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ORIGINAL RESEARCH

Validation of the Hemodynamic Classification System for Hemodynamic-Related Events in Patients With Durable Left Ventricular Assist Devices

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BACKGROUND: Durable left ventricular assist device (dLVAD) physiology predisposes to right heart failure (RHF) and aortic insufficiency (AI), recently labeled hemodynamic-related events (HDREs). We sought to validate the recently proposed dLVAD Hemodynamic Classification System for HDREs.

METHODS: RHF and AI HDREs were adjudicated, staged, and phenotyped on the basis of the Hemodynamic Classification System assessed at 6 months after dLVAD implantation. The primary outcome was a composite of HF hospitalization or cardiovascular death between 6 and 24 months after dLVAD implantation.

RESULTS: Among 183 qualifying consecutive patients with 6-month assessments, RHF HDRE was adjudicated in all cases and AI HDRE in 161 (88.0%). Overall, 53 (29.0%) patients developed an RHF HDRE and 26 (16.0%) an AI HDRE (phenotypes: 39 isolated RHF, 15 isolated AI, 11 combined RHF–AI, 3 not adjudicated). At pre-dLVAD assessment, age and pulmonary artery pulsatility index were independently associated with RHF HDRE and pre-dLVAD AI and systolic pulmonary artery pressure with AI HDRE. RHF HDRE (adjusted hazard ratio [HR], 2.69 [95% CI, 1.14–6.34]; *P*=0.024), AI HDRE (adjusted HR, 4.21 [95% CI, 1.70–10.40]; *P*=0.002), and HDRE phenotypes (isolated RHF/AI HDRE versus no HDRE: adjusted HR, 2.80 [95% CI, 1.03–7.62]; *P*=0.044; combined RHF/AI HDRE versus no HDRE: adjusted HR, 4.53 [95% CI, 1.33–15.35]; *P*=0.015) were associated with the primary outcome. A graded increase in primary outcome was observed with increasing RHF and AI stages.

CONCLUSIONS: We validated the dLVAD Hemodynamic Classification System for HDREs as a valuable tool to identify pathophysiological and clinical clusters of patients, linking it with significant prognostic implications. Its adoption may pave the way for targeted strategies aimed at mitigating HDREs and enhancing the long-term success of dLVAD support.

Key Words: advanced heart failure ■ aortic insufficiency ■ Hemodynamic Classification System ■ left ventricular assist device ■ right heart failure

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CLINICAL PERSPECTIVE

What Is New?

- The Hemodynamic Classification System allows practical staging and phenotyping of right heart failure and aortic insufficiency in patients with durable left ventricular assist devices.
- Both subclinical and overt hemodynamic-related events are frequent early after left ventricular assist device implantation and independently predict adverse outcomes.

What Are the Clinical Implications?

- Structured multimodal follow-up using the Hemodynamic Classification System may enable earlier recognition and intervention to improve long-term outcomes in recipients of left ventricular assist devices.

Nonstandard Abbreviations and Acronyms

AI	aortic insufficiency
AV	aortic valve
CF	continuous flow
CPEX	cardiopulmonary exercise testing
dLVAD	durable left ventricular assist device
HCS	Hemodynamic Classification System
HDRE	hemodynamic-related event
HRAE	hemocompatibility-related adverse event
HT	heart transplantation
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
RHC	right heart catheterization
RHF	right heart failure

The clinical outcomes of patients with advanced heart failure (HF) supported with a durable left ventricular assist device (dLVAD) are constantly improving.[1,2] The focus of care providers and the scientific community on hemocompatibility-related adverse events (HRAEs) has prompted giant leaps forward in dLVAD technology and patient management, leading to declining rates of the morbidity and death associated with HRAEs.[2–5,6] As a consequence, dLVAD support now approaches a 60% 5-year survival,[7] unveiling hemodynamic-related events (HDREs) as the driver of late morbidity, by hampering the durability of the pump–patient continuum.

The proposed HDRE designation,[3,8] comprising right heart failure (RHF) and aortic insufficiency (AI), poses the emphasis on the relationship between long-term continuous flow (CF) physiology and the development of these increasingly recognized dLVAD complications. Although the emergence of HDREs may originate from preexisting patient-specific cardiomyopathy features and valve abnormalities, dLVAD CF can induce hemodynamic aberrancies that drive and exacerbate the development of overt HDREs.

Importantly, while the prevention and management of these complications is conceivably entrenched in hemodynamic optimization, the absence of shared classification and staging systems based on objective multiparametric assessment precludes a formal evaluation of HDREs' prevalence and severity and the knowledge necessary to develop clinical strategies to mitigate HDREs.

The reported incidence of late RHF strongly varies from 8% to 45% on the basis of the adopted definition, assessment modality, and post-dLVAD time frame.[9–12] Similarly, the incidence and the trajectory of post-dLVAD AI over the long term remain a matter of debate.[13,14] As a consequence, the clinical phenotypes, the triggers, the trajectories, and the prognostic relevance of post-dLVAD RHF and AI remain largely unclear.

Therefore, the dLVAD Hemodynamic Classification System (HCS) of HDREs was recently proposed[8] to provide a uniform clinical framework able to identify, stage, and phenotype HDREs in clinical studies and real-world practice. The dLVAD HCS adjudicates and stages HDREs based on a multidimensional approach comprising instrumental, hemodynamic and clinical criteria of RHF/AI, and further classifies HDRE phenotypes based on the presence of isolated or combined RHF/AI criteria.[8] Although the primary aim of the dLVAD HCS is to encourage a more profound comprehension of HDREs for the advancement of technology and management, its applicability in identifying pathophysiological and clinical clusters, as well as its prognostic implications, have never been tested.

Hence, we sought to evaluate the applicability and clinical relevance of the dLVAD HCS in a large real-world cohort of consecutive patients with a dLVAD with available comprehensive clinical, echocardiographic, and hemodynamic assessment and long-term clinical follow-up.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

All patients with advanced HF undergoing implantation with a CF durable dLVAD at a quaternary

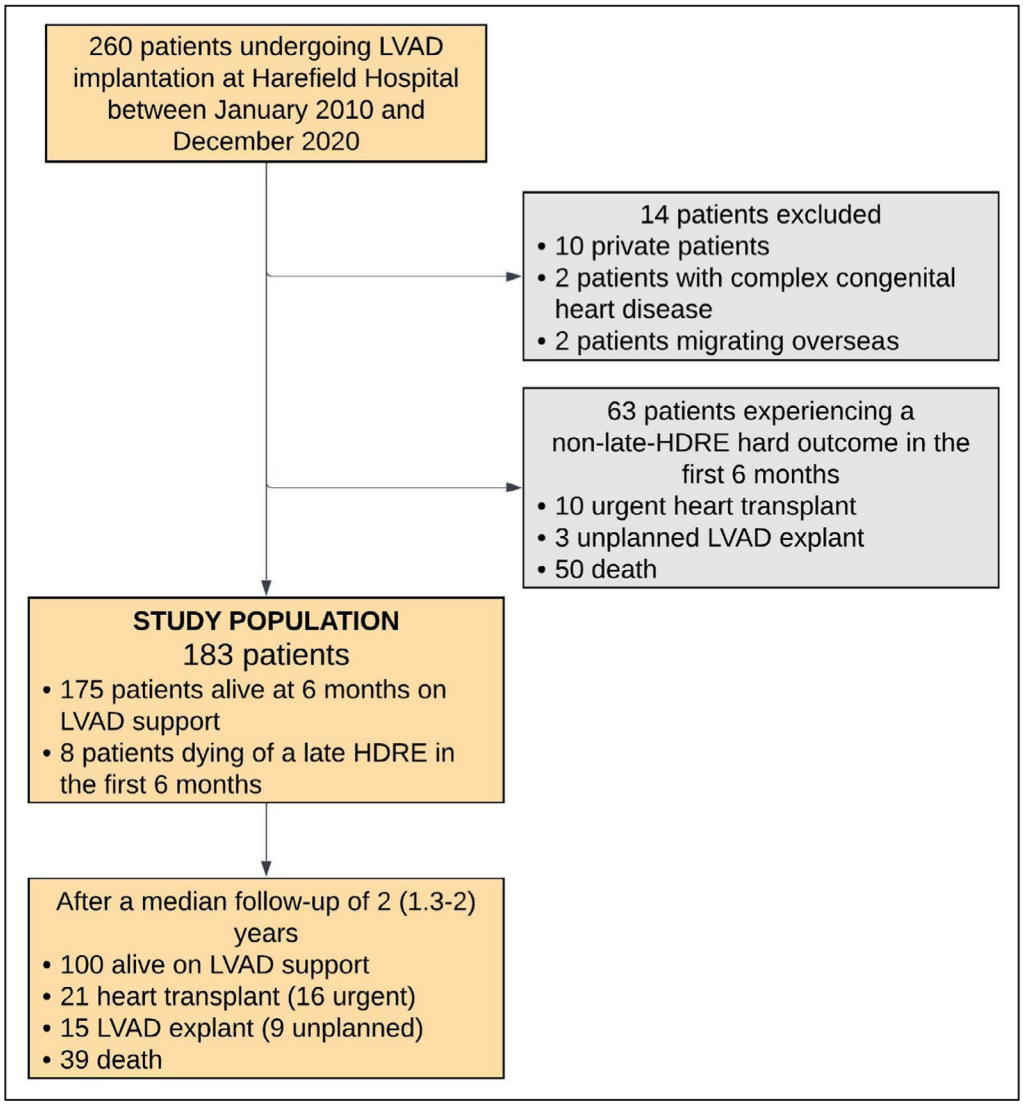


Figure 1. Study population flowchart.
HDRE indicates hemodynamic-related event; and LVAD, left ventricular assist device.

cardiogenic shock and advanced HF institution between January 2010 and December 2020 were retrospectively included in the dedicated dLVAD registry.

Data on patients with a dLVAD were obtained from the hospital archives and from the UK National Health Service prospective database on dLVAD. The local institutional review board approved this work for submission and publication and advised that no specific informed consent was required due to the retrospective nature of the study and the use of fully anonymized data, which are part of an ongoing audit.

All patients alive on dLVAD support at 6 months after implant or those dying of a late HDRE (defined as occurring after 30 days from implant) before the 6-month assessment were included in the present analysis. The study population flowchart is reported in Figure 1.

At 6-month evaluation, a comprehensive assessment of clinical data, echocardiogram, right heart catheterization (RHC), and cardiopulmonary exercise testing (CPEX) was routinely performed following a dedicated prospective clinical practice protocol.[15] All echocardiographic, RHC, and CPEX examinations and outpatient visits were retrospectively reviewed.

Hemodynamic Classification System

The HCS proposed by Grinstein et al[8] was adopted to adjudicate, stage, and phenotype HDREs (Table 1). Briefly, the classification system proposes tiers of HDRE intensity based on the presence of given instrumental, hemodynamic, and clinical criteria of RHF/AI, and further classifies HDRE phenotypes

Table 1. Hemodynamic Classification System*

Intensity	Clinical phenotypes	
	AI HDRE	RHF HDRE
Tier 1 (mild)		
Instrumental criteria	Mild/moderate or greater AI on TTE	Moderate or greater RV dysfunction on TTE
Hemodynamic criteria	PCWP, 16–20 mm Hg AND LVAD flow within 1 L/min of measured output	RAP, 13–16 mm Hg OR PAPi <2
Tier 2 (moderate)		
Instrumental/clinical criteria	Moderate or greater AI on TTE	Moderate or greater RV dysfunction on TTE AND Clinical and laboratory evidence of RHF†
Hemodynamic/clinical criteria	PCWP >20 mm Hg OR LVAD flow ≥1 L/min of measured output	RAP >16 mm Hg OR Need for oral pulmonary vasodilators due to RHF and persistently elevated PVR
Tier 3 (severe)		
Instrumental/clinical criteria	Moderate or greater AI on TTE	Moderate or greater RV dysfunction on TTE AND Clinical and laboratory evidence of RHF*
Hemodynamic/clinical criteria	PCWP >20 mm Hg OR LVAD flow ≥1 L/min of measured output AND Need for inotropes or valvular intervention to maintain adequate LVAD flow or progressive end-organ dysfunction or death attributable to AI	RAP ≥16 mm Hg AND RHF hospitalization with need for inotropes, inhaled vasodilators or RVAD or progressive end-organ dysfunction or death attributable to RHF

HDREs were diagnosed on the basis on the Hemodynamic Classification System proposed by Grinstein et al.[8] The classification proposes tiers of HDRE intensity based on the presence of given instrumental, hemodynamic, and clinical criteria of RHF/AI, and further classifies HDRE phenotypes on the basis of the presence of isolated or both RHF and AI criteria. A given intensity tier was diagnosed when both the instrumental and hemodynamic criteria were satisfied. The combined phenotype was diagnosed when both RHF and AI criteria were met. AI indicates aortic insufficiency; dLVAD, left ventricular assist device; HDRE, hemodynamic-related event; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHF, right heart failure; RV, right ventricle; RVAD, right ventricular assist device; and TTE, transthoracic echocardiogram.

*Adapted from Grinstein et al.[8]

†Clinical and laboratory features of RHF as defined by the Academic Research Consortium.[8]

based on the presence of isolated or both RHF/AI criteria. For the purpose of the present study, the following pragmatic adaptations were performed: (1) The hemodynamic criteria were measured at the patient's actual dLVAD flow, instead of a fixed dLVAD flow set to 2.2 L/min per m^2; (2) AI severity was also adjudicated among patients with Doppler arterial pressure >80 mm Hg; (3) the combined AI and RHF phenotype was defined by the presence of both AI and RHF criteria; and (4) tier 3a and 3b events were pooled together (severe HDREs).

The HDRE presence, intensity, and phenotype were diagnosed on the basis of the 6-month comprehensive clinical and instrumental assessment.

Study Outcomes

All causes of death, dLVAD explant, or heart transplantation (HT); pump thrombosis events; and HF hospitalizations were reviewed and retrospectively adjudicated. Clinical events attributed to AI, including HF hospitalizations, aortic valve (AV) interventions, AI-related urgent HT, and AI-related death, and the clinical events attributed to late RHF according to the Academic Research Consortium definition,[8] were reviewed and retrospectively adjudicated.

The primary outcome was a composite of first HF hospitalization or cardiovascular death. Secondary clinical outcomes comprised a composite of AV-related and RHF-related clinical events (including AI/RHF-related HF hospitalization requiring inotropes/mechanical circulatory support, all-cause death, urgent HT, or AV intervention); all-cause death; and the composite of all-cause death, urgent HT, or unplanned dLVAD explant. HRAEs (stroke, gastrointestinal bleeding, pump thrombosis) were also evaluated. Study outcomes were evaluated from the 6-month assessment up to 2 years thereafter. Follow-up was censored when HT, dLVAD explant, or death occurred. Early right ventricular (RV) failure was defined according to the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classification.[16]

Statistical Analysis

Categorical variables are expressed as number and percentage, and the χ^2 test was used for comparison. Continuous variables were summarized as mean±SD or median (interquartile range) and compared using

Student's *t* test or the Wilcoxon rank-sum test on the basis of the distribution of the data, with the choice of test informed by the assessment of normality.

Patient characteristics, including patient history, pre-dLVAD assessment (clinical, biochemical, echocardiographic, and hemodynamic), periprocedural dLVAD management and hospitalization course, and 6-month assessment, were evaluated according to the presence or absence of HDREs (both RHF/AI) and to HDRE phenotypes (none versus isolated RHF/AI versus combined RHF/AI).

Univariate and multivariate logistic regression analyses were performed to identify at pre-dLVAD assessment the predictors of RHF and AI HDRE development at 6 months. Age, sex, and all the univariate predictors associated with a $P<0.10$ to HDRE development were included in the multivariate model. The 8 patients dying because of a late HDRE between 30 days and 6 months after dLVAD implant (see Results) were included in the pre-dLVAD model only.

Kaplan–Meier survival curves and log-rank *P* values were used to evaluate the impact of HDRE intensity and phenotype on study outcomes.

Univariate and multivariate Cox regression analyses were performed to identify the association of HDRE intensity and phenotype with study outcomes. In the intensity analysis, moderate and severe HDREs were analyzed together. Two multivariate adjustments were carried: The first adjusted for in-study outcome predictors identified in a prior analysis from the same cohort (age, concomitant other cardiac surgery during dLVAD implant, early INTERMACS RV failure, 6-month heart rate, no therapy with renin–angiotensin–aldosterone system inhibitors)[15]; the second adjusted for validated predictors of long-term death (elevated preimplant blood urea nitrogen, prior coronary artery bypass graft or valve procedure, and HRAEs; ventricular arrhythmias; and estimated glomerular filtration rate <60 mL/min per 1.73 m^2 evaluated at 6-month assessment).[17] Importantly, each of the identified covariates in the first model has clinical relevance, biological plausibility, and established associations with adverse outcomes in prior LVAD populations. A directed acyclic graph illustrating the assumed relationships between patient characteristics, HDREs, and clinical outcomes is reported in Figure S1. The 8 patients who died due to a late HDRE between 30 days and 6 months after dLVAD implantation were excluded from the 6-month HDRE characterization and the outcome models, as 6-month covariates were not available.

A $P<0.05$ was considered statistically significant. No corrections for multiple comparisons were performed. Statistical analyses were conducted using SPSS version 24.0 (SPSS Inc., Chicago, IL), RStudio version 1.3.1093 (Posit Software, Boston, MA), and STATA version 17 (StataCorp, College Station, TX). We used the Strengthening the Reporting of Observational Studies in Epidemiology cohort checklist when writing our report.[18]

RESULTS

Study Population

Among 260 patients undergoing dLVAD implantation at our institution between January 2010 and December 2020, 12 patients were excluded for administrative reasons, 2 patients because of complex congenital disease, and 63 patients who experienced a nonlate–HDRE-related hard outcome in the first 6 months after dLVAD implantation. The causes of nonlate–HDRE-related hard outcome are detailed in Table S1. Of note, among patients experiencing a nonlate–HDRE-related hard outcome, the incidence of early RVF was high (n=43 [68.3%]), and early RVF was frequently adjudicated to be the cause of the hard outcome (n=6 early RVF-related death, n=4 early RVF-related urgent heart transplant). In the final study population of 183 patients (Figure 1), 175 were alive on dLVAD support at 6 months, and 8 patients died because of a late HDRE (all RHF HDREs) between 30 days and 6 months after dLVAD implant.

Mean age at dLVAD implant was 47±13 years, 82% were men, and 28.9% were affected by ischemic cardiomyopathy. Most patients underwent dLVAD implantation with a HeartWare (Medtronic, Minneapolis, MN) pump (93.5%; Table 2).

HDRE Incidence, Intensity, and Phenotypes

At 6-month assessment, RHF HDREs could be evaluated in all patients, while AI HDREs could not in 22 (12.0%) patients lacking a comprehensive hemodynamic assessment. Overall, 53 (29.0%) patients developed an RHF HDRE, and 26 (16.0%) an AI HDRE. Of these, 39 (57.4%) had an isolated RHF phenotype, 15 (22.1%) an isolated AI phenotype, 11 (16.2%) a combined RHF–AI phenotype, and 3 (4.4%) could not be adjudicated. Among patients with RHF HDREs, the event was mild in 28 (52.8%), moderate in 2 (3.8%), and severe in 23 (43.4%). Among patients with an AI HDRE, the event was mild in 20 (76.9%), moderate in 6 (23.1%), and never severe (Figure 2). The HDRE instrumental hemodynamics and clinical criteria are reported in Table 2.

The characteristics of the cohort, including pre-dLVAD history; dLVAD index hospitalization course; and 6-month clinical, echocardiographic, and hemodynamic assessment, stratified by RHF HDRE and AI HDRE at 6-month assessment, are reported in Tables 3 and 4.

Right HF HDRE

Patients developing an RHF HDRE were more likely to require an intensive bundle of care before dLVAD

Table 2. Individual Instrumental, Hemodynamic, and Clinical Criteria of RHF and AI HDREs in the Study Cohort Based on the Hemodynamic Classification System

	Study population, n (%) (n=183)
AI HDRE	26 (16.0)
AI Intensity	
Tier 1: mild, %	20 (12.4)
Tier 2: moderate, %	6 (3.7)
Tier 3: severe, %	0 (0)
AI any instrumental criteria, %	105 (57.4)
Aortic regurgitation	
Mild, %	77 (42.1)
Moderate or greater, %	28 (15.3)
AI any hemodynamic/clinical criteria, %	42 (26.1)
Wedge pressure, mm Hg	
16–20 mm Hg	31 (19.1)
>20 mm Hg	16 (9.9)
LVAD flow minus CO ≥1 L/min, %	36 (23.2)
AI requiring intervention (1–6 mo after dLVAD), %	0 (0)
AI causing severe decompensation/death (1–6 mo after dLVAD), %	0 (0)
RHF HDRE	53 (29.0)
RHF intensity	
Tier 1: mild, %	28 (15.3)
Tier 2: moderate, %	2 (0.1)
Tier 3: severe, %	23 (12.6)
RHF any instrumental criteria, %	88 (48.1)
RV dysfunction moderate or greater on TTE, %	83 (45.4)
Late clinical RHF (1–6 mo after dLVAD), %	32 (17.5)
RHF any hemodynamic/clinical criteria, %	87 (47.5)
Right atrial pressure ≥16 mm Hg, %	15 (8.9)
PAPi <2, %	53 (35.8)
Need for oral pulmonary vasodilators, %	28 (17.0)
PVR >3 WU (6-mo RHC), %	28 (18.3)
RHF hospitalization (1–6 mo after dLVAD), %	26 (14.2)
Requiring inotropes	23 (88.5)
Requiring inhaled pulmonary vasodilators, %	0 (0)
Requiring RVAD, %	0 (0)
Death due to RHF (1–6 mo after dLVAD), %	8 (4.4)

AI indicates aortic insufficiency; CO, cardiac output; dLVAD, durable left ventricular assist device; HDRE, hemodynamic-related event; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHF, right heart failure; RV, right ventricle; RVAD, right ventricular assist device; and TTE, transthoracic echocardiogram.

implantation, including vasoactive drugs, temporary mechanical circulatory support, mechanical ventilation, and renal replacement therapy. Also, their pre-dLVAD hemodynamics were consistent with worse RV function. After dLVAD implantation, they were more likely to experience early RHF and require RV assist device implantation and, at discharge, to present RV dilation and dysfunction, along with hepatorenal damage. In the first 6 months, they were more likely to experience HRAEs, driven by major bleedings. At 6-month assessment, they were more likely to have echocardiographic and hemodynamic features of suboptimal left ventricular (LV) unloading, RV dysfunction, and peripheral congestion, together with hepatorenal damage and hypoalbuminemia. Their functional capacity was also more compromised, as objectively evaluated at CPEX.

Among pre-dLVAD characteristics, age (per-year increase: hazard ratio [HR], 1.03 [95% CI, 1.00–1.07]) and pre-dLVAD pulmonary artery pulsatility index (per unit decrease: HR, 1.38 [95% CI, 1.06–1.79]) were independently associated with the development of RHF HDRE (Table 5).

Aortic Insufficiency HDRE

Patients developing an AI HDRE were more likely to have pre-dLVAD AI (34.8% versus 17.2%, *P*=0.056). Also, they were more likely to undergo concomitant AV replacement during dLVAD implantation (19.2% versus 6.0%, *P*=0.039). The in-hospital and first 6-month course were similar regardless of subsequent AI HDRE development. At 6-month assessment, patients with AI HDREs were more likely to present with higher dLVAD flows coupled with echocardiographic and hemodynamic features of suboptimal LV unloading, RV dysfunction, and peripheral congestion. Their functional capacity was also more compromised, as objectively evaluated at CPEX.

Among pre-dLVAD characteristics, pre-dLVAD AI (HR, 3.42 [95% CI, 1.15–10.24]) and pre-dLVAD systolic pulmonary artery pressure (per mm Hg increase: HR, 1.05 [95% CI, 1.02–1.09]) were independently associated with the development of AI HDRE (Table 5).

HDRE Phenotypes

The characteristics of the cohort, including pre-dLVAD history; dLVAD index hospitalization course; and 6-month clinical, echocardiographic, and hemodynamic assessment, stratified by HDRE phenotypes at 6-month assessment, are reported in Tables S2 and S3. A selection of relevant clinical and instrumental characteristics stratified by HDRE phenotype is reported in Figure 3. Overall, patients with the combined RHF–AI HDRE phenotype required the most intensive bundle of critical care pre-dLVAD implantation, showed the most prominent hemodynamic features of pre-dLVAD RV dysfunction, and had the highest rate of AV replacement during dLVAD implantation. Following dLVAD implant, they experienced the highest incidence of early post-dLVAD RV failure. At hospital discharge, overall, they exhibited the most prominent suboptimal LV unloading, RV

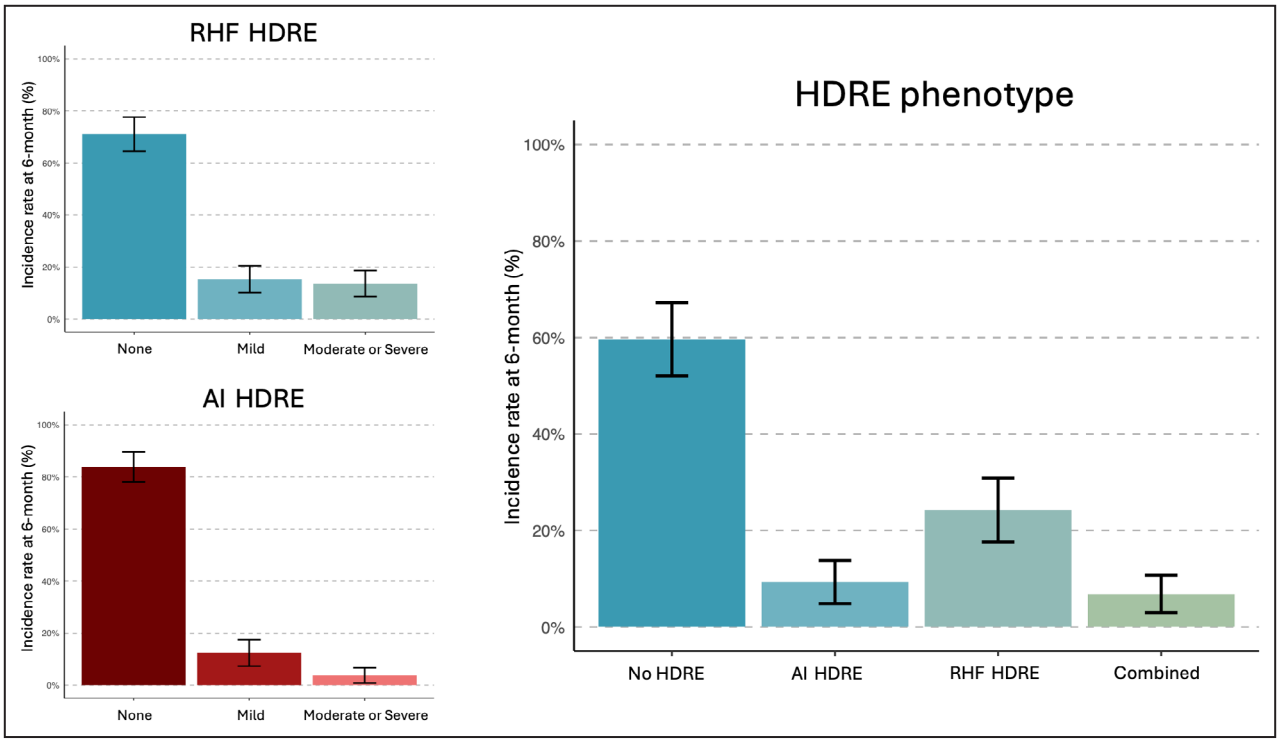


Figure 2. HDREs incidence, intensity, and phenotypes at 6-month post-dLVAD assessment in the study cohort.
Rates are surrounded by their 95% CIs. AI indicates aortic insufficiency; dLVAD, durable left ventricular assist device; HDRE, hemodynamic-related event; and RHF, right heart failure.

dysfunction, peripheral congestion, and renal damage. At 6 months, patients with the combined RHF–AI HDRE phenotype presented with the highest heart rate and, at RHC, had the lowest rate of optimal hemodynamic profile (defined as cardiac index ≥2.2 L/min per m^2, wedge pressure <18 mm Hg and right atrial pressure <12 mm Hg),[19,20] the highest right atrial pressure and the lowest pulmonary artery pulsatility index. Despite preserved dLVAD flow, they had the lowest cardiac index and the highest LV filling pressures. At 6-month echocardiographic assessment, they had the lowest rate of optimal echocardiographic profile (defined as neutral interventricular septal position, mitral regurgitation less than moderate, and at least intermittent AV opening),[21] and the highest occurrence of more than mild AI, more than mild tricuspid regurgitation, and persistent valve closure. Combined RHF–AI HDREs had the worst functional capacity at CPEX (Figure 3).

HDREs and Outcomes

At a median follow-up of 2 (interquartile range, 1.3–2.0) years after the 6-month assessment, 39 patients had died, 16 patients underwent urgent HT, and 9 patients underwent unplanned dLVAD explant. HF hospitalizations occurred in 24 patients and cardiovascular death in 17 patients. RHF-related events occurred in 26 patients, including 23 hospitalizations (18 requiring inotropes, 2 requiring nitric oxide, 4 requiring RV assist device), 8 deaths, and 5 HTs. AI-related events occurred in 9 patients, including 8 hospitalizations requiring inotropes, 8 AV interventions, 4 deaths, and 0 HTs. Overall, 69 patients experienced an HRAE.

Right HF HDRE

RHF HDRE at 6 months after implantation was associated with the primary outcome (HR, 3.13 [95% CI, 1.44–6.79]; *P*=0.004), and with all secondary outcomes, including HRAEs (Table 6). After multivariate adjustment for in-study outcome predictors, RHF HDREs remained independently associated with the primary outcome (adjusted HR, 2.69 [95% CI, 1.14–6.34]; *P*=0.024; Figure 4). Results were consistent when adjusting for validated predictors of long-term death (adjusted HR, 1.53 [95% CI, 1.01–2.34]; *P*=0.047).

The severity of RHF HDREs was associated with the primary outcome (mild RHF versus no RHF: HR, 3.00 [95% CI, 1.26–7.16]; *P*=0.013; moderate/severe RHF versus no RHF: HR, 3.42 [95% CI, 1.11–10.57]; *P*=0.032; Figure S2). The association of RHF HDRE severity with secondary outcomes is reported in Table S4.

Aortic Insufficiency HDRE

AI HDRE at 6 months after implantation was associated with the primary outcome (HR, 3.72 [95% CI, 1.65–8.39]; *P*=0.002), with RHF/AI-related clinical

Table 3. Characteristics of the Study Cohort Including Pre-dLVAD History, Clinical Presentation, Pre-dLVAD Echocardiographic and Hemodynamic Profiles, dLVAD Periprocedural Course and Hospital Discharge Assessment Stratified by RHF HDRE and AI HDRE

	Overall (n=183)	No AI HDRE (n=135)	AI HDRE (n=26)	*P* value	No RHF HDRE (n=130)	RHF HDRE (n=53)	*P* value
History							
Age, y, mean±SD	47±13	47±12	48±12	0.889	47±13	48±12	0.853
Male sex, n (%)	150 (82.0)	111 (82.2)	23 (88.5)	0.573	108 (83.1)	42 (79.2)	0.532
BMI, kg/m^2, mean±SD	26±4	26±4	26±4	0.840	26±5	26±4	0.626
Ischemic cardiomyopathy, n (%)	52 (28.9)	39 (29.5)	6 (23.1)	0.637	40 (30.8)	12 (24.0)	0.463
ICD, n (%)	97 (53.9)	69 (52.3	19 (73.1)	0.055	66 (50.8	31 (62.0)	0.186
Prior sternotomy, n (%)	24 (15.5)	18 (15.9)	2 (8.3)	0.526	14 (12.5)	10 (23.3)	0.135
Clinical presentation							
INTERMACS classification				0.799			0.185
1–2, n (%)	122 (67.8)	87 (66.0)	19 (73.1)		87 (67.0)	35 (70)	
3, n (%)	48 (26.7)	36 (27.3)	7 (26.9)		34 (26.2)	14 (28.0)	
≥4, n (%)	10 (5.6)	9 (6.9)	0 (0)		9 (7.0)	1 (2)	
Need for inotropes, n (%)	135 (75.4)	97 (73.5)	22 (84.6)	0.321	90 (69.8)	45 (90.0)	0.004
Need for vasopressors, n (%)	21 (11.7)	13 (9.8)	5 (19.2)	0.181	11 (8.5)	10 (20.0)	0.039
Need for AMCS, n (%)	58 (31.9)	41 (30.6)	8 (30.8)	1.000	35 (26.9)	23 (44.2)	0.034
Need for ventilatory support, n (%)	38 (20.8)	24 (17.8)	6 (23.1)	0.583	19 (14.6)	19 (35.8)	0.002
Need for CRRT, n (%)	17 (9.4)	11 (8.3)	3 (11.5)	0.704	6 (4.6)	11 (22.0)	<0.001
Anemia, n (%)	54 (29.5)	42 (31.1)	8 (30.8)	1.000	34 (26.2)	20 (37.7)	0.153
Thrombocytopenia, n (%)	142 (78.9)	27 (20.5)	5 (19.2)	1.000	107 (82.3)	35 (70.0)	0.101
GFR <60 mL/min per 1.73 m^2, n (%)	39 (21.3)	24 (17.8)	7 (26.9)	0.285	29 (22.3)	10 (18.9)	0.693
Hyperbilirubinemia, n (%)	34 (18.6)	27 (20.0)	5 (19.2)	1.000	19 (14.6)	15 (28.3)	0.037
Hypoalbuminemia, n (%)	79 (43.2)	55 (40.7)	12 (46.2)	0.667	51 (39.2)	28 (52.8)	0.102
Pre-LVAD implant echocardiography and hemodynamics							
LVEDD, mm, mean±SD	66 (12)	66 (12)	67 (12)	0.541	66 (12)	66 (12)	0.978
LVEF, %, mean±SD	22 (11)	21 (10)	23.1 (11)	0.423	22 (11)	20 (10)	0.171
RV/LV basal diameter, median (interquartile range)	0.66 (0.60–0.74)	0.65 (0.56–0.74)	0.69 (0.62–0.77)	0.377	0.67 (0.58–0.64)	0.66 (0.61–0.71)	0.809
TAPSE, mm, mean±SD	14 (4)	14 (4.1)	14 (6)	0.869	14 (5)	13 (4)	0.268
RV dysfunction moderate or greater, n (%)	74 (51)	57 (51.8)	11 (61.1)	0.813	49 (48.5)	25 (56.8)	0.694
MR greater than mild, n (%)	118 (67.5)	86 (67.2)	7 (26.))	1.000	89 (70.1)	29 (60.4)	0.803
TR greater than mild, n (%)	73 (41.7)	57 (44.9)	8 (30.7)	0.500	51 (41.1)	22 (43.1)	0.266
Any aortic regurgitation, n (%)	28 (20.1)	20 (17.2)	8 (34.8)	0.056	22 (19.0)	12 (27.9)	0.158
Heart rate, bpm, mean±SD	85 (19)	85 (18)	80 (18)	0.173	83 (19)	90 (18)	0.024
Mean BP, mm Hg, mean±SD	76 (11)	76 (11)	78 (10)	0.476	77 (11)	76 (10)	0.684
Cardiac index, L/min per m^2, mean±SD	1.74 (0.54)	1.74 (0.55)	1.70 (0.47)	0.803	1.76 (0.49)	1.69 (0.66)	0.472
Wedge pressure, mm Hg, mean±SD	25 (8)	25 (8)	28 (7)	0.063	25 (8)	25 (7)	0.994
SPAP, mm Hg, mean±SD	53 (17)	51 (16)	63 (18)	0.001	54 (17)	51 (15)	0.393
RAP, mm Hg, mean±SD	13 (6)	13 (7)	14 (6)	0.388	12 (7)	14 (6)	0.054
PAPi, mean±SD	3.0 (3.7)	2.8 (3.4)	3.8 (5.7)	0.306	3.3 (4.2)	2.0 (1.5)	0.031
RAP/WP, mean±SD	0.50 (0.25)	0.50 (0.24)	0.49 (0.23)	0.863	0.47 (0.25)	0.58 (0.25)	0.024
Perioperative characteristics							
Heartware, n (%)	171 (93.5)	124 (91.9)	20 (96.2)	0.724	118 (90.7)	53 (100)	0.091

(*Continued*)

Table 3. Continued

	Overall (n=183)	No AI HDRE (n=135)	AI HDRE (n=26)	*P* value	No RHF HDRE (n=130)	RHF HDRE (n=53)	*P* value
CPB, n (%)	167 (92.8)	124 (93.9)	25 (96.2)	1.000	121 (93.1)	46 (92.0)	0.757
CPB time, min, mean±SD	80 (29)	80 (30)	85 (32)	0.587	76 (27)	89 (34)	0.035
Conc. other cardiac surgery, n (%)	18 (9.9)	8 (6.0)	5 (19.2)	0.039	10 (7.7)	8 (15.4)	0.167
Early RV failure, n (%)	83 (45.4)	58 (43.0)	16 (61.5)	0.090	44 (33.8)	39 (73.6)	<0.001
Need for RVAD, n (%)	13 (7.2)	12 (9.0)	1 (3.8)	0.696	6 (4.6)	7 (13.7)	0.049
Predischarge assessment							
LVEDD, mm, mean±SD	59 (12)	59 (12)	63 (10)	0.103	59 (12)	58 (12)	0.464
LVEF, %, mean±SD	17 (11)	18 (12)	14 (8)	0.151	17 (11)	18 (12)	0.795
Aortic valve opening, n ()	82 (46.9)	58 (45.7)	13 (50.0)	0.830	66 (50.8)	16 (35.6)	0.086
RV septal position				0.095			0.011
Leftward, n (%)	37 (21.5)	34 (26.8)	2 (7.7)		21 (16.4)	16 (36.4)	
Neutral, n (%)	87 (50.6)	59 (46.5)	16 (61.5)		66 (51.6)	21 (47.7)	
Rightward, n (%)	48 (27.9)	34 (26.8)	8 (30.8)		41 (32.0)	7 (15.9)	
Dilated RV, n (%)	59 (36.4)	40 (32.5)	12 (52.2)	0.096	34 (28.3)	25 (59.5)	<0.001
TAPSE, mm, mean±SD	9.54 (2.91)	9.56 (2.97)	8.96 (2.96)	0.374	9.89 (2.94)	8.50 (2.56)	0.013
RV dysfunction moderate or greater, n (%)	85 (49.7)	62 (49.6)	15 (60.0)	0.722	44 (34.9)	41 (91.1)	<0.001
MR greater than mild, n (%)	41 (23.6)	29 (22.8)	6 (23.1)	1.000	26 (20.0)	15 (34.1)	0.066
TR greater than mild, n (%)	50 (28.6)	38 (29.9)	10 (38.5)	0.487	23 (17.7)	27 (60.0)	<0.001
Any aortic regurgitation, n (%)	80 (52.3)	60 (47.2)	20 (76.9)	0.005	61 (46.9)	25 (55.6)	0.205
Anemia, n (%)	25 (13.7)	21 (15.6)	4 (15.4)	1.000	18 (13.8)	7 (13.2)	1.000
GFR <60 mL/min per 1.73 m^2 (%)	20 (11.0)	12 (9.0)	4 (15.4)	0.298	11 (8.5)	9 (17.3)	0.114
Hyperbilirubinemia, n (%)	8 (4.6)	6 (4.7)	1 (3.8)	1.000	1 (0.8)	7 (14.3)	<0.001

AI indicates aortic insufficiency; AMCS, acute mechanical circulatory support; BMI, body mass index; BP, blood pressure; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; dLVAD, durable left ventricular assist device; GFR, glomerular filtration rate; HDRE, hemodynamic-related event; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PAPi, pulmonary artery pulsatility index; RAP, right atrial pressure; RHF, right heart failure; RV, right ventricular; RVAD, right ventricular assist device; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane excursion; TR, tricuspid regurgitation; VT/VF, ventricular tachycardia/ventricular fibrillation, and WP, wedge pressure.

events, and with all-cause death but not with the composite of all-cause death, urgent HT, or dLVAD explant, nor with HRAEs (Table 6). After multivariate adjustment for in-study outcome predictors, AI HDREs remained independently associated with the primary outcome (adjusted HR, 4.21 [95% CI, 1.70–10.40]; *P*=0.002; Figure 4). Results were consistent when adjusting for validated predictors of long-term death (adjusted HR, 2.74 [95% CI, 1.53–4.87]; *P*<0.001).

The severity of AI HDREs was associated with the primary outcome (mild AI versus no AI: HR, 2.70 [95% CI, 1.04–7.02]; *P*=0.042; moderate/severe AI versus no AI: HR, 8.76 [95% CI, 2.83–27.17]; *P*<0.001; Figure S2). The association of AI HDRE severity with secondary outcomes is reported in Table S4.

HDRE Phenotypes

A stepwise increase in the risk on primary outcome occurrence was observed according to the HDRE phenotype (isolated RHF/AI HDRE versus no HDRE: HR, 3.31 [95% CI, 1.33–8.25]; *P*=0.010; combined RHF/AI HDRE versus no HDRE: HR, 7.38 [95% CI, 2.41–22.63]; *P*<0.001; Figure 5). Similarly, a gradient of risk according to HDRE phenotype was observed for RHF/AI-related events; all-cause death; and the composite of all-cause death, urgent HT, or dLVAD explant, while only the combined RHF/AI phenotype was associated with HRAEs (Table S5).

After multivariate adjustment for in-study outcome predictors, HDRE phenotype remained independently associated with the primary outcome (isolated RHF/AI HDRE versus no HDRE: adjusted HR, 2.80 [95% CI, 1.03–7.62]; *P*=0.044; combined RHF/AI HDRE versus no HDRE: adjusted HR, 4.53 [95% CI, 1.33–15.35]; *P*=0.015). Results were consistent when adjusting for validated predictors of long-term death (isolated RHF/AI HDRE versus no HDRE: adjusted HR, 2.77 [95% CI, 1.05–7.28]; *P*=0.039; combined RHF/AI HDRE versus no HDRE: adjusted HR, 5.00 [95% CI, 1.46–17.09]; *P*=0.010).

Table 4. Six-Month Clinical, Echocardiographic, and Hemodynamic Assessment in the Study Population Stratified by RHF HDRE and AI HDRE

	Overall (n=183)	No AI HDRE (n=135)	AI HDRE (n=26)	*P* value	No RHF HDRE (n=130)	RHF HDRE (n=53)	*P* value
6-mo assessment and events							
Mean BP, mm Hg, mean±SD	82 (11)	82 (11)	83 (11)	0.921	81 (10)	84 (12)	0.176
HR, bpm, mean±SD	75 (13)	73 (12)	79 (13)	0.071	72 (12)	82 (12)	<0.001
LVAD flow, L/min, mean±SD	5.08 (0.80)	4.98 (0.82)	5.40 (0.54)	0.044	5.14 (0.87)	4.94 (0.60)	0.194
LVAD speed, rpm, median (interquartile range)	2700 (2600–2865)	2700 (2630–2900)	2700 (2600–2875)	0.346	2700 (2600–2800)	2760 (2615–2900)	0.326
Sustained VT/VF, n (%)	4 (2.2)	3 (2.2)	1 (3.8)	0.509	3 (2.3)	1 (1.9)	1.000
Major bleeding, n (%)	58 (31.7)	45 (33.3)	9 (34.6)	1.000	28 (21.5)	30 (56.6)	<0.001
Major infection, n (%)	102 (55.7)	73 (54.1)	14 (53.8)	1.000	75 (57.7)	27 (50.9)	0.417
Neurological event, n (%)	32 (17.5)	19 (14.1)	7 (26.9)	0.141	24 (18.5)	8 (15.1)	0.672
Pump thrombosis, n (%)	5 (2.7)	3 (2.2)	0 (0.0)	1.000	4 (3.1)	1 (1.9)	1.000
Dialysis, n (%)	29 (15.8)	20 (14.8)	5 (19.2)	0.560	13 (10.0)	16 (30.2)	0.001
Anemia, n (%)	17 (10.8)	7 (6.2)	3 (12.0)	0.388	9 (7.8)	8 (19.0)	0.076
GFR <60 mL/min per 1.73 m^2, n (%)	20 (13.2)	12 (11.2)	5 (20.0)	0.316	11 (10.0)	9 (22.0)	0.063
Hyperbilirubinemia, n (%)	6 (3.8)	4 (3.5)	2 (8.0)	0.298	2 (1.7)	4 (9.5)	0.044
Hypoalbuminemia, n (%)	151 (96.2)	109 (96.5)	23 (92.0)	0.285	113 (98.3)	38 (90.5)	0.044
6-mo echocardiography and hemodynamics							
Optimal echo profile, n (%)	41 (23.8)	34 (26.8)	2 (7.7)	0.042	36 (28.1)	5 (11.4)	0.025
LVEDD, mm, mean±SD	60 (11)	60 (11)	66 (13)	0.013	60 (11)	61 (11)	0.505
LVEF, %, mean±SD	19 (14)	20 (14)	18 (15)	0.440	20 (13)	19 (14)	0.884
Aortic valve opening, n (%)	85 (48.6)	63 (49.6)	8 (30.8)	0.088	70 (53.8)	15 (33.3)	0.024
RV septal position				0.424			0.094
Leftward, n (%)	23 (13.3)	18 (14.2)	3 (11.5)		13 (10.2)	10 (22.2)	
Neutral, n (%)	93 (53.8)	72 (56.7)	12 (46.2)		69 (53.9)	24 (53.3)	
Rightward, n (%)	57 (32.9)	37 (29.1)	11 (42.3)		46 (35.9)	11 (24.4)	
Dilated RV, n (%)	54 (36.5)	40 (32.8)	14 (53.8)	0.037	38 (31.1)	26 (60.5)	<0.001
TAPSE, mm, mean±SD	9.60 (2.87)	9.53 (2.84)	9.87 (2.58)	0.603	9.82 (2.87)	8.85 (2.79)	0.084
RV dysfunction moderate or greater, n (%)	88 (48.2)	58 (46.4)	16 (64)	0.434	37 (29.6)	45 (100)	<0.001
MR greater than mild, n (%)	38 (21.8)	24 (18.9)	7 (26.9)	0.421	20 (15.4)	18 (40.9)	0.001
TR greater than mild, n (%)	44 (25.6)	28 (22.4)	12 (48.0)	0.013	19 (14.8)	25 (56.8)	<0.001
Any aortic regurgitation, n (%)	94 (61.4)	68 (53.5)	26 (100)	<0.001	70 (53.8)	35 (77.8)	0.003
Optimal hemodynamic profile, n (%)	64 (41.8)	59 (46.5)	5 (19.2)	0.015	51 (45.9)	13 (31.0)	0.102
Cardiac index, L/min per m^2, mean±SD	2.34 (0.53)	2.36 (0.53)	2.26 (0.51)	0.413	2.38 (0.54)	2.24 (0.49)	0.130
Wedge pressure, mm Hg, mean±SD	12 (6)	11 (5)	19 (3)	<0.001	11 (6)	15 (7)	0.002
SPAP, mm Hg, mean±SD	32 (11)	30 (8)	44 (12)	<0.001	31 (11)	35 (10)	0.042
RAP, mm Hg, mean±SD	8 (6)	7 (5)	12 (5)	<0.001	6 (4)	13 (7)	<0.001
PAPi, mean±SD	3.9 (4.3)	4.2 (4.6)	2.5 (1.7)	0.069	4.6 (4.3)	2.3 (3.9)	0.004
RAP/WP, mean±SD	0.71 (0.44)	0.73 (0.47)	0.63 (0.28)	0.336	0.61 (0.36)	0.96 (0.54)	<0.001
RVSWi, mean±SD	6.00 (2.90)	5.77 (2.90)	6.93 (2.77)	0.079	6.52 (2.86)	4.62 (2.57)	<0.001

AI indicates aortic insufficiency; BP, blood pressure; GFR, glomerular filtration rate; HDRE, hemodynamic-related event; HR, heart rate; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PAPi, pulmonary artery pulsatility index; RAP, right atrial pressure; RAP/WP, right atrial pressure/wedge pressure ratio; RHF, right heart failure; RV, right ventricle; RVSWi, right ventricular stroke work index; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VF, ventricular fibrillation; VT, ventricular tachycardia; and WP, wedge pressure.

DISCUSSION

This study represents the first clinical, real-world validation of the recently proposed dLVAD HCS[8] to identify, stage, and phenotype HDREs in patients with advanced HF supported by a CF dLVAD. The main findings of the study can be summarized as follows:

1. The dLVAD HCS can be applied in clinical practice with elevated feasibility. This system identifies clusters of patients with specific pathophysiological, clinical, and hemodynamic features and carries relevant prognostic implications.
2. A significant incidence of RHF HDRE (29%) and AI HDRE (16%) is already present at 6 months post-dLVAD implant, and it is predicted by disease-specific pre-dLVAD characteristics.
3. RHF HDRE and AI HDRE are independently associated with adverse clinical outcomes up to 2.5 years of follow-up. The prognostic relevance is already evident for mild HDREs, and HDRE severity further negatively impacts clinical outcomes.
4. RHF and AI present simultaneously in roughly one-sixth of patients with HDREs at 6 months after dLVAD implantation. This combined phenotype entails the most prominent suboptimal left ventricular unloading, RV dysfunction, peripheral congestion, renal damage, and impaired functional capacity markers and is associated with the worst prognosis.

Pathophysiology and Clinical Relevance of HDREs

As survival on dLVAD support has improved in parallel to dLVAD technology advancements and HRAE decline,[4,22] the goals of care and research focus must now comprise late-stage complications currently dominated by RHF and AI.[2,3] These phenomena, collectively referred to as HDREs, pose challenges to the long-term durability of dLVAD support and necessitate a deeper comprehension on the underlying causes, contributing factors, incidence, trajectories, and prognostic implications. The patient-specific preexisting cardiomyopathy features and valve abnormalities interact with the dLVAD CF physiology leading to early hemodynamic aberrancies that, while subclinical, may be the drivers of late, irreversible overt HDREs, if not addressed at prior stages through mechanical and pharmacological hemodynamic optimization. CF dLVAD, in the setting of compromised LV contractility, promotes ventriculoarterial uncoupling with resulting persistent AV closure.[23–26] This mechanism, together with CF-related inflammatory and matrix metalloproteinase activation,[27] drives AV degeneration, AV leaflet fusion, and malcoaptation, eventually resulting in progressive AI. Concurrently, among patients with a predisposing RV physiology and geometry,[28] the dLVAD CF-related increase in RV preload may counterbalance the benefits of mechanical RV afterload reduction and, together with the impairment of septal contribution to RV systolic function, may unmask and precipitate RHF.[11,28–32] These hemodynamic aberrancies may further interact, so that the increase in RV afterload imposed by the AI may worsen RV function and, conversely, RV preload intolerance may preclude the increase of dLVAD speed to enhance LV unloading.

Validation of the HCS

The proposed dLVAD HCS of HDREs allows us for the first time to rigorously but practically classify these complex and multifaceted clinical scenarios, providing the ground to improve HDRE understanding and to develop mitigation strategies. Here, we report several important findings. First, the dLVAD HCS of HDREs could be practically applied in a real-world cohort of consecutive patients with a dLVAD with high feasibility. At our institution, a dedicated clinical practice protocol is implemented, comprising comprehensive serial assessment of clinical data, echocardiogram, RHC, and CPEX at prespecified time points[15]: every 6 months for clinical and echocardiographic evaluations, and every 12 months for RHC and CPEX, or sooner if clinically indicated. While such comprehensive assessments may not be feasible at all centers, the strong prognostic relevance of subclinical hemodynamic and anatomic abnormalities identified by the HCS supports the rationale for a structured, multimodal follow-up approach to detect, and potentially correct hemodynamic aberrancies early in the HDRE's natural history. Further prospective research is warranted to define the progression patterns of HDREs and determine the optimal frequency and clinical utility of serial multimodal monitoring in ambulatory patients with a dLVAD.[15] Of note, peak oxygen consumption at CPEX was associated with the presence and phenotype of HDREs, suggesting its potential to refine HDRE diagnosis and staging; this represents an important focus for future research.

Incidence and Prognostic Impact of HDREs

RHF HDRE was present in 1 of 3 patients with a dLVAD at the 6-month postimplant assessment. This is higher than previous reports,[9,11,12] mirroring the inclusion of subclinical aberrancies (tier 1: mild RHF HDRE) in the classification system. Indeed, the incidence of clinical RHF (tier 2/3: moderate/severe RHF HDRE) was 13.7%, closely to what has been reported in INTERMACS.[9] However, we emphasize the importance of subclinical

Table 5. Predictors of RHF HDRE and AI HDRE Development at 6 Months Assessed Before dLVAD Implant

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
RHF HDRE predictors before dLVAD implantation				
Age, per y increase	1.00 (0.98–1.03)	0.872	1.03 (1.00–1.07)	0.047
Sex	0.71 (0.31–1.65)	0.429	…	NS
Pre-LVAD PAPi, per unit decrease	0.77 (0.60–0.98)	0.036	1.38 (1.06–1.79)	0.015
≥3 inotropes	4.44 (1.50–13.25)	0.008	…	NS
Vasopressor	2.71 (1.04–7.04)	0.041	…	NS
Temporary MCS	1.98 (0.98–4.02)	0.058	…	NS
Mechanical ventilation	2.75 (1.26–6.01)	0.011	…	NS
Renal replacement therapy	5.17 (1.72–15.49)	0.003	…	NS
Total bilirubin, per mg/dL increase	1.54 (1.07–2.22)	0.021	…	NS
AI HDRE predictors before dLVAD implantation				
Age, per y increase	1.00 (0.97–1.03)	0.886	…	NS
Sex	1.70 (0.47–6.13)	0.421	…	NS
ICD	2.59 (1.02–6.59)	0.046	…	NS
Pre-LVAD aortic insufficiency	2.40 (0.90–6.43)	0.082	3.42 (1.15–10.24)	0.028
Pre-LVAD systolic PAP, per mm Hg increase	1.05 (10.02–1.08)	0.002	1.05 (1.02–1.09)	0.002

AI indicates aortic insufficiency; dLVAD, durable left ventricular assist device; HDRE, hemodynamic-related event; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MCS, mechanical circulatory support; NS, not significant; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; and RHF, right heart failure.

aberrancies, as mild RHF HDRE was associated with a 3-fold increase in the occurrence of HF hospitalization or cardiovascular death at 2 years, establishing the need to recognize, and potentially counteract, instrumental aberrancies. Of note, we observed a markedly low incidence of moderate RHF HDRE (0.1%) compared with mild (15.3%) and severe (12.6%) RHF HDREs. This pattern likely reflects a covariation between the instrumental/clinical criteria defining RHF and the care setting in which these events are managed. Specifically, most patients presenting with clinical RHF at our institution received in-hospital treatment with inotropes, inhaled vasodilators, or temporary mechanical circulatory support, leading to classification within the severe RHF HDRE category. This trend may indicate a center-specific practice of early and aggressive RHF management or could suggest that the current classification system may need refinement to better capture the full spectrum of RHF severity. Future multicenter validations are warranted to determine whether these findings are generalizable and whether refinements in the HCS criteria could enhance the granularity of RHF severity stratification.

An AI HDRE was observed in 1 of 6 patients with a dLVAD after 6 months, being of moderate intensity in 3.7% of patients, and never clinically evident. While this is consistent with the more progressive nature of post-dLVAD AI and reinforces the role of long-term CF-related hemodynamic aberrancies in guiding the process, it is notable that the relative risk of long-term adverse events is remarkably higher for a moderate subclinical AI HDRE as compared with a moderate/severe clinical RHF HDRE (8.8-fold versus 3.4-fold risk of HF hospitalization or cardiovascular death). Importantly, the rates of clinical AI after 2 years of dLVAD support is consistently higher in the literature suggesting the rapidly progressive nature of this HDRE.[33,34] Finally, RHF HDRE, but not AI HDRE, was associated with the development of HRAEs. While reinforcing the nuanced understanding of the hemodynamic intricacies influencing end-organ function and device hemocompatibility,[19] the diverging association of RHF and AI with HRAEs is likely explained by the specific HDRE's pathophysiological consequences. Specifically, RHF promotes multiorgan dysfunction through systemic congestion,[35,36] while the consequences of AI on end-organ function may become evident only at a later stage when antegrade perfusion is compromised. Gastrointestinal bleeding dominated HRAEs, thus reinforcing the potential association with increased backward venous pressure and mucosal congestion in RHF.

Predictors of HDRE Development

We identified HDRE-specific predictors among routinely assessed characteristics before dLVAD implant. Pre-dLVAD pulmonary artery pulsatility index is the most potent predictor of 6-month RHF HDREs. While consistent with prior literature highlighting pulmonary artery pulsatility index as a major predictor of early

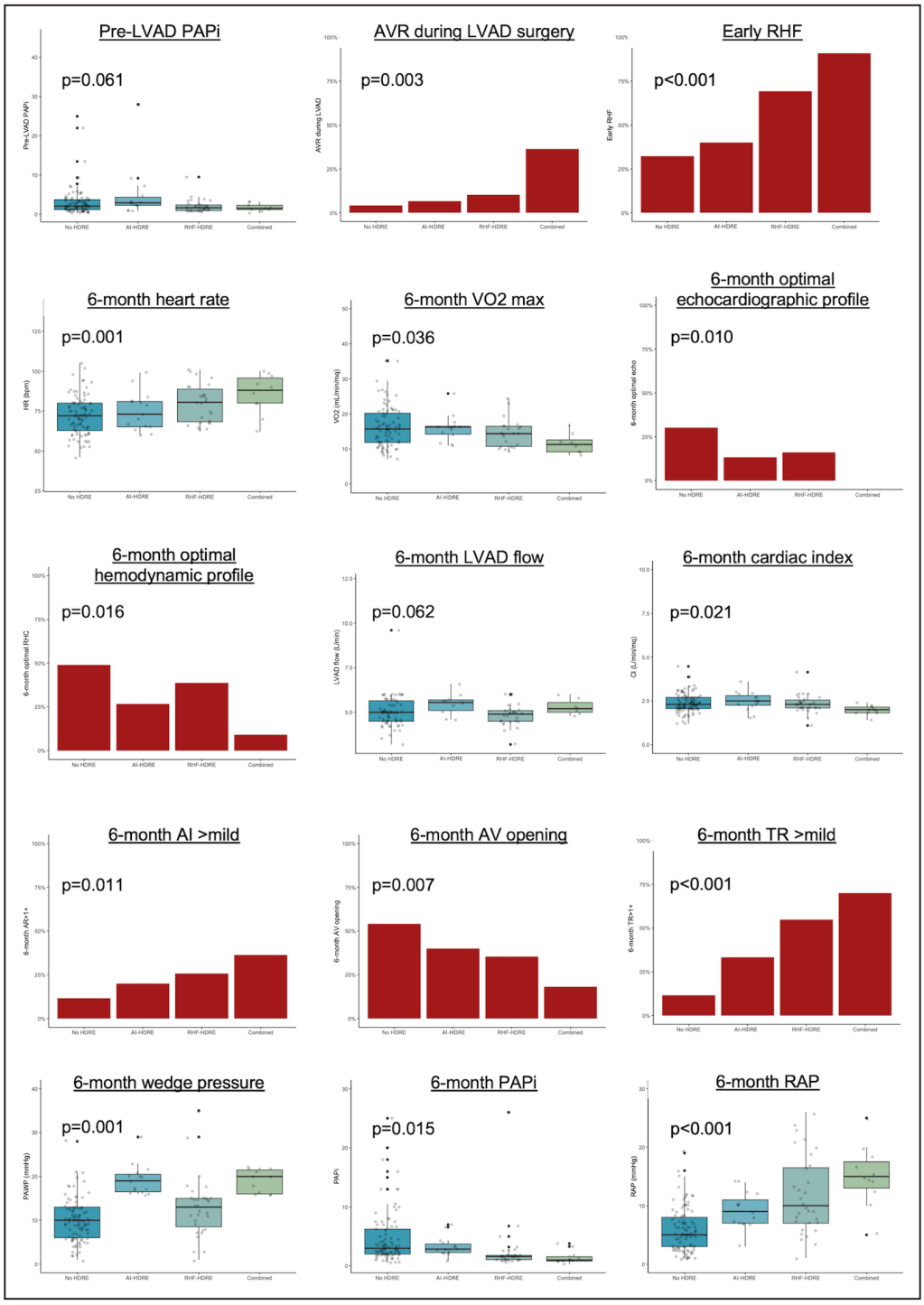


Figure 3. Selection of relevant clinical and instrumental characteristics at different time points stratified by HDRE phenotypes.

The HDRE phenotypes identified by the Hemodynamic Classification System correspond to relevant pathophysiological clusters, present with specific clinical, echocardiographic, and hemodynamic patterns, and are associated with functional capacity. Optimal echocardiographic profile denotes the presence of neutral interventricular septal position, mitral regurgitation less than moderate and (at least intermittent) aortic valve opening, as proposed by the International Society for Heart and Lung Transplantation guidelines.[21] The optimal hemodynamic profile denotes the presence of a cardiac index ≥2.2 L/min per m^2, wedge pressure <18 mm Hg, and right atrial pressure <12 mm Hg assessed at right heart catheterization, as previously proposed and validated.[19,20] AI indicates aortic insufficiency; AVR, aortic valve replacement; HDRE, hemodynamic-related event; LVAD, left ventricular assist device; PAPi, pulmonary artery pulsatility index; RAP, right atrial pressure; RHF, right heart failure; and TR, tricuspid regurgitation.

Table 6. Association of RHF and AI HDREs With Clinical Outcomes

	RHF HDRE		AI HDRE	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HF hospitalization or cardiovascular death	3.13 (1.44–6.79)	0.004	3.72 (1.65–8.39)	0.002
AV/RHF-related clinical events	3.08 (1.37–6.91)	0.006	4.35 (1.88–10.06)	<0.001
All-cause death, urgent HT, or unplanned LVAD explant	1.92 (1.15–3.20)	0.013	1.75 (0.93–3.29)	0.083
All-cause death	2.36 (1.24–4.47)	0.009	2.75 (1.32–5.74)	0.007
HRAEs	1.87 (1.13–3.11)	0.006	1.44 (0.76–2.73)	0.260

AV indicates aortic valve; HF, heart failure; HRAE, hemocompatibility-related adverse events; HT, heart transplant; LVAD, left ventricular assist device; and RHF, right heart failure.

post-dLVAD RHF,[32,37,38] our finding extends its clinical relevance to the less characterized late RHF setting and establishes a continuum among the preexisting cardiomyopathy, acute postimplant RHF and late RV dysfunction on dLVAD support. Also, pre-dLVAD AI was associated with a 3.4-fold increase in AI HDRE, in line with prior literature.[13,39] Interestingly, also pre-dLVAD systolic pulmonary artery pressure was a strong predictor of AI HDRE. While we do not have a definite explanation for this finding, one might argue that higher systolic pulmonary artery pressure may mirror those more compromised patients who will experience early persistent AV closure. Of note, whether higher pulmonary artery pressure (reflecting elevated LV pressure) may mask AI by reducing transvalvular AI flow before dLVAD implantation is another hypothesis to be explored in future studies. Importantly, although preimplant predictors of HDREs may inform clinical decision-making, their prognostic implications should be weighed alongside patient-specific factors such as physiological reserve, comorbidities, and treatment goals (bridge to transplant/candidacy versus destination therapy), rather than serving as absolute contraindications to dLVAD implantation.

HDRE Phenotypes

A nonnegligible proportion of patients affected by HDREs (roughly 1/6), presented with combined AI and RHF, after only 6 months of CF support. These patients were the most critically ill already before dLVAD implantation, had the most complex periprocedural course, and at 6 months presented the most compromised objective functional capacity, a well-known determinant of prognosis and quality of life among dLVAD carriers.[40] Indeed, this subgroup displayed a 7.4-fold increased risk of the primary outcome at 2 years. Notably, these patients had the most prominent features of suboptimal LV unloading coupled with elevated right atrial pressure, highlighting the challenge of pump speed optimization in patients with features of combined primary LV and RV failure.[41] These patients, if refractory to diuretic and pump speed optimization, are most likely the ones that benefit most from early consideration of urgent HT, before end-organ damage and overt contraindications develop.

Clinical Perspective and Future Directions

In conclusion, our findings highlight the potential clinical utility of the HCS in identifying both subclinical and overt HDREs in patients supported with dLVADs. Early detection of HDREs, particularly through multiparametric assessments including echocardiography and RHC, can guide timely interventions aimed at optimizing hemodynamics and improving long-term outcomes. Moreover, the identification of pre-LVAD predictors for HDREs can inform individualized risk stratification, although such variables should be integrated into a holistic decision-making process rather than serve as exclusion criteria. This approach may help enhance the durability of dLVAD support and improve patient-centered outcomes. Looking ahead, further validation of the HCS in larger, multicenter cohorts is warranted to assess its utility across diverse clinical settings and over extended follow-up. Additionally, prospective trials are needed to evaluate whether structured, serial, multimodal monitoring can improve outcomes by enabling earlier intervention. Investigating HDRE progression trajectories and their responsiveness to tailored interventions will be key to refining patient management.

Study Limitations

The results of the present analysis must be interpreted considering several limitations. First, this is a retrospective, single-center registry. Despite a clinical practice protocol comprehensive of serial echocardiographic and hemodynamic assessments, prospective and multicenter validation of the dLVAD HCS is warranted. Second, we validated the use of the dLVAD HCS early after dLVAD implantation. Its performance at different time points and, particularly, the relevance of HDRE trajectories remain an important focus to be assessed in dedicated studies. Third, we applied some variations to the initially proposed HCS: Hemodynamics were evaluated according to the patient's dLVAD flow (instead of the proposed standardized 2.2 L/min per m^2),

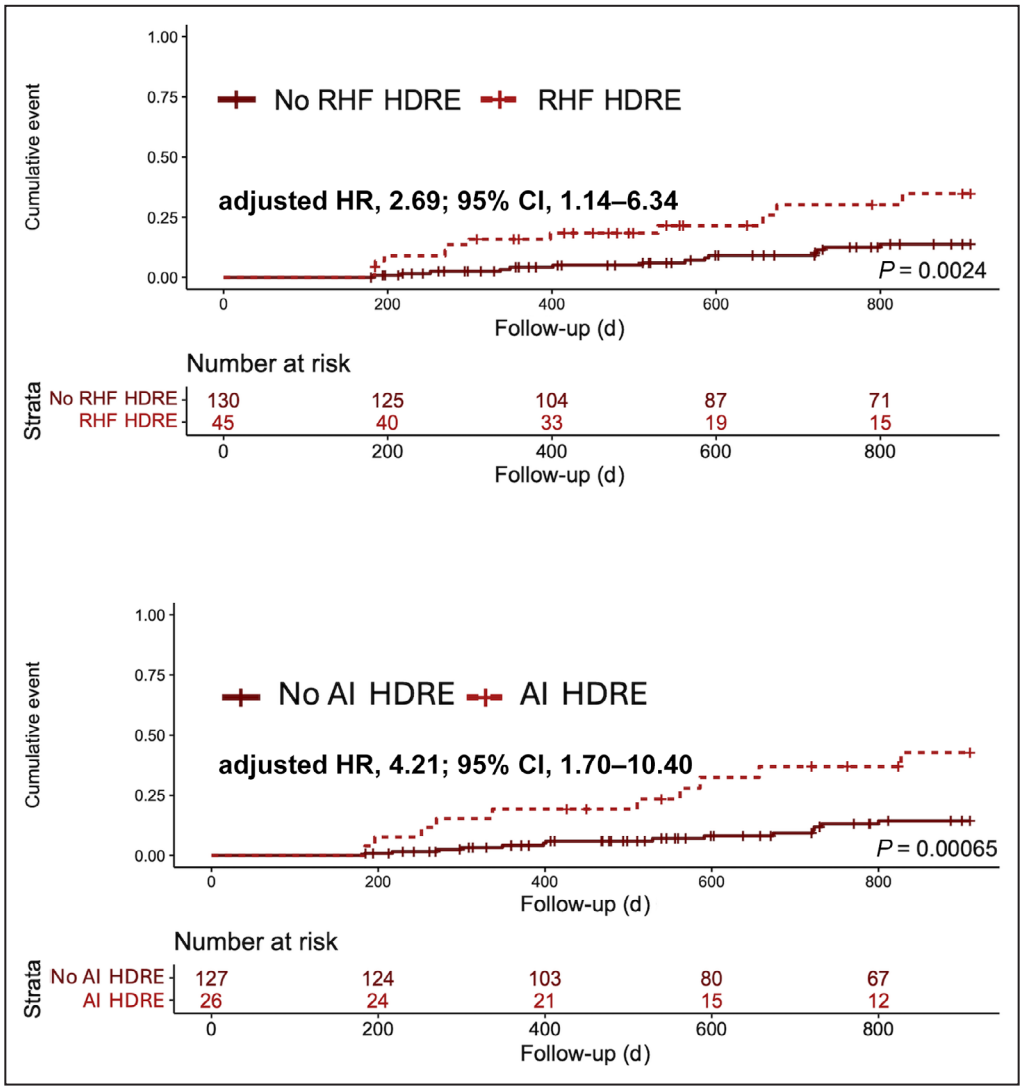


Figure 4. Association of HDREs with the primary outcome.
AI HDRE and RHF HDRE at 6 months after dLVAD implant are independently associated with HF hospitalization of cardiovascular death at 2.5 years after dLVAD implant. AI indicates aortic insufficiency; HDRE, hemodynamic-related event; HR, hazard ratio; and RHF, right heart failure.

and AI severity was attributed to the patient's blood pressure (instead of only among patients with Doppler blood pressure <80 mm Hg). Despite being less pathophysiologically sound, these adaptations are likely necessary for broad HCS implementation, and they also reflect the true burden of hemodynamic derangements and AI flow severity to which the patient's cardiovascular system is actually subject. Importantly, the HCS nicely provided stepwise risk stratification despite these variations. Of note, echocardiographic AI severity was evaluated on the basis of standard metrics; however, dLVAD-specific metrics accounting for CF physiology might refine AI staging.[33,34] Fourth, echocardiographic predictors of late HDREs before LVAD implantation were determined among the prespecified set of reported variables. Whether more advanced echocardiographic parameters of aortic anatomy or RV function might refine prediction of late HDREs remains an interesting open question. Fifth, the estimated HDRE incidence should be inherently considered on the prevalent population at 6-month assessment as patients with a nonlate–HDRE-related hard outcome were excluded from the analysis. Additionally, while our primary outcome analyses were based on a moderate number of events, some secondary and subgroup analyses, particularly those involving less prevalent predictors of HDREs, may be subject to small-sample bias, and larger studies will be needed to confirm our findings. Also, as no formal correction for multiple testing was applied, we acknowledge the potential for type I error, particularly for associations with *P* values near the significance threshold. Of note, across the study, a

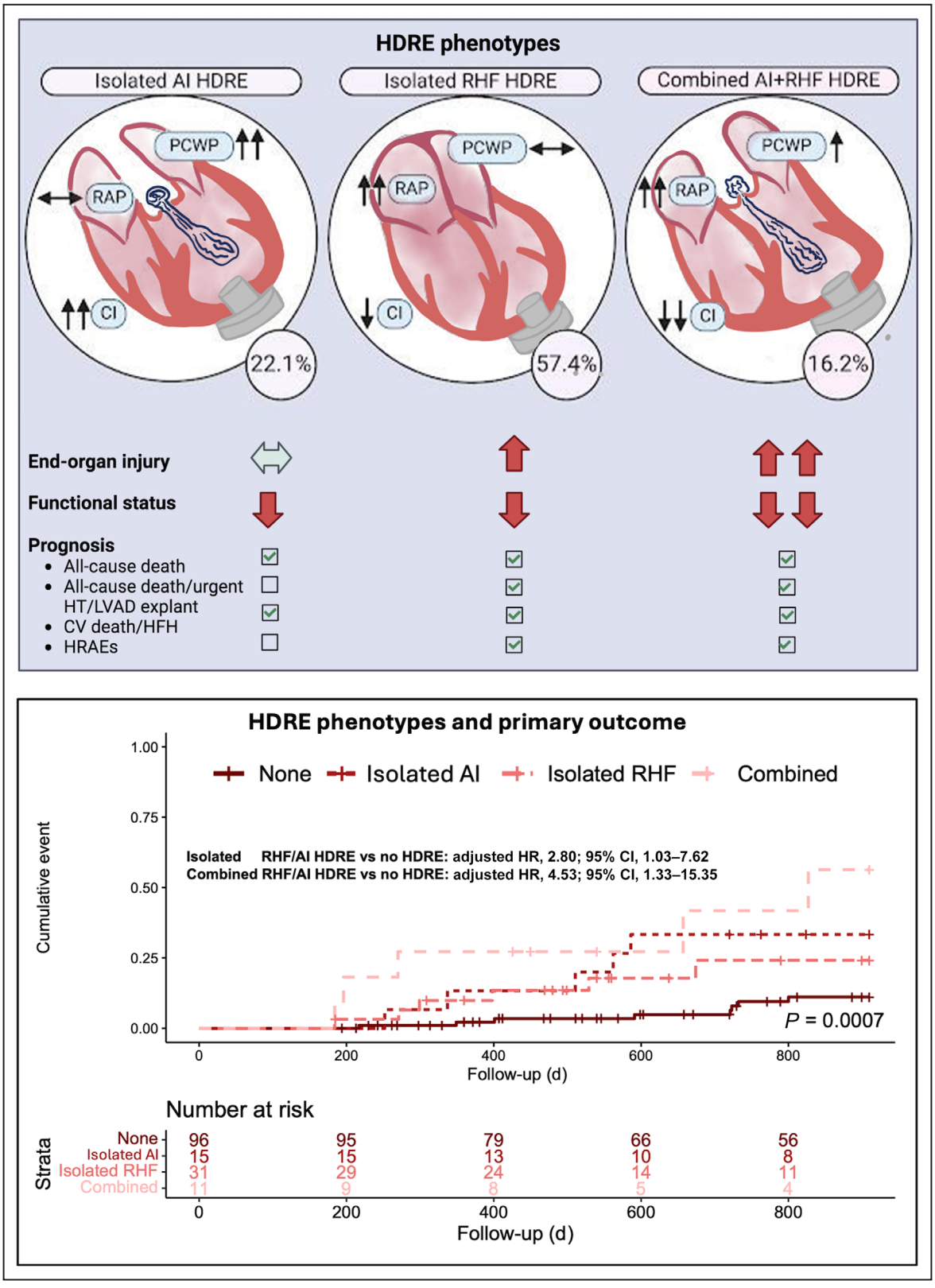


Figure 5. HDRE phenotypes and their association with the primary outcome.
The HDRE phenotypes identified by the Hemodynamic Classification System correspond to relevant pathophysiological clusters, present with specific clinical, echocardiographic, and hemodynamic patterns, and provide incremental prognostic value. The HDRE phenotype could not be adjudicated in 3 (4.4%) patients. AI indicates aortic insufficiency; CI, cardiac index; HDRE, hemodynamic-related event; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; and RHF, right heart failure.

total of 326 statistical tests were performed, of which 127 yielded *P* values <0.05. This observation, along with the fact that many of the observed associations, including those with *P* values near 0.05, were internally consistent, biologically plausible, and supported by multiple complementary end points, support their potential relevance despite the absence of formal multiplicity correction. Finally, in our cohort, most devices were hybrid levitation centrifugal flow pumps (HeartWare). While the progress in device iterations of contemporary centrifugal flow pumps (HeartMate III, Abbott Laboratories, Chicago, IL) has consistently resulted in reduced HRAEs, the impact on HDREs is unclear,[42–44] and a direct randomized comparison between HeartWare and HeartMate III is lacking. Accordingly, prospective validation among patients supported with a magnetically levitating centrifugal pump according to current dLVAD patient selection, surgical implantation techniques and management of concomitant valvular diseases is warranted to assess the contemporary incidence, phenotypes, and prognostic relevance of HDREs according to the HCS.

CONCLUSIONS

The dLVAD HCS for HDREs identifies pathophysiological and clinical clusters of patients with relevant prognostic implications. AI and RHF HDREs occur early after dLVAD implantation in a significant proportion of patients and are associated with late HF events. The severity and phenotype of HDREs add granularity in patients' classification and provide incremental prognostic value. The implementation of the dLVAD HCS has the potential to lay the bases to build strategies aiming at mitigating HDREs and improve the durability of the pump–patient continuum.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5
Figures S1–S2

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