3)	0.91
Laboratory values			
Serum creatinine (mg/dl)	106.00 (84.00–146.00)	106.00 (82.00–144.00)	0.43
ASAT (U/l)	33.00 (22.00–70.00)	30.00 (21.00–55.00)	0.002
Total bilirubin (mg/dl)	1.18 (0.74–1.90)	1.40 (0.90–2.27)	<0.001
Albumin (g/dl)	499.91 (410.07–579.60)	521.64 (440.50–579.60)	0.010
Haemoglobin (g/dl)	12.00 (10.30–13.60)	11.75 (10.20–13.30)	0.17
Haemodynamics			
RA pressure (mmHg)	10.00 (6.00–14.00)	11.00 (8.00–16.00)	<0.001
PCWP (mmHg)	24.00 (17.00–30.00)	25.00 (20.00–30.00)	0.005
PAP, systolic (mmHg)	51.00 (38.00–62.00)	53.00 (41.75–65.00)	0.003
Echocardiography			
TAPSE (mm)	15.00 (12.00–17.00)	14.00 (11.00–16.00)	<0.001
No aortic regurgitation, *n* (%)	1043 (67.8)	397 (54.8)	<0.001
Severe mitral regurgitation, *n* (%)	162 (11.1)	223 (30.3)	<0.001
LVEF grade <20%, *n* (%)	779 (57.2)	431 (64.2)	0.010
RVF			<0.001
Normal	279 (24.4)	89 (15.6)	
Mild	334 (29.2)	105 (18.4)	
Moderate	389 (34.1)	274 (48.1)	
Severe	140 (12.3)	102 (17.9)	

Normally distributed variables are presented as means (standard deviations) and not normally distributed variables are medians (interquartile range).

ASAT: aspartate aminotransferase; ECMO: extracorporeal membrane oxygenation; HF: heart failure; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVEF: left ventricular ejection fraction; PAP: pulmonary atrial pressure; PCWP: pulmonary capillary wedge pressure; RA: right atrium; RVF: right ventricular function; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

Pre-left ventricular device tricuspid regurgitation and early mortality

In total, 271 (10.9%) patients died within 30 days. The 30-day mortality was comparable between patients with none-to-mild TR versus moderate-to-severe TR (10.8% vs 10.9%; *P* = 0.99). Procedural and hospital outcomes in patients with none-to-mild and moderate-to-severe TR are presented in Table 2.

Table 2: Procedural characteristics and early outcomes

	None-to-mild TR	Moderate-to-severe TR	*P*-value
Device			0.005
HeartMate II LVAS	484 (29.5)	186 (24.2)	
HeartWare HVAD	841 (51.3)	452 (58.8)	
HeartMate3	241 (14.7)	95 (12.4)	
Other	74 (4.5)	36 (4.7)	
CPB time	79.00 (58.00–108.00)	80.00 (60.00–111.00)	0.22
ICU/CCU stay (days)	10.00 (5.00–23.00)	10.00 (5.00–22.00)	0.81
Hospital stay (days)	29.00 (21.00–43.00)	31.00 (21.00–44.00)	0.18
Discontinuation of IV inotropes (days) (%)			0.30
1–7	558 (55.0)	295 (58.4)	
8–13	184 (18.1)	97 (19.2)	
14–27	168 (16.6)	73 (14.5)	
>27	103 (10.1)	38 (7.5)	
Temporary RVAD	66 (3.9)	39 (4.8)	0.32
30-Day mortality, *n* (%)	184 (10.9)	87 (10.8)	>0.99

Normally distributed variables are presented as means (standard deviations) and not normally distributed variables are medians (interquartile ranges).
CCU: coronary care unit; CPB: cardiopulmonary bypass; ICU: intensive care unit; IV: intravenous; LVAS: left ventricular assist system; RVAD: right ventricular assist device; TR: tricuspid regurgitation.

The conceptual paths of the SEM are shown in Fig. 1 and the regression estimates and significance, in Table 3. Overall, the model fitted well, as indicated by the fit indices in Table 3. Although the total effect of TR on 30-day mortality was insignificant, the path TR to RA pressure to creatinine was significantly associated with 30-day mortality ($P = 0.035$) (Table 3). Additionally, the path TR to RA pressure to bilirubin was significantly associated with 30-day mortality ($P = 0.027$) (Table 3). However, the path TR to RA pressure to international normalized ratio was not associated with 30-day mortality ($P = 0.057$) (Table 3).

Pre-left ventricular assist device tricuspid regurgitation and late mortality

A total of 626 of 2410 thirty-day survivors died during the long-term (>30 days) follow-up period. Survival after 30 days, stratified to none-to-mild TR versus moderate-to-severe TR at baseline, is presented in Fig. 2 and differed significantly between strata ($P = 0.015$).

The Spearman correlation between pre-LVAD TR and pre-LVAD RVF was 0.22 ($P < 0.001$). Therefore, these variables were combined into 1 variable. In Fig. 3 the population is stratified to different levels of right ventricle dysfunction with or without significant TR. Three years after implant, the Kaplan–Meier survival estimate was lower in patients with both moderate-to-severe TR and RVF [54%, 95% confidence interval (CI) 47–61] compared to patients with

good RVF and none-to-mild TR (68%, 95% CI 64–73). In a sensitivity analysis with only complete cases, the group with both moderate-to-severe TR and RVF pre-LVAD had survival and hazard ratios comparable to those of patients with none-to-mild TR and moderate-to-severe RVF pre-LVAD (Supplementary Material, Figs S2 and S3). RVF did seem to be conditionally missing based on observed variables (Supplementary Material, Table S6).

Table 3: Estimates of the paths of the structural equation model

Regressions	Path[a]	β-Estimate (95% CI)	*P*-value
Mortality ~			
Bilirubin	f	0.056 (0.003–0.080)	>0.001
Creatinine	e	0.001 (0.001–0.001)	>0.001
INR	g	0.121 (0.033–0.209)	0.007
Age	i	0.016 (0.010–0.021)	>0.001
TR per 1 grade	h	-0.047 (-0.101 to 0.007)	0.087
RA pressure ~			
TR	a	0.805 (0.464–1.146)	>0.001
Bilirubin ~			
RA pressure	c	0.048 (0.023–0.072)	0.002
Creatinine ~			
RA pressure	b	1.159 (0.341–1.977)	0.015
INR ~			
RA pressure	d	0.011 (0.003–0.019)	0.011
Indirect effects of TR			
Direct effect	h	-0.047 (-0.101 to 0.007)	0.087
RA pressure—creatinine	a–b–e	0.001 (0.001–0.001)	0.035
RA pressure—bilirubin	a–c–f	0.002 (0.001–0.003)	0.027
RA pressure—INR	a–d–g	0.001 (0.000–0.001)	0.058
Total effect		-0.043 (-0.098 to 0.012)	0.12
Fit measures			
χ^2		>0.001	
Non-normed fit index		0.95	
Comparative fit index		0.98	
Root mean square error of approximation (95% CI)		0.051 (0.037–0.065)	
Standardized root mean square residual		0.065	

[a]Paths correspond to the paths specified in Fig. 1.

CI: confidence interval; INR: internationalized normal ratio; RA: right atrium; TR: tricuspid regurgitation.

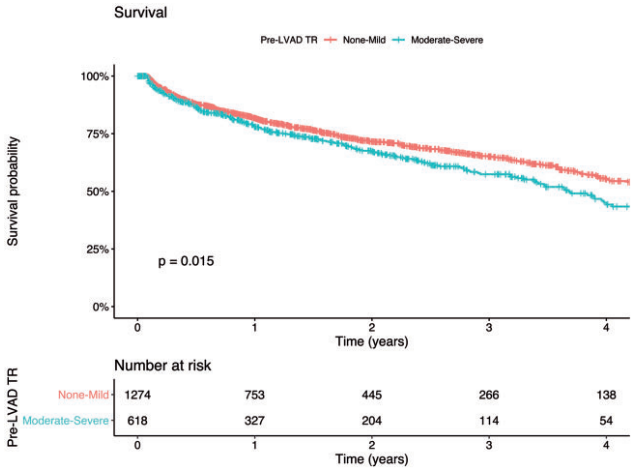


Figure 2: Kaplan–Meier curve of late survival (includes only 30-day survivors) after LVAD implant stratified to pre-LVAD TR grade. LVAD: left ventricular assist device; TR: tricuspid regurgitation.

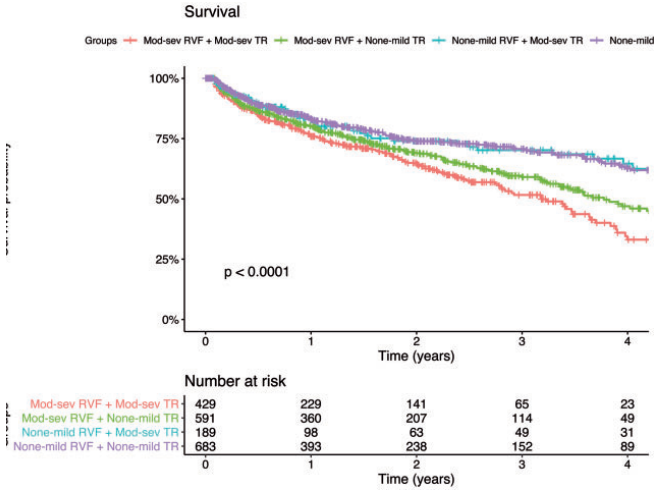


Figure 3: Kaplan–Meier curve of late survival (includes only 30-day survivors) after left ventricular assist device implant stratified to pre-left ventricular assist device TR grade with or without right ventricular dysfunction. Of note, data from the first imputed data set are used. RVF: right ventricular failure, mod: moderate; sev: severe; TR: tricuspid regurgitation.

Evolution of tricuspid regurgitation

During the follow-up period, 914 (48%) patients had 1 or more echocardiograms, with 3113 echocardiograms in total (mean 3.4, range 1–8) (Supplementary Material, Fig. S4). Figure 4A presents the probabilities of having moderate-to-severe TR after an LVAD implant, stratified to pre-LVAD TR severity. The odds of moderate-to-severe TR after an LVAD implant decreased over

time and became comparable after ~1.4 years in patients with moderate-to-severe TR pre-LVAD versus patients with none-to-mild TR pre-LVAD.

In patients with moderate-to-severe TR pre-LVAD, no significant differences were observed in the course of TR post-LVAD among different levels of pre-LVAD RV ejection fraction impairment, pre-LVAD pulmonary hypertension, pre-LVAD mitral regurgitation, pre-LVAD rhythm, duration of cardiac diagnoses, an implantable cardioverter-defibrillator or pre-LVAD RA pressure (Supplementary Material, Figs S5–S11), except for patients with idiopathic dilated myopathy. In these patients post-LVAD TR decreased faster compared to patients with other diagnoses (Fig. 4B), but the odds of moderate-to-severe TR became comparable after ~2.5 years. The difference in the odds of moderate-to- severe TR was observed predominantly in patients with other diagnoses (e.g. myocarditis and toxic or postpartum myopathy) compared to patients with idiopathic dilated myopathy (Fig. 4B). To gain insight into the possibility of informative censoring (survival bias), the longitudinal evolution of TR was jointly modelled with a survival model and compared with the estimates of the mixed model (Supplementary Material, Table S7). Some sensitivity was observed in both the effect size and standard errors (Supplementary Material, Table S8); however, the direction of the effect did not change, nor did the significance. Hence, the decrease in the probability of TR after LVAD cannot be solely explained by survival bias.

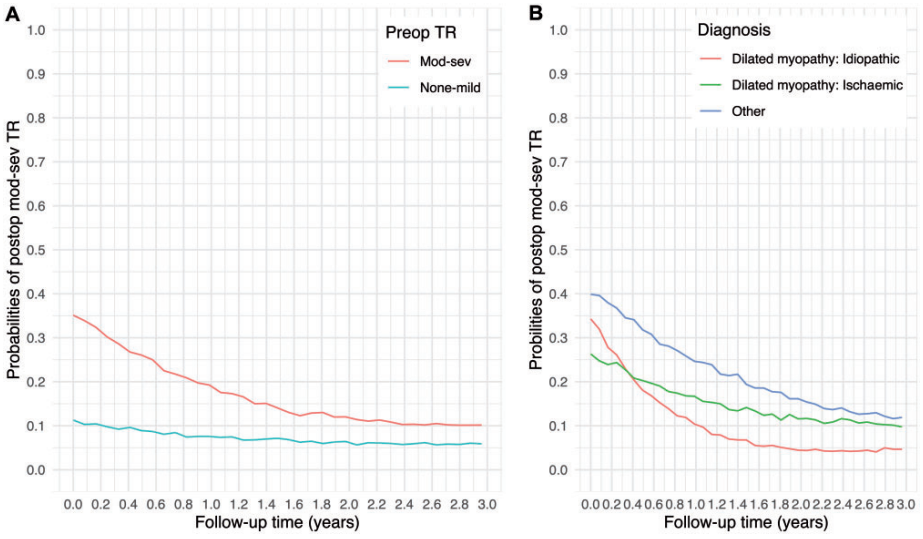


Figure 4: (A) Effects plot of the probability of TR after left ventricular assist device (LVAD) implant stratified to pre-LVAD. (B) Effects plot of the evolution of TR after LVAD (in patients with moderate-to-severe TR pre-LVAD) TR. mod-sev: moderate to severe; postop: postoperative; preop: preoperative; TR: tricuspid regurgitation.

Post-left ventricular assist device tricuspid regurgitation and mortality

Moderate-to-severe TR post-LVAD was associated with increased mortality (hazard ratio 1.16, 95% CI 1.06–1.30; *P* = 0.001), as estimated by the joint model adjusted for several baseline variables including RV dysfunction (Supplementary Material, Table S7).

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the outcomes. Estimates of the evolution of TR did not change considerably if patients with pre-LVAD ECMO were excluded (Supplementary Material, Tables S9 and S10). Including the centre as a random effect did not change estimates (Supplementary Material, Table S11). Furthermore, centres that tended to repair the tricuspid valve in the setting of moderate-to-severe TR pre-LVAD had similar evolutions of post-LVAD TR in patients without tricuspid valve intervention compared to centres that were not inclined to repair the tricuspid valve (Supplementary Material, Fig. S12). Excluding patients with an RV assist device implant during the follow-up period did not considerably change the estimates of the longitudinal evolution or of survival (Supplementary Material, Tables S12 and S13).

DISCUSSION

This study explores the clinical impact of pre-LVAD and post-LVAD TR on 30-day and late mortality and the course of post- LVAD TR in the survivors. Interesting observations were noted: both pre- and post-LVAD TR seemed to be associated with reduced survival. Nevertheless, on average, TR resolved ‘spontaneously’ after an LVAD implant, which was not solely due to survival bias.

Early and late mortality

We hypothesized that TR is part of an entire pathway that may lead to higher 30-day mortality, i.e. mediated by other variables. To gain insight in this hypothesis, we developed a conceptual model with several paths (Fig. 1). When this model was tested, it fit well, suggesting that TR may not be directly related to 30-day mortality but that by increasing other risk factors it is indirectly associated with 30-day mortality. Notably, we did not include RVF in the pathways because of the circular relation with the severity of TR, which cannot be modelled. The impaired RVF can lead to TR due to RV/annulus dilation, but also the other way around due to volume or pressure overload [7]. Furthermore, TR was chosen in the model because TR is associated with renal dysfunction in the literature [9].

The investigators of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) found TR to be associated with reduced late survival [13]. Assessing the Kaplan–Meier curve of the combined variables, it seems that pre-LVAD-impaired RVF is the

driving factor in late mortality after an LVAD implant; however, impaired RVF accompanied by TR resulted in an even worse survival. These data may suggest that pre-LVAD TR in the setting of impaired RVF adds extra late risk, which can partly be explained by the negative spiral that ensues when TR is present in the setting of impaired RVF, leading to more dysfunction. Furthermore, TR together with impaired RVF is associated more with renal failure than with isolated TR or impaired RVF alone [14, 15]. Nevertheless, it has to be noted that confounding may be present here, and, in a sensitivity analysis with complete cases, pre-LVAD RVF did seem to be the driving factor regardless of pre-LVAD TR. RVF was conditionality missing upon other observed baseline variables, suggesting the missing at random mechanism. Multiple imputation is more valid in missing-at-random scenarios [16].

Evolution of tricuspid regurgitation

TR decreases without intervention after an LVAD implant, and this decrease is not solely based on patients dying of TR. Overall, an immediate decrease of ~65% is observed from moderate-to-severe TR to non-to-mild TR in patients with moderate-to-severe TR pre-LVAD. Other studies comparing point estimates over time noted comparable results [1, 4]. The decrease in TR may be explained by the fact that LVAD support reduces pulmonary pressures, subsequently reducing the pressure overload of the right ventricle, which leads to right ventricle remodelling and regression of the tricuspid valve annulus dilatation. The remodelling in turn leads to resolution of functional TR.

Furthermore, it seems that TR decreases more quickly in patients with idiopathic cardiomyopathy compared to other cardiomyopathies. However, later in the follow-up period, this difference disappears. Furthermore, these results can be explained by confounding because the models were univariable, and some misclassifications in TR grade will be present, which can bias outcome in the small subgroups.

Clinical implications and rationale for eventual tricuspid valve surgery

The observations of this study in respect to concomitant tricuspid valve surgery can be interpreted in 2 ways. First, one can argue that concomitant surgery of the tricuspid valve is warranted, because both preoperative and postoperative TR are associated with increased mortality. It has to be noted that this study by design cannot establish a causal relationship between TR and mortality, and TR may just be a marker of significant RVF. Second, one can argue that a less aggressive strategy is warranted because, on average, the TR will resolve after LVAD implantation without any further intervention.

Current guidelines advise consideration of tricuspid valve surgery in the presence of moderate or severe TR at baseline. Current practice notwithstanding, we may be overtreating patients with unnecessary concomitant tricuspid valve surgery if we follow the guidelines. This deficit also may explain why previous studies comparing patients with and without concomitant tricuspid valve surgery were unable to find an effect [2]. Some patients will not benefit because

TR will resolve without an intervention. Therefore, the key point seems to be appropriate patient selection, taking into account the aetiology of TR, the severity of RV dysfunction and the underlying myocardial disease when deciding to perform concomitant surgery. Anwer et al. [17] proposed that atrial fibrillation should be included in this decision process. We were not able to show a significant effect of pre-LVAD atrial fibrillation on the odds of significant TR post-LVAD with the subgroup analyses, but there were only a few patients in the atrial fibrillation group. Functional TR has a chance to reduce spontaneously, whereas primary TR (e.g. caused by a pacemaker or an implantable cardioverter-defibrillator lead) probably will not. Furthermore, functional TR has not only been caused by tricuspid valve annular dilatation but also by valve tethering [18]. In the case of severe tethering, tricuspid annuloplasty may not be enough to reduce TR [19].

Future perspectives

Future studies should focus on understanding the different mechanisms and concomitant factors contributing to significant TR and finding the appropriate predictors of TR after LVAD implantation, preferably in a longitudinal prospective dedicated data set encompassing RV functional and dimensional, pulmonary and haemodynamic parameters. Therefore, we recently set up the Serial Multiparametric Evaluation of Right Ventricular Function After Left Ventricular Assist Device Implantation (EuroEchoVAD) study (see clinicaltrails.org, NCT03552679) to investigate the evolution of RVF, TR and other echocardiographic parameters before and after LVAD implantation. The findings of the study will enhance the prediction of the early and late development of postoperative RVF, the course of TR severity and the subsequent mortality and morbidity. Furthermore, novel transcatheter devices to treat tricuspid valve regurgitation are on the horizon. These devices have the potential to become interesting addenda in the treatment of functional TR in the setting of LVAD implantation. However, several challenges need to be addressed before they can enter daily clinical practice [20].

Limitations

This study has several limitations common to retrospective registry

analyses. EUROMACS is not designed to address the specific questions in this study. Therefore, there is a limited amount of data collected with a focus on the right ventricle, or these data are not uniformly collected. Furthermore, it has to be emphasized that misspecification may be present in a registry and that follow-up is suboptimal, which can introduce bias. We prevented more loss of data by imputation of the missing data in order to generate more power in the analysis. Nevertheless, some variables could not be imputed due to excessive missingness, and we could not use the longitudinal trajectory of TR in the imputation model. Additionally, follow-up data on TR were not collected at prespecified, regular intervals and assessing TR remains challenging [21]. However, we used mixed models, which can handle these unstructured data sets, and TR was dichotomized in these models to create a more robust measurement.

Unfortunately, in some subgroups, the sample size was small, and it was not known if patients had tricusispid valve surgery during the follow-up period. Advanced path models are used to shed some light on the impact of TR on 30-day mortality via other variables. However, due to the circular relationship with RVF, the true effect of TR on mortality may be impossible to estimate. Thereafter, the mechanism of TR was not recorded in the registry. Presumably, most of the TR is functional in nature, supported by the fact that TR is associated with RVF and its symptoms/treatment.

CONCLUSIONS

Moderate-to-severe TR pre-LVAD is positively correlated with worse RVF pre-LVAD and is associated with worse late mortality. However, overall, TR decreases after the LVAD is implanted, regardless of pre-LVAD pulmonary hypertension or right ventricle function. Hence, in the majority of the patients, additional tricuspid valve surgery may be redundant. Therefore, patient selection for concomitant tricuspid valve surgery should not be based solely on TR grade alone. Further studies are urgently needed to tackle this clinical dilemma in the era of durable mechanical circulatory support.

REFERENCES

1. Piacentino V 3rd, Williams ML, Depp T, Garcia-Huerta K, Blue L, Lodge AJ et al. Impact of tricuspid valve regurgitation in patients treated with implantable left ventricular assist devices. Ann Thorac Surg 2011;91: 1342–6; discussion 6–7.
2. Veen KM, Etnel JRG, Takkenberg J. Tricuspid valve disease: surgical outcome. In: Soliman OI, ten Cate FJ (eds). Practical Manual of Tricuspid Valve Diseases. Cham: Springer International Publishing, 2018, 305–27.
3. Morgan JA, Paone G, Nemeh HW, Murthy R, Williams CT, Lanfear DE et al. Impact of continuous-flow left ventricular assist device support on right ventricular function. J Heart Lung Transplant 2013;32:398–403.
4. Atluri P, Fairman AS, MacArthur JW, Goldstone AB, Cohen JE, Howard JL et al. Continuous flow left ventricular assist device implant significantly improves pulmonary hypertension, right ventricular contractility, and tricuspid valve competence. J Card Surg 2013;28:770–5.
5. Lee S, Kamdar F, Madlon-Kay R, Boyle A, Colvin-Adams M, Pritzker M et al. Effects of the HeartMate II continuous-flow left ventricular assist device on right ventricular function. J Heart Lung Transplant 2010;29: 209–15.
6. de By TM, Mohacsi P, Gummert J, Bushnaq H, Krabatsch T, Gustafsson F et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first annual report. Eur J Cardiothorac Surg 2015; 47:770–6; discussion 6–7.
7. Deo SV, Daly RC, Altarabsheh SE, Hasin T, Zhao Y, Shah IK et al. Predictive value of the model for end-stage liver disease score in patients undergoing left ventricular assist device implantation. ASAIO J 2013;59:57–62.
8. Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. J Am Coll Cardiol 2013;61: 313–21.
9. Maeder MT, Holst DP, Kaye DM. Tricuspid regurgitation contributes to renal dysfunction in patients with heart failure. J Card Fail 2008;14: 824–30.
10. Wu Y, Takkenberg JJ, Grunkemeier GL. Measuring follow-up completeness. Ann Thorac Surg 2008;85:1155–7.
11. Rizopoulos D. Joint Models for Longitudinal and Time-to-Event Data: With Applications in R. New York: Chapman and Hall/CRC, 2012.
12. Kirklin JK, Xie R, Cowger J, de By T, Nakatani T, Schueler S et al. Second annual report from the ISHLT Mechanically Assisted Circulatory Support Registry. J Heart Lung Transplant 2018;37:685–91.
13. Song HK, Gelow JM, Mudd J, Chien C, Tibayan FA, Hollifield K et al. Limited utility of tricuspid valve repair at the time of left ventricular assist device implantation. Ann Thorac Surg 2016;101:2168–75.
14. Fender EA, Zack CJ, Nishimura RA. Isolated tricuspid regurgitation: outcomes and therapeutic interventions. Heart 2018;104:798–806.
15. Agricola E, Marini C, Stella S, Monello A, Fisicaro A, Tufaro V et al. Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. J Cardiovasc Med (Hagerstown) 2017;18:60–8.

16. Papageorgiou G, Grant SW, Takkenberg JJM, Mokhles MM. Statistical primer: how to deal with missing data in scientific research? Interact CardioVasc Thorac Surg 2018;27:153–8.

17. Anwer LA, Tchantchaleishvili V, Poddi S, Daly RC, Joyce LD, Kushwaha SS et al. Atrial fibrillation should guide prophylactic tricuspid procedures during left ventricular assist device implantation. ASAIO J 2018;64: 586–93.

18. Tornos Mas P, Rodriguez-Palomares JF, Antunes MJ. Secondary tricuspid valve regurgitation: a forgotten entity. Heart 2015;101:1840–8.

19. Fukuda S, Song JM, Gillinov AM, McCarthy PM, Daimon M, Kongsaerepong V et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. Circulation 2005;111: 975–9.

20. Chang CC, Veen KM, Hahn RT, Bogers A, Latib A, Oei FBS et al. Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. Eur Heart J 2020;41: 1932–40.

21. Grant AD, Thavendiranathan P, Rodriguez LL, Kwon D, Marwick TH. Development of a consensus algorithm to improve interobserver agreement and accuracy in the determination of tricuspid regurgitation severity. J Am Soc Echocardiogr 2014;27:277–84.

SUPPLEMENTARY MATERIAL

CONTENTS

SUPPLEMENTARY TEXT 1: ELABORATION MEDIATION. MULTIPLE IMPUTATION AND MIXED-MODELS

Mediation analysis

Historically medical statistics have been focused to describe the relation between independent and dependent variables. However, in order to understand the mechanism that underlie a phenomena a more causal approach is warranted. Furthermore – if the purpose of the study is to assess the impact of a single risk factor – not addressing known causal pathways in multivariable models may result in spurious estimates, because a confounder has a two-way effect (e.g. it is an underlying factor which can both affect the outcome as well as the variable of interest). A mediator can only be affected by the variable of interest (and not the other way around). Therefore, we conducted mediation analysis. These analysis were initially developed by Baron and Kennedy (1). However, in the following decades multiple methods were developed to address mediation.

Structural equation model

We used a structural equation model (SEM), frequently used in behavioral sciences (2). These models are mainly used to work with latent variables (e.g. "motivation"), which cannot be measured directly, but can also be used in mediation analyses, in which all variables are measured (3). A SEM contains exogenous variables (variables that are not predicted by others) and endogenous variables (variables that are predicted). In a SEM a endogenous variable can be both an independent variable (predictor) or dependent variable (predicted). A common way to present a SEM is with a path diagram. In this diagram the arrows denote the presumed causal relation. Curved two-headed arrows present the covariation between variables. The R statistical package "lavaan" was used to conduct the median analysis (4). This package can handle categorical data. Notably, exogenous ordinal data should be incorporated as numerical data. The WLSMV estimator is used when categorical data is incorporated in the model. This estimator uses diagonally weighted least squares to estimate the model parameters, however it will use the full weight matrix to compute robust standard errors, and a mean- and variance-adjusted test statistic (4).

Several fit indices exist to give an indication of the fit of a SEM. The most common used is the chi-squared, in which a $p>0.05$ is an indication of a good fit. However, in large samples the chi-squared is nearly always significantly different (5). Other measures are:

Comparative fit Index

A value ranging from 0 to 1 of which >0.95 is an indication of a good fit.

Non-normed Fit Index

>0.95 is an indication of a good fit

Root Mean Square Error of Approximation

If higher limit of the confidence interval is <0.08 the model is considered well fitted.

Standardized Root Mean Square Residual

<0.08 is an indication of a good fit.

Generalized mixedmodels

All models had random intercepts for patients. Natural splines for time were added to establish flexibility over time. The marginal probabilities were obtained using a Monte Carlo sampling procedure. For each combination of follow-up time and covariate of interest 3000 patients are generated with random effect values coming from the normal distribution $N(0, \sigma_b^2)$, where σ_b^2 denotes the estimated variance of the random effects from the model. The mean of the 3000 calculated probabilities is taken as estimate.

All models contained the following covariates: time (with splines), the risk factor and the interaction between the risk factor and time.

Missing values

Multiple imputation by chained equations using the statistical "MICE" package in R was used to impute missing values (6). All baseline variables with < 50% missing were imputed, above 50% missing was considered excessive missingness (Supplementary Table 3). Imputations were done based upon the other baseline variables. In case of highly correlated variables the variable with highest clinical value was chosen as predictor (Supplementary Table 4). Correlation was tested with Pearson R or Spearman rho, as appropriate. Five imputed datasets were generated using this method using 5 iterations each. Convergence was visually checked in convergence plots. The imputations were visually checked by strip plots and density plots. The imputed datasets were used for the logistic regression models, structural equation models, ordinal regression models. Estimates, standard errors and model comparison tests were pooled according to Rubins' rules (7). In the cox model part of the joint model the first imputed dataset was used. In a sensitivity analyses the estimates and variance was compared with the pooled estimate and variance according to Rubins rules, which was comparable.

REFERENCES SUPPLEMENTARY TEXT 1

1. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173-82.
2. Zhang Z. Structural equation modeling in the context of clinical research. Ann Transl Med. 2017;5(5):102.
3. Gunzler D, Chen T, Wu P, Zhang H. Introduction to mediation analysis with structural equation modeling. Shanghai Arch Psychiatry. 2013;25(6):390-4.
4. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. 2012. 2012;48(2):36.
5. Hooper D, Coughlan J, Mullen MR. Structural Equation Modelling: Guidelines for Determining Model Fit. Electronic Journal of Business Research Methods. 2008;6(1):53-9.
6. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. 2011. 2011;45(3):67.
7. Rubin DB. Multiple Imputation for Nonresponse in Surveys: Wiley; 1987. 258 p.

Supplementary Table 1: List of participating centers as of 31 December 2016

Country	City, Hospital
Austria	Innsbruck, Universitätskliniken
Azerbaijan	Baku, Central Clinic Hospital
Belarus	Minsk, National Institute 'Cardiology'
Belgium	Aalst, Onze Lieve Vrouwenziekenhuis
	Gent, Universitair Ziekenhuis Gent
	Leuven, Katholieke Universiteit Leuven
Czech Republic	Prague, Institute for Experimental Cardiac Surgery (IKEM)
	Brno, Center for Cardiovascular and Transplant Surgery
Denmark	Århus, Århus University Hospital Skejby
	Copenhagen, Rigshospitalet
France	Le Plessis-Robinson, Centre Chirurgical Marie Lannelongue
Germany	Berlin, Deutsches Herzzentrum Berlin
	Lübeck, Universitätsklinikum Schleswig Holstein
	Bad Oeynhausen, Herz- und Diabeteszentrum Nordrhein-Westfalen
	Hamburg, Universitätsklinikum Eppendorf
	Freiburg, Universitäts Herzzentrum Freiburg - Bad Krozingen
	Jena, Universitäts-Herzzentrum Thüringen
	Karlsburg, Klinikum Karlsburg
	Köln, Universitätsklinikum Köln, AöR
Greece	Athens, Onassis Cardiac Surgery Center
	Thessaloniki, Aristotle University of Thessaloniki
Hungary	Budapest, Heart Center of the Semmelweis University
	Budapest, Gottsegen György Hungarian Institute of Cardiology
Italy	Bologna, Ospedale S. Orsola
	Rome, Ospedale San Camillo
	Milan, Ospedale Niguarda Ca'Granda
	Bergamo, Ospedale Papa Giovanni XXIII
	Naples, Ospedale dei Colli
	Palermo, ISMETT
	Rome, Ospedale Pediatrico Bambino Gesù
	Torino, Regina Margherita Children's Hospital
Kazakhstan	Astana, National Research Cardiac Surgery Center
Netherlands	Groningen, Universitair Medisch Centrum Groningen
	Rotterdam, Erasmus Medisch Centrum
	Utrecht, Universitair Medisch Centrum Utrecht
Norway	Oslo, Rikshospitalet
Poland	Warsaw, Childrens Memorial Hospital
	Zabrze, Silesian Heart Center

Supplementary Table 1: List of participating centers as of 31 December 2016 (continued)

Country	City, Hospital
Spain	Pamplona, Clínica Universidad de Navarra
	ESPAMACS, Madrid, collective of 7 hospitals
Switzerland	Bern, University Hospital Bern (Inselspital)
	Zürich, Kinderspital Zürich
Turkey	Izmir, Ege University School of Medicine
	Istanbul, Florence Nightingale Hospital
	Ankara, Bashkent University Hospital
	Ankara, Yüksek Ihtisas Hospital

Supplementary Table 2: Number of removed variables

	Mean	Mean - 3SD	Mean + 3 SD	#removed variables
Age	53.39	16.62	90.16	0
LVSF	11.13	-8.12	30.38	3
TAPSE	14.53	1.96	27.09	11
Systolic BP	101.14	50.81	151.46	15
Diastolic BP	65.05	28.6	101.5	20
BSA	2.28	-6.04	10.6	29
Pulmonary artery systolic pressure	52.58	-3.56	108.72	15
Pulmonary artery diastolic pressure	26.42	-6.42	59.26	21
RA pressure	11.41	-11.23	34.06	14
Pulmonary artery wedge pressure	23.83	-2.49	50.14	3
PVR	284.66	-386.64	955.96	10
Sodium	131.14	29.2	233.08	4
Potassium	4.25	-11.44	19.94	3
Blood Urea Nitrogen	61.82	-61.54	185.18	28
Creatinine	206.07	-2797.03	3209.16	13
ALAT	163.6	-1814.26	2141.46	23
ASAT	310.75	-4179.29	4800.79	27
LDH	610.45	-3586.34	4807.24	24
Total bilirubin	2.17	-30.08	34.42	4
Pro BNP	10090.11	-25295.82	45476.05	20
Cholesterol	3.86	-10.87	18.6	1
WBC	35.72	-1443.86	1515.29	6
Reticulocytes	12.95	-39.79	65.69	3
Hemoglobin	15.12	-44.04	74.29	55
Platelet	208.59	-55.41	472.6	22
INR	1.61	-3.71	6.93	6
PTT	41.12	-25.67	107.9	32

Supplementary Table 2: Number of removed variables (continued)

	Mean	Mean - 3SD	Mean + 3 SD	#removed variables
pH	13.45	-621.82	648.72	1
Lactate	4.99	-38.27	48.26	16
BicarbonatHCO3	24.16	11.17	37.14	14
CRPC reactive protein	11.09	-157.12	179.3	18
LVEDD2	63.08	-36.33	162.48	6
Pulmonary Artery Pressure Mean	35.97	-30.71	102.66	1
Pa Capillary Wedge Pressure	25.04	0.99	49.08	0

Supplementary Table 3: Missing data (alphabetic order)

Variable	Count missing	Percentage missing
ACE inhibitors	469	18,.8
Acenocoumarol	1152	46.2
Age	22	0.9
Albumin	1290	51.7
Aldosterone antagonist	508	20.4
Amiodarone	529	21.2
Anticoagulant therapy	537	21.5
Antiplatelet drugt herapy	605	24.2
Aortic regurgitation	234	9.4
ARB	508	20.4
Ascites	807	32.3
Betablockers	500	20.0
Bicarbonat HCO3	1352	54.2
Bloodtype	15	0.6
Blood Urea Nitrogen	641	25.7
Bosentan	1095	43.9
BSA	353	14.1
Cancer Other Than Local SkinCancer	342	13.7
Cardia cArrest	337	13.5
Cardiac Index	528	21.2
Cardiac Output	1419	56.9
Cardiac Surgery	329	13.2
Cholesterol	1824	73.1
Connective Tissue Or Inflammatory	383	15.3
COPD	337	13.5
CPB Time	249	10.0
Creatinine	633	25.4
CRPC reactive protein	574	23.0
Cumadine	2155	86.3

Supplementary Table 3: Missing data (alphabetic order) (continued)

Variable	Count missing	Percentage missing
ICD	257	10.3
Diabetes	135	5.4
Dialysis	165	6.6
Diastolic BP	483	19.4
ECG rhythm	437	17.5
ECMO	90	3.6
Ethnic origin	340	13.6
Feeding Tube	410	16.4
Gender	0	0.0
Hemoglobin	415	16.6
History Of Neurological Event	373	14.9
History Of Previous Alcohol Abuse	1367	54.8
Hospital stay	562	22.5
IABP	341	13.7
Iloprost	1096	43.9
INR	362	14.5
INTERMACS class	99	4.0
Intubation	332	13.3
Lactate	1704	68.3
LDHP	852	34.1
Loop diuretics	472	18.9
LVEDD2	453	18.1
LVEDV	1975	79.1
LvEf Percent	405	16.2
LVESD	1277	51.2
LVESV	2059	82.5
LVSF	2101	84.2
Major Infections	344	13.8
Major MI	339	13.6
Marcumar	1892	75.8
Marital status	710	28.4
Mitral regurgitation	299	12.0
Multiple intropes	393	15.7
Neseritide	519	20.8
Nitric Oxide	527	21.1
NT Pro BNP	1670	66.9
Number of inotropes	403	16.1
Pa Capillary Wedge Pressure	2468	98.9
pH	1263	50.6
Phenprocoumon	967	38.7

Supplementary Table 3: Missing data (alphabetic order) (continued)

Variable	Count missing	Percentage missing
Platelet	448	17.9
Positive Blood Cultures	578	23.2
Potassium	509	20.4
Primary Diagnosis	350	14.0
PTT	536	21.5
Pulmonary artery diastolic pressure	1169	46.8
Pulmonary Artery Pressure Mean	1091	43.7
Pulmonary artery systolic pressure	1155	46.3
Pulmonary artery wedge pressure	1323	53.0
Pulmonary Regurgitation	854	34.2
PVR	1748	70.0
RA pressure	1214	48.6
Reason For Admission	306	12.3
Reticulocytes	2273	91.1
Rhesusfactor	15	0.6
R value at peak	2473	99.1
RVEF	784	31.4
RvEf Percent	1382	55.4
ASAT	469	18.8
ALAT	1043	41.8
Sildenafil	1056	42.3
Smoking History	1066	42.7
Sodium	508	20.4
SVR	1842	73.8
Symptomatic Peripheral Vascular Disease	371	14.9
Systolic BP	719	28.8
TAPSE	1395	55.9
Time since first cardiac diagnosis	449	18.0
Total bilirubin	560	22.4
Transfusion History	1572	63.0
Tricuspid regurgitation	0	0.0
Ultrafiltration	336	13.5
Ventilation	704	28.2
Ventilator	346	13.9
Peripheral edema	544	21.8
VO max	2355	94.4
Warfarin	1132	45.4
WBC	365	14.6

Supplementary Table 4: Variables included in multiple imputation

Included in imputation	
Rhesusfactor	BSA
Gender	Pulmonary artery systolic pressure[2]
Mitral regurgitation	Pulmonary artery diastolic pressure[2]
Tricuspid regurgitation	RA pressure
Aortic regurgitation	Sodium
Peripheral edema	Potassium
ECG rhythm	Blood Urea Nitrogen
Neseritide	Creatinine
ARBO	ALAT[3]
Amiodarone	ASAT
ACE inhibitors	LDH
Betablockers	Total bilirubin
Aldosterone antagonist	WBC
Loopdiuretics	Hemoglobin
Phenprocoumon	Platelet
Antiplatelet drug therapy	INR
Anticoagulant therapy	PTT
Nitric Oxide	CRPC reactive protein
Time since first cardiac diagnosis	LVESD
Primary Diagnosis	LvEf Percent
ICD	Pulmonary Artery Pressure Mean
Cardiac Arrest	Diastolic BP
Dialysis	Systolic BP
Intubation[1]	*Legend*
Major MI	1: Not a predictor due to high correlation with Ventilation
Cardiac Surgery	
Positive Blood Cultures	2: Not a predictor due to high correlation with Pulmonary Artery Pressure Mean
Major Infections	
IABP	3: Not a predictor due to high correlation ASAT
Ultrafiltration	
Ventilator	
Feeding Tube	
ECMO	
INTERMACS class	
Diabetes	
COPD	
Symptomatic Peripheral Vascular Disease	
Connective Tissue Or Inflammatory	
Carotid Artery Disease	

Supplementary Table 4: Variables included in multiple imputation (continued)

Included in imputation
History Of Neurological Event
Cancer Other Than Local Skin Cancer
Smoking History
RVF
Ascites
Pulmonary Regurgitation
Sildenafil
Iloprost
Bosentan
Multiple Intropes
Age

Supplementary Table 5: Uni- multivariable ordinal logistic regression

	Univariable		Multivariable	
Characteristic	OR (95% CI)	P – value	OR (95% CI)	P – value
Bloodtype A	Reference			
Bloodtype AB	1.13 (0.81 to 1.57)	0.46	-	-
Bloodtype B	1.02 (0.82 to 1.26)	0.89	-	-
Bloodtype O	0.95 (0.81 to 1.12)	0.55	-	-
Rhesusfactor Positive	0.98 (0.81 to 1.2)	0.88	-	-
Male gender	0.97 (0.8 to 1.18)	0.79	-	-
No mitral regurgitation	Reference			
Trivial mitral regurgitation	1.68 (1.16 to 2.43)	0.007	1.62 (1.07 to 2.47)	0.025
Mild mitral regurgitation	4.87 (3.43 to 6.91)	<0.001	3.34 (2.25 to 4.94)	<0.001
Moderate mitral regurgitation	8.35 (5.96 to 11.68)	<0.001	5.23 (3.59 to 7.61)	<0.001
Severe mitralregurgitation	15.2 (10.4 to 22.21)	<0.001	9.62 (5.97 to 15.5)	<0.001
No aortic regurgitation	Reference			
Trivial aortic regurgitation	1.69 (1.41 to 2.02)	<0.001	1.22 (0.97 to 1.54)	0.088
Mild aortic regurgitation	2.53 (2 to 3.2)	<0.001	1.5 (1.12 to 2.02)	0.008
Moderate aortic regurgitation	2 (1.3 to 3.06)	0.002	1.47 (0.88 to 2.47)	0.14
Severe Aortic regurgitation	1.53 (0.74 to 3.15)	0.25	0.76 (0.35 to 1.62)	0.46
No peripheral edema				
Mild peripheral edema	1.55 (1.27 to 1.9)	<0.001	1.39 (1.06 to 1.82)	0.018
Moderate peripheral edema	1.85 (1.48 to 2.31)	<0.001	1.27 (0.99 to 1.62)	0.057
Severe peripheral edema	1.56 (1.21 to 2.01)	0.001	1.36 (1 to 1.85)	0.048
Sinus	Reference			
Atrial fibrillation	1.22 (0.98 to 1.52)	0.071	1.22 (0.96 to 1.56)	0.10
Other	1.59 (0.92 to 2.74)	0.094	1.35 (0.77 to 2.38)	0.28

Supplementary Table 5: Uni- multivariable ordinal logistic regression (continued)

	Univariable		Multivariable	
Paced	1.48 (1.22 to 1.8)	0	1.12 (0.86 to 1.45)	0.38
Medication on admission				
Neseritide	0.55 (0.27 to 1.12)	0.088	0.87 (0.21 to 3.55)	0.81
ARB	0.75 (0.59 to 0.96)	0.025	0.8 (0.6 to 1.07)	0.12
Amiodarone	0.8 (0.66 to 0.97)	0.022	0.82 (0.68 to 1)	0.055
ACE inhibitors	1.01 (0.83 to 1.24)	0.92	-	-
Beta-blockers	1.26 (1.08 to 1.48)	0.004	0.96 (0.75 to 1.24)	0.76
Aldosterone antagonist	1.31 (1.1 to 1.57)	0.004	0.97 (0.81 to 1.16)	0.70
Loop diuretics	1.56 (1.28 to 1.9)	<0.001	1.38 (1.13 to 1.69)	0.002
Phenprocoumon*	0.91 (0.63 to 1.33)	0.60		
Antiplatelet drug therapy (yes vs no)	0.63 (0.53 to 0.74)	<0.001	0.83 (0.68 to 1.01)	0.057
Anticoagulant therapy drugs (yes vs no)	0.8 (0.67 to 0.94)	0.009	0.88 (0.68 to 1.13)	0.29
Nitric Oxide	0.58 (0.38 to 0.91)	0.020	0.96 (0.43 to 2.13)	0.90
Sildenafil	0.98 (0.78 to 1.24)	0.87	-	-
Iloprost	0.9 (0.69 to 1.16)	0.38	-	-
Bosentan	1.12 (0.92 to 1.38)	0.25	-	-
Multiple inotropes (>2)	0.84 (0.67 to 1.06)	0.13	-	--
-Cardiac diagnosis less than one month	Reference			
Cardiac diagnosis one month to a year	2.1 (1.6 to 2.75)	<0.001	1.01 (0.7 to 1.46)	0.96
Cardiac diagnosis one to two years	3.77 (2.65 to 5.35)	<0.001	1.27 (0.82 to 1.96)	0.28
Cardiac diagnosis over two years	3.36 (2.66 to 4.23)	<0.001	1.13 (0.75 to 1.68)	0.55
Primary diagnosis: Coronary artery disease	Reference			
Primary diagnosis: Idiopathic dilated myopathy	2.18 (1.63 to 2.92)	<0.001	1.31 (0.98 to 1.75)	0.066
Primary diagnosis: Ischemic dilated myopathy	1.2 (0.91 to 1.58)	0.20	1.08 (0.81 to 1.42)	0.61
Primary diagnosis: Other dilated myopathy	1.45 (1.09 to 1.93)	0.010	1.34 (1.01 to 1.78)	0.045
ICD Device	1.61 (1.39 to 1.88)	<0.001	1.31 (0.98 to 1.75)	0.066
Cardiac arrest	0.47 (0.33 to 0.66)	<0.001	1.17 (0.92 to 1.47)	0.20
Dialysis	0.8 (0.53 to 1.22)	0.31	0.77 (0.54 to 1.09)	0.13
Intubated	0.46 (0.36 to 0.58)	<0.001	0.97 (0.72 to 1.3)	0.83
Major MI	0.57 (0.47 to 0.7)	<0.001	1.12 (0.86 to 1.46)	0.38
Cardiac surgery	1.02 (0.81 to 1.29)	0.84	-	-
Positive blood cultures	0.52 (0.38 to 0.71)	<0.001	0.76 (0.48 to 1.21)	0.23
Major Infections	0.52 (0.39 to 0.7)	<0.001	0.93 (0.62 to 1.37)	0.69
IABP	0.56 (0.44 to 0.72)	<0.001	0.86 (0.63 to 1.18)	0.34
Ultrafiltration*	0.72 (0.49 to 1.07)	0.099	1.47 (0.87 to 2.48)	0.14
Ventilator*	0.41 (0.31 to 0.55)	<0.001	-	-
Feeding tube	0.32 (0.24 to 0.43)	<0.001	0.7 (0.46 to 1.07)	0.096

Supplementary Table 5: Uni- multivariable ordinal logistic regression (continued)

	Univariable		Multivariable	
ECMO	0.46 (0.36 to 0.59)	<0.001	0.91 (0.62 to 1.34)	0.64
INTERMACS class 1	Reference			
INTERMACS class 2	1.81 (1.43 to 2.3)	<0.001	1.07 (0.76 to 1.51)	0.69
INTERMACS class 3	1.77 (1.39 to 2.26)	<0.001	1.06 (0.74 to 1.53)	0.73
INTERMACS class >4	2.41 (1.88 to 3.09)	<0.001	1.18 (0.81 to 1.72)	0.37
Diabetes	1.12 (0.95 to 1.31)	0.19	-	-
COPD	0.87 (0.65 to 1.16)	0.33	-	-
Symptomatic peripheral vascular disease	0.8 (0.57 to 1.14)	0.21	-	-
connective tissue or inflammatory disease	0.99 (0.34 to 2.85)	0.98	-	-
Carotid Artery Disease	1.01 (0.53 to 1.93)	0.97	-	-
Prior neurological event: None	Reference			
Prior neurological event: CVA	0.87 (0.65 to 1.15)	0.32	-	-
Prior neurological event: ICB	0.62 (0.28 to 1.36)	0.22	-	-
Prior neurological event: TIA	0.83 (0.55 to 1.25)	0.36	-	-
Cancer other than local skin cancer	0.98 (0.66 to 1.46)	0.92	-	-
Smoking history	0.51 (0.43 to 0.6)	<0.001	0.75 (0.59 to 0.94)	0.016
RVEF: Normal	Reference			
RVEF: Mild impairment	1.51 (1.2 to 1.91)	0.001	1.4 (1.09 to 1.79)	0.009
RVEF: Moderate impairment	2.79 (2.19 to 3.57)	<0.001	2.33 (1.74 to 3.12)	<0.001
RVEF: Severe impairment	2.92 (2.18 to 3.92)	<0.001	2.96 (2.18 to 4.01)	<0.001
Ascites	1.48 (1.08 to 2.04)	0.020	1.07 (0.8 to 1.43)	0.62
No Pulmonary regurgitation	Reference			
Trivial Pulmonary regurgitation	1.78 (1.48 to 2.15)	<0.001	1.28 (1.05 to 1.55)	0.013
Mild Pulmonary regurgitation	4.43 (3.39 to 5.79)	<0.001	2.73 (2.12 to 3.5)	<0.001
Moderate Pulmonary regurgitation	8.03 (5.28 to 12.21)	<0.001	4.47 (2.88 to 6.93)	<0.001
Severe Pulmonary regurgitation	4.02 (1.66 to 9.75)	0.006	3.05 (1.31 to 7.13)	0.015
Continuous variables				
Age per 10 years	0.97 (0.92 to 1.03)	0.39	-	-
Systolic BP per 10 mmHg	0.93 (0.88 to 0.98)	0.011	0.94 (0.9 to 0.99)	0.027
Diastolic BP per 10 mmHG	1.03 (0.97 to 1.1)	0.36	-	-
BSA	0.21 (0 to 8.59)	0.39	-	-
Pulmonary artery systolic pressure per 10 mmHG	1.16 (1.1 to 1.23)	<0.001	-	-
Pulmonary artery diastolic pressure per 10 mmHG	1.26 (1.15 to 1.37)	<0.001	-	-
RA pressure per 1 mmHG	1.04 (1.03 to 1.06)	<0.001	1.05 (1.02 to 1.08)	0.009
Sodium per 50	0.77 (0.64 to 0.91)	0.003	0.82 (0.67 to 1)	0.050
Potassium per 10	0.86 (0.34 to 2.21)	0.75	-	-
Blood urea nitrogen per 50	0.93 (0.84 to 1.03)	0.16	-	-
Creatinine per 50	0.98 (0.94 to 1.02)	0.33	-	-

Supplementary Table 5: Uni- multivariable ordinal logistic regression (continued)

	Univariable		Multivariable	
*ALAT per 50	0.98 (0.97 to 1)	0.031	-	-
ASAT per 50	0.99 (0.98 to 1)	0.019	1.01 (1 to 1.02)	0.14
LDH per 50	0.97 (0.96 to 0.98)	<0.001	0.98 (0.96 to 1)	0.027
Total bilirubin per 1	1.05 (1.01 to 1.09)	0.01	1.02 (1 to 1.07)	0.336
WBC per 10	0.95 (1 to 1.04)	0.28	-	-
Hemoglobin	0.98 (0.95 to 1.01)	0.27	-	-
Platelet per 50	0.98 (0.94 to 1.04)	0.56	-	-
INR per 1	0.95 (0.86 to 1.05)	0.30	-	-
PTT per 1	0.99 (0.98 to 0.99)	<0.001	0.99 (0.99 to 1)	0.014
LVESD per 1	1 (1 to 1.01)	0.46	-	-
LvEfPercent per 1	1 (0.99 to 1.01)	0.83	-	-
PulmonaryArteryPressureMean per 10	1.02 (1.01 to 1.02)	0.003	1 (0.85 to 1.17)	0.966

Supplementary Table 6: Baseline variables stratified to missing versus not missing of right ventricular function (RVF).

	RVF Missing	RVF not missing	P-value
Demographics			
n	784	1712	
Age, y			
Male sex, n (%)	617 (78.7)	1456 (85.0)	<0.001
Body surface area, m2	1.98 [1.83, 2.12]	1.96 [1.81, 2.11]	0.200
White race, n (%)	458 (89.5)	1402 (85.3)	0.003
Ischemic etiology HF, n (%)	231 (46.4)	640 (38.8)	0.008
≥2 years since first diagnosis	312 (61.5)	993 (64.5)	0.001
Destination therapy	105 (13.4)	317 (18.5)	0.002
Ascites	19 (7.2)	171 (12.0)	0.031
Rhythm, n (%)			<0.001
• Sinus	200 (42.0)	937 (59.2)	
• Atrial fibrillation	64 (13.4)	291 (18.4)	
• Paced	191 (40.1)	320 (20.2)	
• Other	21 (4.4)	35 (2.2)	
INTERMACS profile, n (%)			<0.001
• 1	118 (16.8)	199 (11.7)	
• 2	283 (40.3)	514 (30.3)	
• 3	187 (26.6)	475 (28.0)	
• ≥4	115 (16.4)	506 (29.9)	
IABP, n (%)	77 (15.1)	154 (9.4)	<0.001
ECMO, n (%)	80 (10.5)	153 (9.3)	0.406
Ventilator (%)	78 (15.3)	198 (12.1)	0.071

Supplementary Table 6: Baseline variables stratified to missing versus not missing of right ventricular function (RVF). (continued)

	RVF Missing	RVF not missing	P-value
Medication, n (%)			
• Loopdiuretics, n (%)	368 (78.8)	1280 (82.2)	0.111
• Use of ≥3 inotropes, n (%)	112 (23.3)	163 (10.0)	<0.001
Laboratory values			
• Serum creatinine, mg/dL	106.00 [84.00, 139.00]	107.00 [83.00, 146.00]	0.474
• ASAT, U/L	35.00 [23.00, 72.75]	31.00 [22.00, 62.00]	0.015
• Total bilirubin, mg/dL	1.20 [0.79, 2.00]	1.24 [0.80, 2.00]	0.652
• Albumin, g/dL	494.11 [405.72, 594.09]	507.15 [420.21, 579.60]	0.969
• Hemoglobin, g/dL	11.30 [9.90, 13.10]	12.10 [10.43, 13.70]	<0.001
Hemodynamic			
• RA pressure, mmHg	10.00 [6.00, 15.00]	10.00 [7.00, 15.00]	0.550
• PCWP, mmHg	23.00 [17.00, 29.00]	25.00 [18.00, 30.00]	0.049
• PAP, systolic, mmHg	48.00 [37.00, 59.00]	52.00 [40.00, 65.00]	0.003
Echocardiographic			
• TAPSE, mm	15.00 [13.00, 18.00]	14.00 [12.00, 17.00]	0.001
• No aortic regurgitation, n (%)	490 (66.6)	950 (62.3)	0.005
• Severe mitral regurgitation, n (%)	100 (19.1)	285 (17.0)	0.098
• LVEF grade <20%, n (%)	233 (51.8)	977 (61.7)	<0.001

Supplementary Table 7: Estimates and standard errors of the mixed model compared to the longitudinal outcome of the joint-model. Both models contained time, with a spline function (1 knot), TR at baseline and their interaction.

Characteristic	Mixed model		Joint model	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-1.826 (0.496)	<0.001	-1.832 (0.146)	<0.001
Time spline 1	-3.028 (0.987)	0.002	-4.504 (0.748)	<0.001
Time spline 2	3.406 (1.065)	0.001	2.966 (1.616)	0.061
Baseline TR	5.876 (0.81)	<0.001	5.848 (0.254)	<0.001
Baseline TR: Time spline 1	-9.979 (1.595)	<0.001	-8.372 (1.072)	<0.001
Baseline TR: Time spline 2	1.05 (1.939)	0.59	2.832 (2.314)	0.21

The direction of effects did not change between the two models and significance remains similar between the two groups, except for the second spline for time, which is not significant in the joint model. Hence, some sensitivity is present, but course over time is comparable between the two models.

Supplementary Table 8: Estimates of the joint model survival part. *time varying covariate as estimated by a mixed model containing time in a Spline function with 1 knot and baseline TR

Characteristic	Hazard ratio (95% confidence interval)	P-value
Age	1.04 (1.03 to 1.06)	<0.001
Male gender	0.83 (0.55 to 1.28)	0.43
Moderate-to-Severe baseline TR	0.84 (0.62 to 1.25)	0.29
Destination therapy	1.04 (0.66 to 1.58)	0.84
Intermacs score (cubic)	0.66 (0.5 to 0.86)	<0.001
ICD	0.98 (0.72 to 1.33)	0.87
Blood urea nitrogen	1 (0.99 to 1)	0.49
Creatinine	1 (1 to 1)	0.24
Sodium	1 (0.99 to 1)	0.25
Pre-LVAD RV function (lin)	1.33 (0.86 to 2.02)	0.19
Ascitis	1.27 (0.81 to 1.94)	0.26
Moderate-to-severe post LVAD TR*	1.16 (1.06 to 1.28)	0.005

Supplementary Table 9: Sensitivity analyses of the generalized mixed model in which patients with preoperative ECMO were excluded.

Characteristic	Mixed model with ECMO patients		Mixed model without ECMO patients	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-2.178 (0.801)	0.007	-2.638 (0.857)	0.002
Time spline 1	-4.117 (1.59)	0.010	-3.32 (1.69)	0.049
Time spline 2	1.948 (1.57)	0.21	2.017 (1.634)	0.22
Baseline TR	5.129 (1.269)	<0.001	5.664 (1.347)	<0.001
Baseline TR: Time spline 1	-7.23 (2.532)	0.004	-8.381 (2.685)	0.002
Baseline TR: Time spline 2	1.362 (2.6)	0.60	1.384 (2.71)	0.61

Supplementary Table 10: Sensitivity analyses of the survival part of the joint model of in which patients with preoperative ECMO were excluded. *time varying covariate as estimated by a mixed model containing time in a Spline function with 1 knot and baseline TR

Characteristic	Hazard ratio (95% confidence interval)	P-value
Age	1.04 (1.03 to 1.06)	<0.001
Male gender	0.8 (0.48 to 1.31)	0.35
Moderate-to-Severe baseline TR	0.89 (0.61 to 1.29)	0.55
Destination therapy	1.02 (0.67 to 1.48)	0.84
Intermacs score (cubic)	0.75 (0.55 to 1.03)	0.07
ICD	1.11 (0.76 to 1.7)	0.63
Blood urea nitrogen	1 (0.99 to 1)	0.49

Supplementary Table 10: Sensitivity analyses of the survival part of the joint model of in which patients with preoperative ECMO were excluded. *time varying covariate as estimated by a mixed model containing time in a Spline function with 1 knot and baseline TR (continued)

Characteristic	Hazard ratio (95% confidence interval)	P-value
Creatinine	1 (1 to 1)	0.54
Sodium	1 (0.99 to 1.01)	0.71
Pre-LVAD RV function (lin)	1.22 (0.81 to 1.93)	0.37
Ascitis	1.18 (0.71 to 1.87)	0.53
Moderate-to-severe post LVAD TR*	1.14 (1.03 to 1.27)	0.008

Supplementary Table 11: Sensitivity analyses of a mixed model containing random intercept for patients versus random intercept for center and patient. Laplace approximation was used in both models. Akaike information criterion for the model with random intercept for patients was 1774 whereas this was 1776 for the model with random intercept for both patient and center.

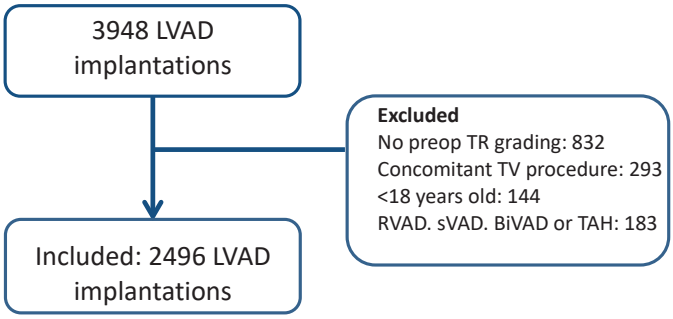
Characteristic	Mixed model with random intercept patients		Mixed model without with nested random effect patient and center	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-5.231 (1.035)	<0.001	-5.202 (1.036)	<0.001
Time spline 1	-3.378 (1.874)	0.071	-3.391 (1.873)	0.070
Time spline 2	3.56 (1.977)	0.072	3.534 (1.973)	0.073
Baseline TR	6.704 (1.579)	<0.001	6.694 (1.578)	<0.001
Baseline TR: Time spline 1	-11.572 (3.123)	<0.001	-11.542 (3.123)	<0.001
Baseline TR: Time spline 2	1.722 (3.86)	0.67	1.723 (3.849)	0.654

Supplementary Table 12: Sensitivy analyses of estimates of the mixed model excluding patients that underwent RVAD during follow-up. Of the 914 patients that had echocradiorapich follow-up 12 patients were excluded.

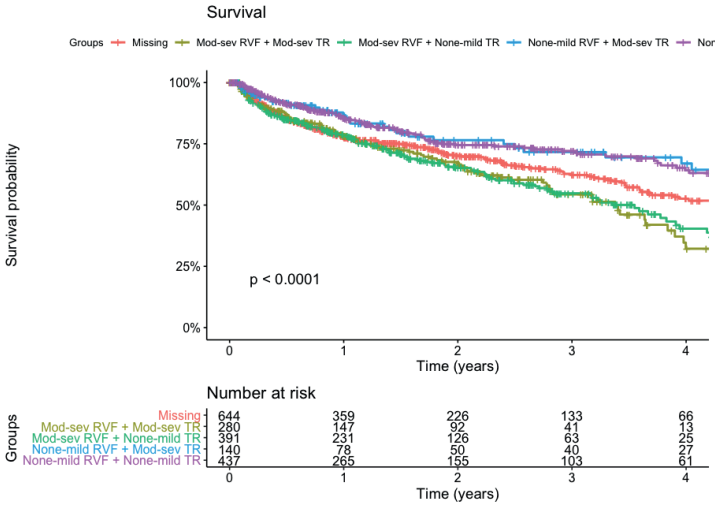
Characteristic	Mixed model all patiens		Mixed model excluding patients with RVAD during follow-up	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-2.178 (0.801)	0.007	-2.262 (0.804)	0.005
Time spline 1	-4.117 (1.59)	0.01	-3.929 (1.593)	0.014
Time spline 2	1.948 (1.57)	0.21	1.941 (1.567)	0.22
Baseline TR	5.129 (1.269)	<0.001	5.235 (1.27)	<0.001
Baseline TR: Time spline 1	-7.23 (2.532)	0.004	-7.422 (2.534)	0.003
Baseline TR: Time spline 2	1.362 (2.6)	0.60	1.346 (2.59)	0.60

Supplementary Table 13: Sensitivity analyses of estimates of the mixed model excluding patients that underwent durable right ventricular assist device during follow-up. Of the 914 patients that had echocardiographic follow-up 12 patients were excluded.

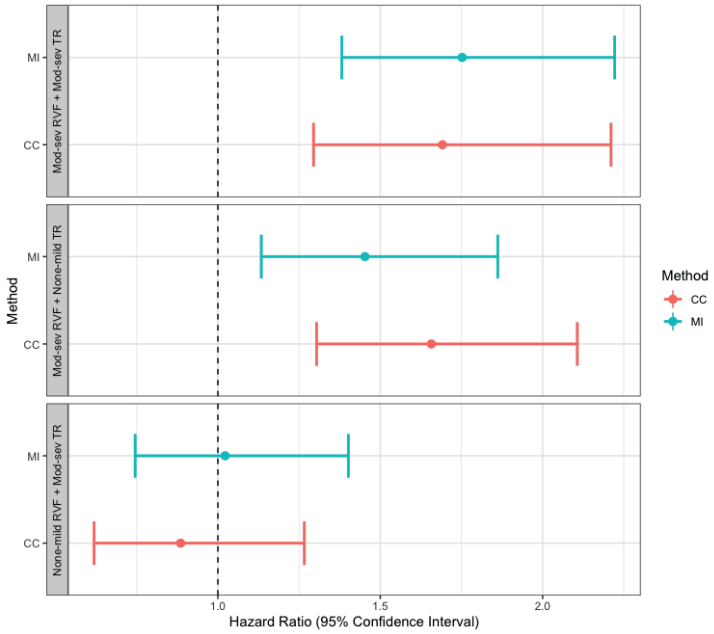
Characteristic	Hazard ratio (95% confidence interval)	P-value
Age	1.04 (1.02 to 1.06)	<0.001
Male gender	0.86 (0.55 to 1.32)	0.50
Moderate-to-Severe baseline TR	0.87 (0.61 to 1.22)	0.44
Destination therapy	1.08 (0.75 to 1.63)	0.71
Intermacs score (cubic)	0.71 (0.54 to 0.93)	0.024
ICD	0.96 (0.66 to 1.38)	0.82
Blood urea nitrogen	1 (0.99 to 1)	0.65
Creatinine	1 (1 to 1.01)	0.12
Sodium	0.99 (0.99 to 1)	0.16
Pre-LVAD RV function (lin)	1.36 (0.87 to 2.02)	0.14
Ascitis	1.37 (0.86 to 2.19)	0.22
Moderate-to-severe post LVAD TR*	1.15 (1.03 to 1.29)	0.010



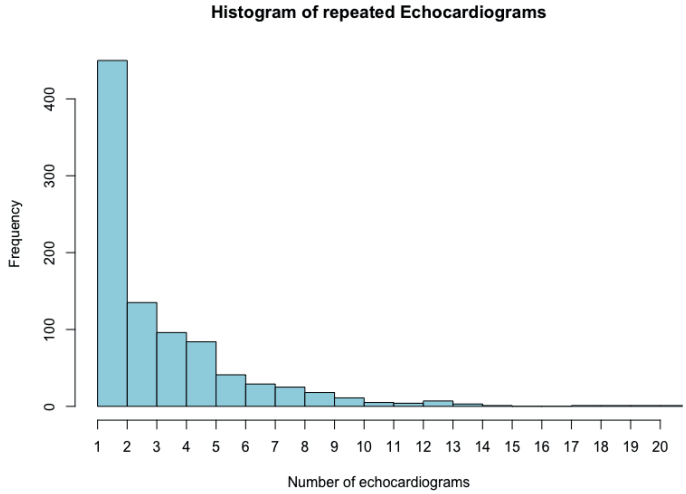
Supplementary Figure 1: Flowchart of inclusion. TR: tricuspid regurgitation, TV: tricuspid vavle, RVAD: right ventricular assist device, sVAD: single ventricle assist device, BiVAD: biventricular assist device, TAH: total artificial heart



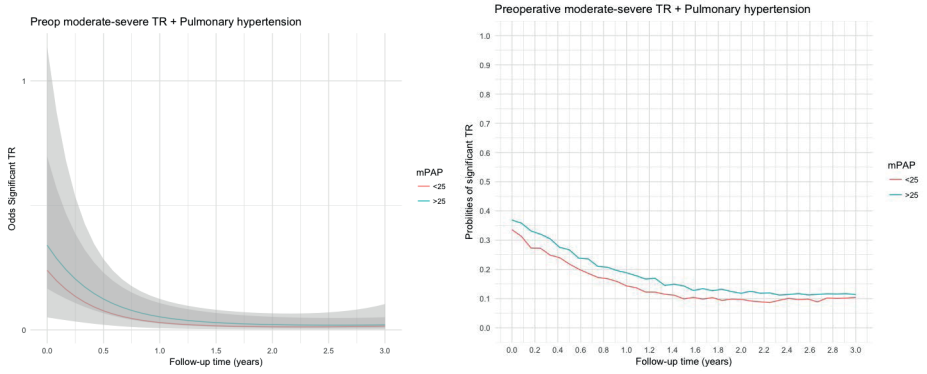
Supplementary Figure 2: Kaplan Meier curve with complete case analyses with missing RVF and a category.



Supplementary Figure 3: Cox proportional hazard ratios derived from complete case (CC) analyses versus multiple imputation (MI). The reference was the group of patient with none-to-mild tricuspid regurgitation and none-to-mild right ventricle dysfunction at baseline.

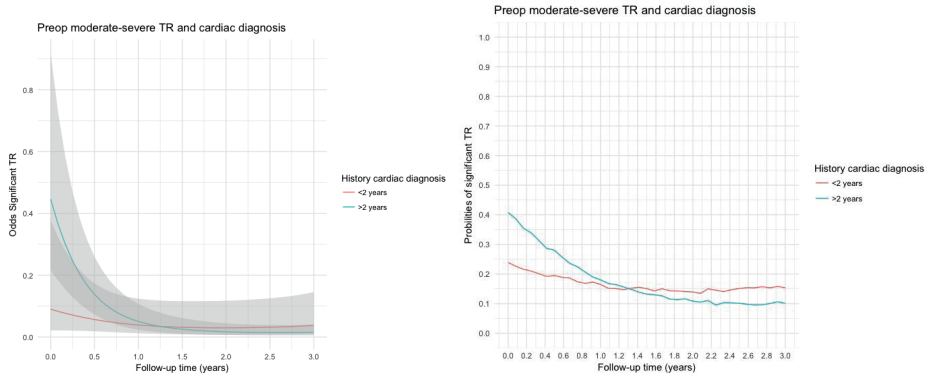


Supplementary Figure 4: Histogram of repeated echocardiograms



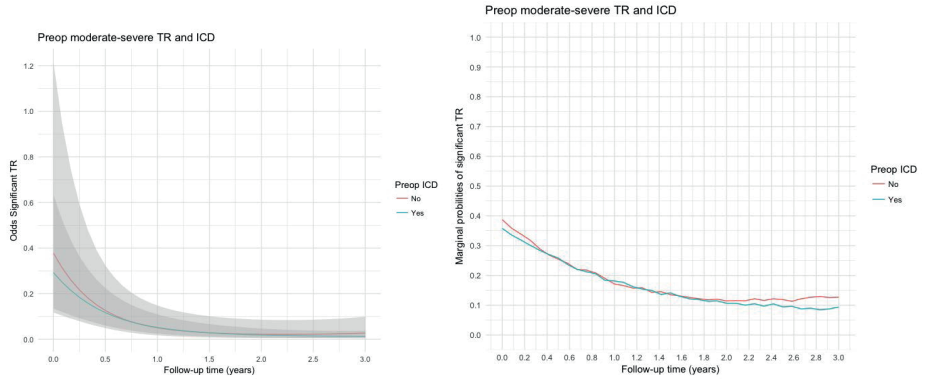
Year	mPAP	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	>25	849	572	391	270	188	132	95
	<25	166	127	83	52	27	15	6
Patients remaining	>25	251	190	140	114	85	64	46
	<25	46	36	26	20	14	8	4

Supplementary Figure 5ab: Effect plots of subgroup pre-LVAD moderate-to-severe TR with or without pulmonary hypertension. No significant differences are found when mean Pulmonary pressure or systolic pulmonary pressure is entered in the model as linear continuous variable. Significant TR = moderate-to-severe tricuspid regurgitation



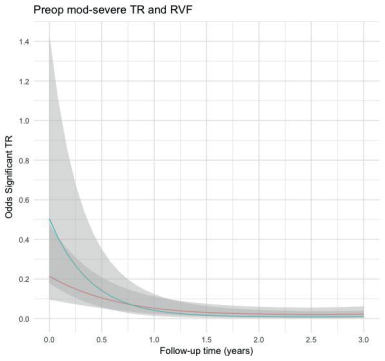
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	>2 years	798	542	365	245	162	111	76
	<2 years	217	157	109	77	53	36	25
Patients remaining	>2 years	216	164	118	97	69	52	36
	<2 years	81	62	48	37	30	20	14

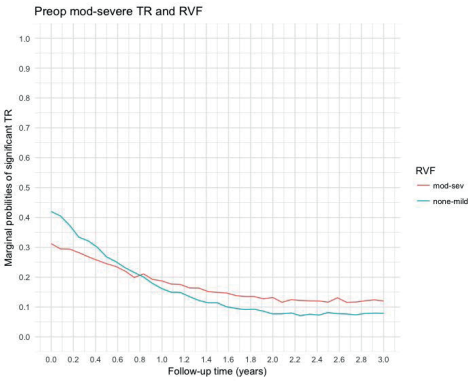
Supplementary Figure6ab: Effect plots of subgroup moderate-to-severe TR >2 or <2 years cardiac diagnosis. Significant TR = moderate-to-severe tricuspid regurgitation



Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	No ICD	743	505	338	223	147	91	54
	ICD	272	194	136	99	68	56	47
Patients remaining	No ICD	200	150	110	90	64	45	26
	ICD	97	76	56	44	35	27	24

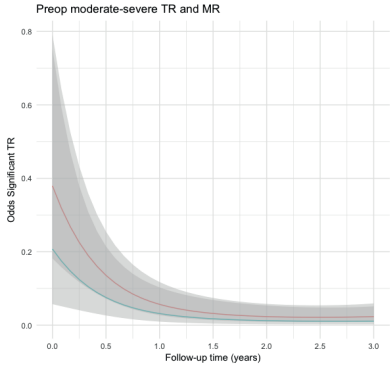
Supplementary Figure 7ab: Effect plots of subgroup moderate-to-severe TR with our without pre-LVAD ICD. Significant TR = moderate-to-severe tricuspid regurgitation

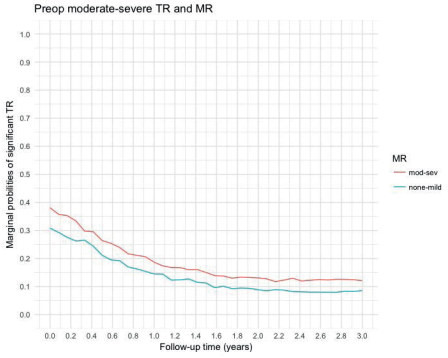




Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	None-mild RVF	342	218	149	106	76	57	45
	Mod-sev RVF	673	481	325	216	139	90	56
Patients remaining	None-Mild RVF	94	71	51	44	36	30	23
	Mod-sev RVF	203	155	115	90	63	42	27

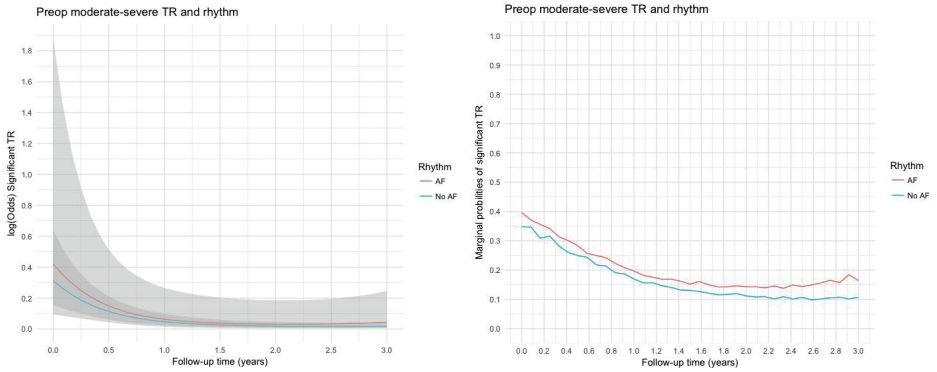
Supplementary Figure 8ab: Effect plots of subgroup moderate–to-severe TR with none-mild RVF or moderate-severe RV dysfunction. Significant TR = moderate-to-severe tricuspid regurgitation





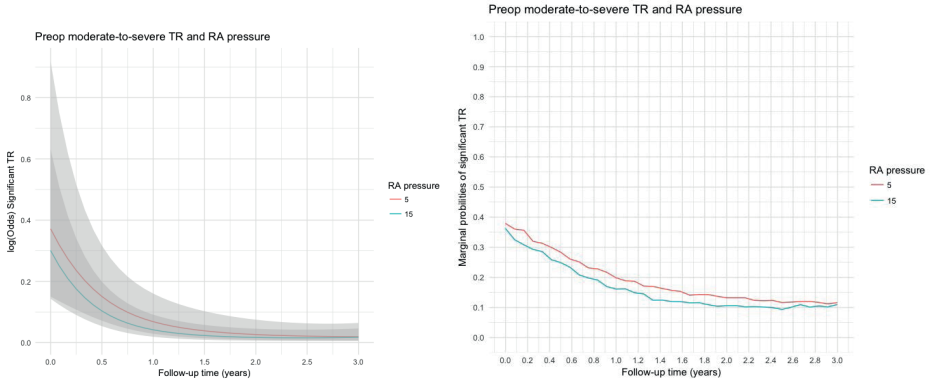
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	None-mild MR	257	185	128	91	62	44	29
	Mod-sev MR	758	514	346	231	153	103	72
Patients remaining	None-Mild MR	82	64	43	36	26	21	12
	Mod-sev MR	215	162	123	98	73	51	38

Supplementary Figure 9ab: Effect plots of subgroup pre-LVAD moderate-to-severe TR with moderate-severe mitral regurgitation (MR) or none-mild MR. Significant TR = moderate-to-severe tricuspid regurgitation



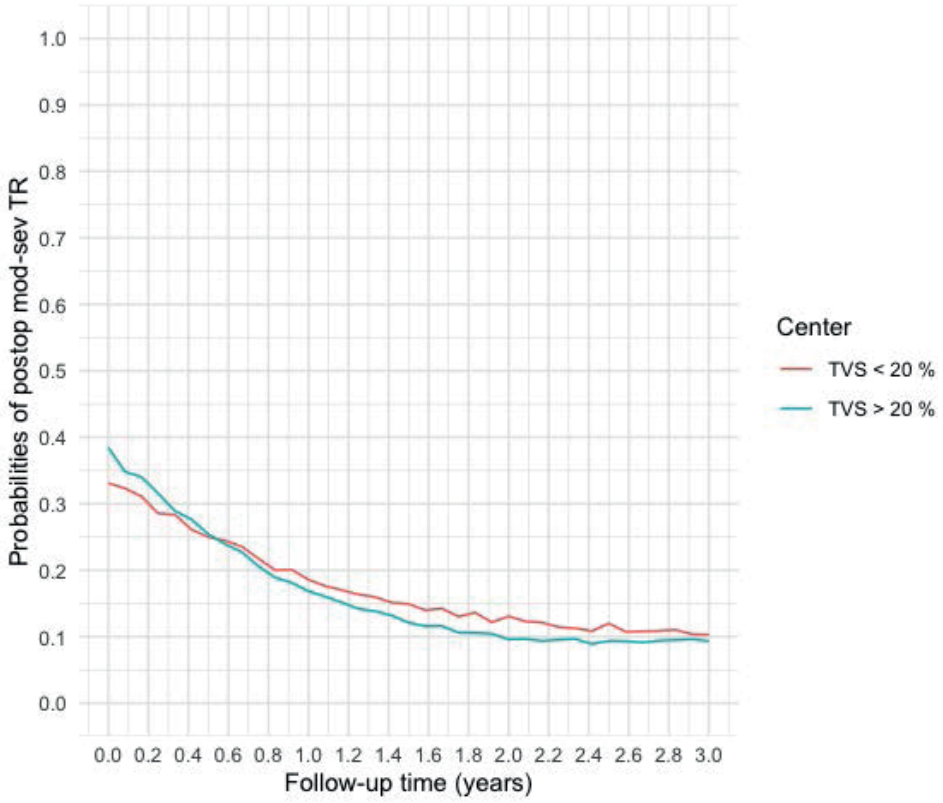
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	AF	130	80	50	34	21	18	14
	No AF	885	619	424	288	194	129	87
Patients remaining	AF	44	30	20	16	10	9	8
	No AF	253	196	146	118	89	63	42

Supplementary Figure 10ab: Effect plots of subgroup pre-LVAD moderate-to-severe TR with or without pre-LVAD AF. Significant TR = moderate-to-severe tricuspid regurgitation



Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	RA peressue 5	130	80	50	34	21	18	14
	RA presure 15	44	30	20	16	10	9	8
Patients remaining	RA peressue 5	253	196	146	118	89	63	42
	RA presure 15							

Supplementary Figure 11ab: Effect plots of pre-LVAD moderate-to-severe TR and (right atrium) RA pressure (5 mmHg and 15 mmHg are chosen as example). RA pressure was modeled as continuous variable. Significant TR = moderate-to-severe tricuspid regurgitation



Supplementary Figure 12: Effectplot of subgroup pre-LVAD moderate-to-severe TR stratified to centers that performed concomitant tricuspid valve surgery in >20% of cases in patients with pre-LVAD moderate-to-severe TR versus centers that performed tricuspid valve surgery in <20% of cases in these patients. Of note, only patients without tricuspid valve intervention are included in this analyses.