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ORIGINAL RESEARCH

Impact of Diabetes and Glycemia on Cardiac Improvement and Adverse Events Following Mechanical Circulatory Support

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BACKGROUND: Type 2 diabetes is prevalent in cardiovascular disease and contributes to excess morbidity and mortality. We sought to investigate the effect of glycemia on functional cardiac improvement, morbidity, and mortality in durable left ventricular assist device (LVAD) recipients.

METHODS AND RESULTS: Consecutive patients with an LVAD were prospectively evaluated (n=531). After excluding patients missing pre-LVAD glycated hemoglobin (HbA1c) measurements or having inadequate post-LVAD follow-up, 375 patients were studied. To assess functional cardiac improvement, we used absolute left ventricular ejection fraction change (ΔLVEF: LVEF post-LVAD–LVEF pre-LVAD). We quantified the association of pre-LVAD HbA1c with ΔLVEF as the primary outcome, and all-cause mortality and LVAD-related adverse event rates (ischemic stroke/transient ischemic attack, intracerebral hemorrhage, gastrointestinal bleeding, LVAD-related infection, device thrombosis) as secondary outcomes. Last, we assessed HbA1c differences pre- and post-LVAD. Patients with type 2 diabetes were older, more likely men suffering ischemic cardiomyopathy, and had longer heart failure duration. Pre-LVAD HbA1c was inversely associated with ΔLVEF in patients with nonischemic cardiomyopathy but not in those with ischemic cardiomyopathy, after adjusting for age, sex, heart failure duration, and left ventricular end-diastolic diameter. Pre-LVAD HbA1c was not associated with all-cause mortality, but higher pre-LVAD HbA1c was shown to increase the risk of intracerebral hemorrhage, LVAD-related infection, and device thrombosis by 3 years on LVAD support (P<0.05 for all). HbA1c decreased from 6.68±1.52% pre-LVAD to 6.11±1.33% post-LVAD (P<0.001).

CONCLUSIONS: Type 2 diabetes and pre-LVAD glycemia modify the potential for functional cardiac improvement and the risk for adverse events on LVAD support. The degree and duration of pre-LVAD glycemic control optimization to favorably affect these outcomes warrants further investigation.

Key Words: diabetes ■ heart assist device ■ heart failure ■ left ventricular assist device ■ myocardial recovery ■ reverse remodeling

Type 2 diabetes (T2D) affects 34.1 million adults in the United States, accounting for 13% of the total adult population, and its prevalence is projected to increase.[1] The association of T2D with cardiovascular disease is well established, with people with diabetes having a substantially increased risk for developing heart failure (HF).[2–5] It has been shown that a 1% increase in serum glycated hemoglobin (HbA1c)

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CLINICAL PERSPECTIVE

What Is New?

- Type 2 diabetes and pre-left ventricular assist device glycemia might affect the potential for functional cardiac improvement and the risk for adverse events on left ventricular assist device support.

What Are the Clinical Implications?

- Optimization of pre-left ventricular assist device glycemic control could improve outcomes in these patients.
- Findings from patients with advanced heart failure receiving mechanical circulatory support could inform the care of patients with earlier stage heart failure and concomitant type 2 diabetes or prediabetes.

Nonstandard Abbreviations and Acronyms

ICM	ischemic cardiomyopathy
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
MCS	mechanical circulatory support
NICM	nonischemic cardiomyopathy
T2D	type 2 diabetes

increases the risk for developing HF by 16%.[6] At the same time, patients with HF exhibit marked insulin resistance,[7] which increases their risk of developing T2D. The above suggest a bidirectional relationship between T2D and HF, with each disease increasing the risk of each other and adversely affecting prognosis and outcomes.[2,8]

HF has long been deemed unidirectional and progressive, inevitably leading to advanced disease. This notion has been challenged by the occurrence of cardiac improvement in different clinical settings, from spontaneous improvement in acute myocarditis and stress-induced cardiomyopathy, to facilitated improvement by electrical or pharmacological therapies, and even advanced HF treated with left ventricular (LV) assist devices (LVADs).[9] Mechanical circulatory support (MCS) with LVADs is an established treatment modality for patients with refractory HF symptoms despite guideline-directed medical therapy. Through volume and pressure unloading of the ailing left ventricle, it can facilitate structural and functional cardiac improvement in varying degrees.[10–17]

In this study, we sought to investigate how T2D and glycemia affect the potential for functional cardiac improvement, as well as morbidity and mortality in patients with advanced HF on durable MCS. Findings from the advanced HF/MCS investigational setting could have prognostic and therapeutic implications for the greater population of patients with earlier stage HF and concomitant T2D or prediabetes.

METHODS

Data Sharing

The data and analytic methods of the study will be made available from the corresponding author upon reasonable request.

Study Population

Patients with advanced HF receiving a continuous-flow LVAD between May 2008 and November 2020 at 1 of the institutions comprising the Utah Cardiac Recovery Program (University of Utah Health and School of Medicine, Intermountain Medical Center, and George E. Wahlen Department of Veterans Affairs Medical Center) were prospectively evaluated. Patients were followed until LVAD explantation due to heart transplantation or cardiac recovery, loss to follow-up, death, or study conclusion in February 2023. The study was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all patients.

Patients with hypertrophic or infiltrative cardiomyopathy, baseline LV ejection fraction (LVEF) ≥40%, consent withdrawal, or inadequate (<3 months) post-LVAD follow-up (early heart transplantation, death, or unavailable echocardiographic follow-up) were excluded. To investigate the effect of T2D and glycemic control on LVAD-mediated cardiac recovery, we also excluded patients with missing HbA1c measurements before LVAD implantation or diagnosed with type 1 diabetes.

Clinical Management and Definitions

Data collection included demographics, comorbidities, medications, laboratory values, and hemodynamic data obtained via right heart catheterization before and closest to LVAD implantation. Cardiac imaging data were obtained before and during LVAD support to assess the structural and functional effects of mechanical unloading on the failing heart. The duration of HF was defined as the time from HF symptom onset to LVAD implantation as ascertained through chart review. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology collaboration 2021 creatinine-based

equation.[18] Patients were considered diabetic if previously diagnosed with T2D or if they had an HbA1c ≥6.5% in the 12-month period preceding LVAD implantation. Pre-LVAD HbA1c was recorded as the average of all available measurements in the 12-month period preceding LVAD implantation, whereas post-LVAD HbA1c was recorded as the average of all available measurements in the 12-month period following LVAD implantation.

The effect of LVAD unloading on cardiac size, shape, and function was assessed by echocardiography and invasive hemodynamic measurements following LVAD implantation and before discharge. LVAD speed was adjusted to optimize flows and left ventricle decompression with positioning of the interventricular and interatrial septa in the midline, minimal mitral valve regurgitation, and intermittent aortic valve opening, in order of decreasing priority. Subsequent speed adjustments were made as indicated by patient symptoms and/or clinical events. Patients were medically managed at the discretion of the treating physicians within the participating institutions per established standard HF and T2D therapy guidelines.

Functional Cardiac Improvement Assessment

Functional cardiac changes on LVAD support were prospectively assessed using a protocol developed and tested at the Utah Cardiac Recovery Program.[11] Transthoracic echocardiograms were performed within the 2 weeks preceding and serially at 1, 3, 6, 9, and 12 months following LVAD implantation. The standard of care clinical protocol entailed 2 sets of echocardiographic measurements: (1) at full LVAD support and (2) after 30 minutes of limited support, at the lowest setting recommended by the device manufacturer (turndown study). The absence of prior stroke, transient ischemic attack, LVAD thrombosis, or hemolysis, along with a therapeutic international normalized ratio, were prerequisites for a turndown study. Complete echocardiographic assessment, including 2-dimensional, M-mode, and Doppler modalities, was performed according to the 2015 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[19]

To quantitatively estimate functional cardiac improvement on LVAD support, we used the following formula: absolute LVEF change (ΔLVEF)=LVEF post-LVAD−LVEF pre-LVAD. For LVEF pre-LVAD we used the measurement before and closest to LVAD implantation, whereas for LVEF post-LVAD we used the maximum LVEF achieved within the 12-month period following LVAD implantation. Pre-turndown LVEF measurements were used, because a turndown study might not have been performed for the reasons mentioned above. We have previously shown that LVEF measurements do not significantly differ between pre- and post-turndown studies.[11,20]

Study Outcomes

The primary outcome was ΔLVEF by 12 months, and the secondary outcomes were all-cause mortality and LVAD-related adverse event rates by 3 years on LVAD support. The following LVAD-related adverse events were prospectively captured using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) definitions and were adjudicated via chart review (C.P.K., I.T.)[21]: ischemic stroke, intracerebral hemorrhage, transient ischemic attack, gastrointestinal bleeding, LVAD-related infection (percutaneous site infection, infection of external or blood-containing surfaces of an implantable component), and device thrombus. Additionally, we assessed glycemia before and following LVAD support, in the subset of patients with available pre- and post-LVAD HbA1c measurements.

Statistical Analysis

Patient baseline characteristics were summarized using standard summary statistics including frequencies, percentages, and means. Measures of variation were presented as mean and SD or median and interquartile range, as appropriate. Differences between patient groups for categorical variables were evaluated using the χ^2 test or Fisher exact test, as appropriate, and continuous variables were evaluated using the 2-group Student *t* test or Mann-Whitney 2-sample test, as appropriate.

Linear regression was used to assess the primary outcome (association of ΔLVEF with pre-LVAD HbA1c). Multivariable linear regression was used to test this association while adjusting for variables that have been suggested to significantly affect functional cardiac improvement, and by extension ΔLVEF in previous studies.[12–17,22] Additionally, we used statistical interaction terms to determine potential modification of HbA1c impact by variables previously shown to affect functional cardiac improvement.[12–17,22] To properly interpret potential interaction effects, data were mean-centered (raw value mean).[23] Linear regression is robust with regard to the assumptions of homogeneity of variance and normality of residual errors,[24,25] and graphical evaluation of the data allowed us to conclude these assumptions were not violated. Robust estimates of variance were reported. We used a paired-sample *t* test to assess the difference in glycemia before and after LVAD support in the subset of patients with available pre- and post-LVAD HbA1c measurements. A 2-sided *P* value <0.05 was considered significant.

Cox proportional hazards regression modeling was used to examine the association between pre-LVAD HbA1c and all-cause mortality or LVAD-related adverse events by 3 years on LVAD support.

RESULTS

Overall, 531 patients receiving durable continuous-flow LVAD were prospectively enrolled within the study period. After excluding patients with hypertrophic or infiltrative cardiomyopathies (n=4), a baseline LVEF ≥40% (n=6), consent withdrawal (n=8), inadequate (<3 months) post-LVAD follow-up due to death or heart transplantation (n=53), unavailable echocardiographic data (n=43), or absent HbA1c measurements before LVAD implantation (n=42), 375 patients comprised our study cohort (Figure 1). After applying the above exclusion criteria, patients with type 1 diabetes were not included in our study.

Baseline demographic and clinical characteristics after stratifying patients into diabetic and nondiabetic are presented in Table 1. Patients with T2D were more likely to be older men with a history of systemic hypertension and a higher body mass index. They had a longer duration of HF and more commonly suffered ischemic cardiomyopathy (ICM). No differences were observed in terms of disease severity as evidenced by New York Heart Association classification and INTERMACS profile or preoperative use of vasoactive agents or temporary MCS. Last, the proportion of patients treated with guideline-directed HF medical therapy pre-LVAD was comparable between the 2 groups, whereas patients with T2D were less commonly on an aldosterone antagonist and more commonly on a diuretic 3 months post-LVAD (Table S1).

Hemodynamic, echocardiographic, and laboratory measurements before LVAD implantation are presented in Table 2. Patients in both the T2D and non-T2D groups had elevated cardiac filling pressures, severely impaired cardiac function, and abnormal cardiac structure. No differences were identified between the 2 groups in baseline hemodynamic and echocardiographic parameters, a higher LVEF, and a thicker interventricular septum in patients with diabetes. Laboratory assessment revealed higher creatinine, blood urea nitrogen, as well as lower estimated glomerular filtration rate, albumin, and alanine aminotransferase values in patients with versus without T2D. As expected, patients with diabetes had higher blood glucose and HbA1c values compared with those without.

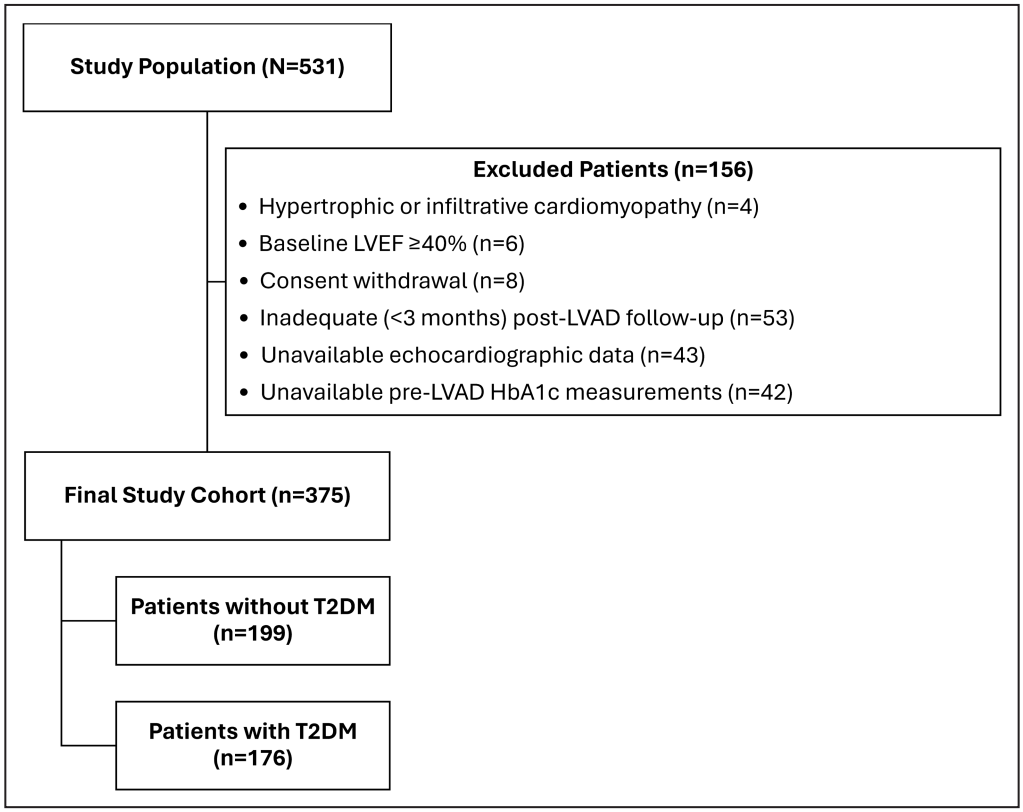


Figure 1. Flow diagram for inclusion and exclusion of patients.
HbA1c indicates glycated hemoglobin; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; and T2DM, type 2 diabetes mellitus.

Table 1. Baseline Demographic and Clinical Characteristics in the Total Cohort and Patients Without and With T2D

Variables	Total cohort (N=375)	Patients without T2D (n=199)	Patients with T2D (n=176)	*P* value
Male sex, n (%)	319 (85.1%)	155 (77.9%)	164 (93.2%)	<0.001
Age, y	59 [49–66]	58 [39–66]	61 [55–66]	<0.001
Race, n (%)				0.85
White	287 (81.8%)	145 (79.7%)	142 (84.0%)	
Black	31 (8.8%)	18 (9.9%)	13 (7.7%)	
American Indian or Alaska Native	14 (4.0%)	7 (3.8%)	7 (4.2%)	
Native Hawaiian or Other Pacific Islander	4 (1.1%)	2 (1.1%)	2 (1.2%)	
Asian	3 (0.9%)	2 (1.1%)	1 (0.6%)	
Not reported or multiple races	12 (3.4%)	8 (4.4%)	4 (2.3%)	
Ethnicity, n (%)				
Hispanic or Latino	25 (7.1%)	13 (7.1%)	12 (7.1%)	0.99
Body mass index, kg/m^2	28.3±5.8	27.5±5.8	29.3±5.7	0.003
Medical history, n (%)				
Smoking	188 (50.0%)	103 (51.8%)	85 (48.3%)	0.50
Hypertension	190 (50.7%)	73 (36.7%)	117 (66.5%)	<0.001
Ethanol use	169 (45.1%)	96 (48.2%)	73 (41.5%)	0.19
Atrial fibrillation	161 (43.1%)	76 (38.2%)	85 (48.6%)	0.04
Previous thoracotomy	98 (26.3%)	39 (19.9%)	59 (33.5%)	0.003
Electrical therapies, n (%)				0.34
None	58 (15.6%)	35 (17.7%)	23 (13.2%)	
CRT-D	177 (47.6%)	88 (44.4%)	89 (51.2%)	
ICD	137 (36.8%)	75 (37.9%)	62 (35.6%)	
Preoperative supportive therapies, n (%)				
Inotrope dependency	260 (69.3%)	134 (67.3%)	126 (71.6%)	0.37
Intra-aortic balloon pump	27 (7.2%)	11 (5.6%)	16 (9.1%)	0.19
Percutaneous VAD/VA-ECMO	22 (6.0%)	16 (8.0%)	6 (3.4%)	0.06
New York Heart Association class IV, n (%)	271 (72.3%)	143 (71.9%)	128 (72.7%)	0.85
Heart failure duration, mo	88.6±84.1	77.1±80.4	101.5±86.5	0.005
Heart failure cause, n (%)				
Ischemic cardiomyopathy	172 (45.9%)	69 (34.7%)	103 (58.5%)	<0.001
INTERMACS profile, n (%)				0.08
1	26 (7.1%)	20 (10.2%)	6 (3.5%)	
2	66 (17.9%)	32 (16.3%)	34 (19.6%)	
3	159 (43.1%)	81 (41.3%)	78 (45.1%)	
≥4	118 (32.0%)	63 (32.1%)	55 (31.8%)	
VAD indication, n (%)				0.05
BTT	212 (56.5%)	117 (58.8%)	95 (54.0%)	
DT	139 (37.1%)	64 (32.2%)	75 (42.6%)	
BTD	13 (3.5%)	10 (5.0%)	3 (1.7%)	
BTR	11 (2.9%)	8 (4.0%)	3 (1.7%)	
VAD type, n (%)				0.29
HeartMate 2	139 (37.1%)	66 (33.2%)	73 (41.5%)	
HeartMate 3	44 (11.7%)	22 (11.1%)	22 (12.5%)	
HeartWare	170 (45.3%)	99 (49.8%)	71 (40.3%)	
Other	22 (5.9%)	12 (6.0%)	10 (5.7%)	
VAD configuration, n (%)				
Centrifugal	199 (56.4%)	110 (59.8%)	89 (52.7%)	0.18

(*Continued*)

Table 1. Continued

Variables	Total cohort (N=375)	Patients without T2D (n=199)	Patients with T2D (n=176)	*P* value
Pre-VAD heart failure medications, n (%)				
β-Blocker	241 (64.3%)	128 (64.3%)	113 (64.2%)	0.98
ARNI/ARB/ACE inhibitor	242 (64.5%)	124 (62.3%)	118 (67.1%)	0.34
Aldosterone antagonist	227 (60.5%)	127 (63.8%)	100 (56.8%)	0.17
Diuretic	354 (94.4%)	185 (93.0%)	169 (96.0%)	0.20
Pre-VAD T2D medications, n (%)				
Insulin	…	…	75 (42.9%)	…
Metformin	…	…	42 (23.9%)	…
DPP-4 inhibitors	…	…	7 (4.0%)	…
GLP-1 agonists	…	…	10 (5.7%)	…
SGLT-2 inhibitors	…	…	2 (1.2%)	…
α-Glucosidase inhibitors	…	…	1 (0.6%)	…

Continuous variables are presented as mean±SD or median [interquartile range]. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BTD, bridge-to-decision; BTR, bridge-to-recovery; BTT, bridge-to-transplant; CRT-D, cardiac resynchronization therapy-defibrillator; DPP-4, dipeptidyl peptidase-4; DT, destination therapy; GLP-1; glucagon-like peptide-1; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes; VAD, ventricular assist device; and VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Glycemia and Functional Cardiac Improvement on LVAD Support

Pre-LVAD HbA1c was inversely associated with ΔLVEF at a univariable level (linear regression coefficient: –1.02; *P* value: 0.05), as shown in Figure 2. The impact of pre-LVAD HbA1c on ΔLVEF was subsequently assessed after adjusting for clinical factors previously shown to associate with functional cardiac improvement on LVAD support, including age, sex, duration of HF symptoms, HF cause, and LV end-diastolic diameter.[12,14,15,22] Statistical interaction terms were created between pre-LVAD HbA1c and the same set of clinical factors to assess for potential effect modification. A significant interaction was identified between pre-LVAD HbA1c and ICM (*P*=0.039). Based on the above, patients were stratified into ICM and non-ICM (NICM). Although pre-LVAD HbA1c was found to be significantly associated with ΔLVEF in patients with NICM after adjusting for age, sex, HF duration, and LV end-diastolic diameter, this was not evident in patients with ICM (Figure 3). The multivariable linear regression models in ICM and NICM are shown in Figure 3.

Glycemia and All-Cause Mortality on LVAD Support

Of 375 patients, 74 (19.7%) were deceased by 3 years on LVAD support (Figure S1). Pre-LVAD HbA1c was not associated with the risk of all-cause mortality by 3 years on LVAD support at a univariable level (hazard ratio [HR], 1.12 [95% CI, 0.95–1.31]; *P*=0.177), or after adjusting for age, sex, duration of HF symptoms, HF cause, and LV end-diastolic diameter (HR, 1.13 [95% CI, 0.96–1.34]; *P*=0.152) (Table S2).

Glycemia and LVAD-Related Adverse Events

Pre-LVAD HbA1c was shown to increase the risk of intracerebral hemorrhage (HR, 1.31 [95% CI, 1.13–1.52]; *P*<0.001), device thrombosis (HR, 1.28 [95% CI, 1.07–1.54]; *P*=0.008), and LVAD-related infection (HR, 1.31 [95% CI, 1.17–1.47]; *P*<0.001), but not ischemic stroke/transient ischemic attack (HR, 1.03 [95% CI, 0.79–1.35]; *P*=0.811), or gastrointestinal bleeding (HR, 1.14 [95% CI, 1.00–1.31]; *P*=0.052) by 3 years on LVAD support. The associations above remained significant after adjusting for age, sex, and LVAD type for all outcomes (Figure S2).

Glycemia Pre- and Post-LVAD Support

In the subset of patients with available HbA1c measurements before and following LVAD support (n=127), HbA1c decreased from 6.68±1.52% pre-LVAD to 6.11±1.33% post-LVAD support (*P*<0.001) (Figure 4).

DISCUSSION

The findings of the present study suggest that T2D and glycemia affect the potential for cardiac functional improvement on LVAD support. Decreased pre-LVAD HbA1c was found to be independently associated with greater ΔLVEF, after adjusting for clinical factors known to associate with LVAD-mediated cardiac recovery, including age, sex, duration of HF symptoms, and LV

Table 2. Baseline Hemodynamic, Echocardiographic, and Laboratory Characteristics in the Total Cohort and Patients Without and With T2D

Variables	Total cohort (N=375)	Patients without T2D (n=199)	Patients with T2D (n=176)	*P* value
Hemodynamic measurements				
Systolic blood pressure, mm Hg	104.6±15.4	103.0±15.2	106.8±15.4	0.06
Diastolic blood pressure, mm Hg	68.3±11.4	68.2±11.1	68.3±11.8	0.94
Mean blood pressure, mm Hg	79.4±12.4	80.0±12.3	78.6±12.5	0.42
Heart rate, bpm	86.6±19.8	88.1±21.3	84.9±17.9	0.15
Mean right atrial pressure, mm Hg	11.7±6.2	11.6±6.5	11.9±5.8	0.66
Systolic right ventricular pressure, mm Hg	51.5±13.7	50.1±13.6	52.9±13.7	0.07
Diastolic right ventricular pressure, mm Hg	7.6±6.7	7.9±7.7	7.2±5.3	0.38
Mean right ventricular pressure, mm Hg	16.1±8.5	15.2±8.1	17.1±8.9	0.19
Systolic pulmonary artery pressure, mm Hg	52.5±14.6	51.5±14.4	53.7±14.8	0.16
Diastolic pulmonary artery pressure, mm Hg	26.4±8.7	26.3±8.6	26.5±8.8	0.84
Mean pulmonary artery pressure, mm Hg	36.9±9.9	36.6±9.6	37.2±10.2	0.55
Pulmonary capillary wedge pressure, mm Hg	24.6±8.2	24.7±8.0	24.5±8.5	0.79
Systemic vascular resistance, dynes×s×cm^{-5}	1458 [1121–1837]	1496 [1162–1853]	1414 [1073–1683]	0.41
Pulmonary vascular resistance, Wood units	3.64±2.35	3.56±2.23	3.73±2.47	0.51
Cardiac output, L/min	3.77±1.29	3.74±1.48	3.81±1.05	0.62
Cardiac index, L/min per m^2	1.86±0.63	1.88±0.72	1.85±0.53	0.72
Echocardiographic measurements				
Left ventricular ejection fraction, %	18.1±6.9	17.2±6.5	19.0±7.2	0.01
Left ventricular end-diastolic diameter, cm	6.77±1.04	6.82±1.01	6.71±1.07	0.33
Interventricular septum thickness end-diastole, cm	0.98±0.42	0.93±0.24	1.04±0.56	0.02
Posterior wall thickness end-diastole, cm	0.95±0.25	0.94±0.24	0.97±0.25	0.31
Laboratory measurements				
Hemoglobin, g/dL	12.3±2.3	12.5±2.4	12.2±2.2	0.20
White blood cell count, ×10^3/μL	8.3±3.5	8.3±3.3	8.3±3.7	0.95
Neutrophil/lymphocyte count ratio	5.2±4.2	5.0±4.1	5.5±4.3	0.21
C-reactive protein, mg/dL	3.2±4.0	3.1±4.3	3.3±3.7	0.73
Platelet count, ×10^3/μL	205 [161–249]	207 [159–244]	202 [164–259]	0.84
International normalized ratio	1.40±1.16	1.40±1.15	1.40±1.18	0.93
Sodium, mEq/L	134.3±5.3	134.5±5.1	134.0±5.5	0.40
Potassium, mEq/L	4.09±0.51	4.08±0.55	4.11±0.45	0.50
Creatinine, mg/dL	1.38±0.52	1.30±0.50	1.47±0.52	0.002
Blood urea nitrogen, mg/dL	27 [20–39]	25 [18–34]	29 [22–44]	<0.001
Estimated glomerular filtration rate, mL/min	67.6±27.6	72.9±29.1	61.6±24.4	<0.001
Aspartate aminotransferase, mg/dL	30 [22–45]	32 [23–47]	27 [21–40]	0.017
Alanine aminotransferase, mg/dL	27 [19–51]	30 [20–61]	25 [17–40]	0.015
Alkaline phosphatase, mg/dL	94 [72–124]	90 [71–115]	99 [74–129]	0.044
Total bilirubin, mg/dL	1.1 [0.7–1.6]	1.2 [0.7–1.8]	1.0 [0.8–1.6]	0.25
Uric acid, mg/dL	8.6±3.1	8.5±3.2	8.8±3.1	0.48
Total serum protein, g/dL	6.97±0.77	7.02±0.75	6.92±0.79	0.24
Albumin, g/dL	3.72±0.47	3.78±0.49	3.66±0.45	0.02
Blood glucose, g/dL	129.0±53.5	114.1±40.9	145.6±60.6	<0.001
Hemoglobin A1c, %	6.4±1.2	5.7±0.4	7.2±1.2	<0.001
B-type natriuretic peptide, pg/mL	1013 [455–1873]	1100 [506–2099]	844 [428–1546]	0.078

Continuous variables are presented as mean±SD or median [interquartile range]. T2D indicates type 2 diabetes.

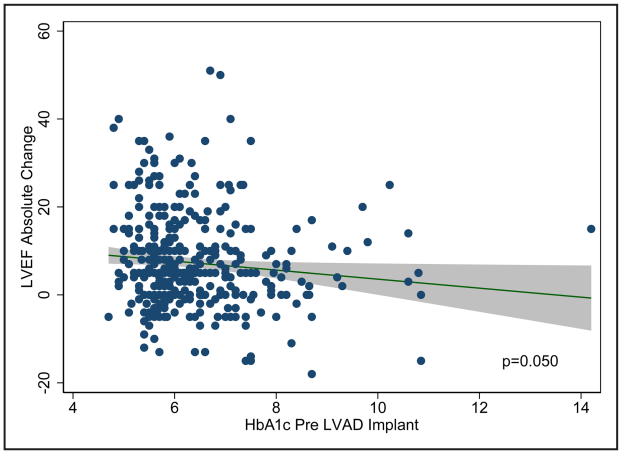


Figure 2. Association of pre-LVAD HbA1c with left ventricular functional improvement (absolute LVEF change: LVEF post-LVAD–LVEF pre-LVAD) at a univariable level.
HbA1c indicates glycated hemoglobin; LVAD: left ventricular assist device; and LVEF, left ventricular ejection fraction.

end-diastolic diameter.[12,14,15,22] This was not evident, however, after stratifying patients based on their underlying HF cause. Decreased pre-LVAD HbA1c was shown to independently associate with increased ΔLVEF in patients with NICM but not in those with ICM, after adjusting for the above-mentioned clinical variables.

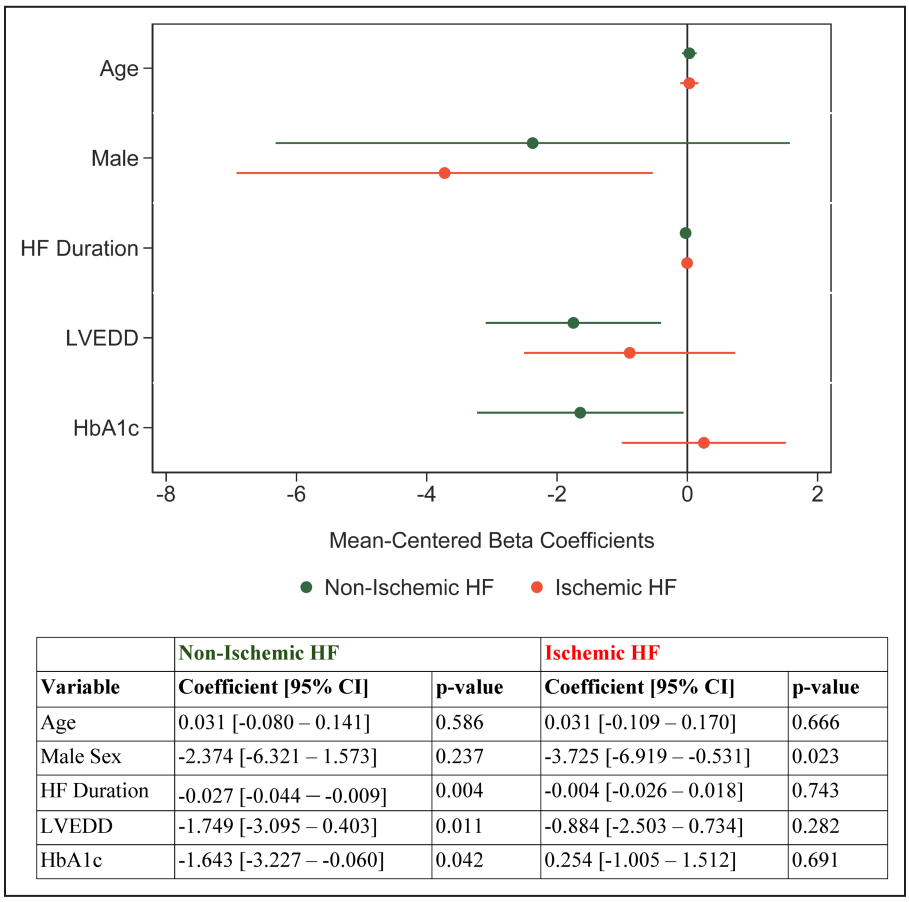
T2D and HF have a bidirectional relationship and are often coexistent.[2,8,26–28] Risk factors for HF, such as hypertension, coronary artery disease, valvular heart disease, chronic kidney disease, and obesity, are often coexistent with T2D and can accelerate LV adverse remodeling and dysfunction; however, HF might develop in their absence.[2,29] Several preclinical and clinical studies have yielded results strongly suggesting that diabetic cardiomyopathy is a unique clinical entity, with hyperglycemia leading to abnormal cardiac structure and function independent of traditional cardiac risk factors.[30,31] Among the potentially implicated pathophysiologic derangements are insulin resistance and impaired insulin signaling, glucotoxicity and lipotoxicity, upregulation of inflammatory pathways, oxidative stress, mitochondrial dysfunction, formation of advanced glycation end-products, and cardiac fibrosis.[27,30–32]

By unloading the failing heart, LVADs create a favorable environment for the reversal of adverse structural and functional cardiac changes,[10–15] with functional cardiac improvement recently shown to associate with improved outcomes on LVAD support.[33,34] Clinical factors previously shown to associate with LVAD-mediated cardiac recovery include a younger age, an underlying NICM, a shorter duration of HF, and smaller left ventricle dimensions.[12,14,15,22] At the cellular and molecular level, it has been suggested that glucose metabolism, mitochondrial function, and myocardial and systemic inflammation might influence cardiac recovery upon mechanical unloading.[35–38] These derangements have been implicated in the pathophysiology of diabetes,[27,30–32] and might explain why T2D could play a role in LVAD-mediated cardiac recovery.

Insulin resistance is a key component of the metabolic syndrome, a cluster of systemic metabolic abnormalities implicated in the pathogenesis of cardiovascular disease.[39] Neurohormonal activation and chronic inflammation appear to be the common final pathway leading to changes in cardiac metabolism and signaling pathways that might contribute to myocardial dysfunction.[28,39] We have previously studied the effect of tissue and serum inflammatory markers on LVAD-mediated myocardial recovery.[38] Circulating levels of cytokines were lower, whereas the signal transducer and activator of transcription-3, an inflammatory response regulator, was less activated in the cardiac tissue of patients significantly improving the function and structure of their heart on an LVAD (responders) compared with nonresponders. As such, pre-LVAD metabolic dysfunction, including both insulin resistance/hyperglycemia and inflammation, seem to affect the potential for myocardial recovery.

It has been suggested that strategies to correct the systemic metabolic derangements associated with insulin resistance could impact the prognosis and outcomes of patients with HF.[28] In a study comparing intensive blood glucose control (target HbA1c ≤6.5%) versus standard of care treatment, combined micro- and macrovascular events risk were reduced by 10%, an effect largely driven by a reduction in the risk of microvascular events, especially nephropathy.[40] In another large study investigating blood glucose reduction, an overall benefit was shown during the period in which the HbA1c curves were separated,[41] whereas in a separate analysis, patients with low coronary artery calcium had the greatest benefit.[42] These findings might be suggestive of a differential effect of improved glycemic control on cardiac reverse remodeling based on the extent of already established macro- and microvascular coronary artery disease. This agrees with our finding that glycemia might play a more pronounced role in affecting functional cardiac improvement in patients with NICM compared with patients with ICM. Furthermore, the relationships between changes in cardiac and systemic metabolism and myocardial recovery are currently under intensive investigation by several groups, including our group,[35–37,43] and the emerging findings might shed additional light into the mechanisms driving the findings of the current study.

T2D is associated with worse outcomes in patients suffering from HF.[8] It has been suggested that even insulin resistance in the absence of overt T2D is independently associated with a worse prognosis.[7] Specifically in patients with advanced HF supported



	Non-Ischemic HF		Ischemic HF	
Variable	**Coefficient [95% CI]**	**p-value**	**Coefficient [95% CI]**	**p-value**
Age	0.031 [-0.080 – 0.141]	0.586	0.031 [-0.109 – 0.170]	0.666
Male Sex	-2.374 [-6.321 – 1.573]	0.237	-3.725 [-6.919 – -0.531]	0.023
HF Duration	-0.027 [-0.044 – -0.009]	0.004	-0.004 [-0.026 – 0.018]	0.743
LVEDD	-1.749 [-3.095 – 0.403]	0.011	-0.884 [-2.503 – 0.734]	0.282
HbA1c	-1.643 [-3.227 – -0.060]	0.042	0.254 [-1.005 – 1.512]	0.691

Figure 3. Main effects between pre-LVAD HbA1c and left ventricular functional improvement (absolute LVEF change: LVEF post-LVAD–LVEF pre-LVAD) in nonischemic and ischemic patients with HF.
HbA1c indicates glycated hemoglobin; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; and LVEF, left ventricular ejection fraction.

with LVADs, prior reports studying the impact of T2D and glycemic control on mortality and LVAD-related adverse events have not been conclusive.[44–47] In a meta-analysis, T2D was not shown to significantly affect all-cause mortality or LVAD-related adverse events.[48] In a recently published observational study of 154 patients with continuous-flow LVADs, patients with and without diabetes had comparable 30-day, 1-year, and 3-year mortality rates; however, T2D was an independent predictor of 5-year mortality (HR, 2.09; *P*=0.004).[49] Additionally, patients with T2D had higher rates of major infection on LVAD support (59% versus 47%, *P*=0.044).[49] In our study, we found that pre-LVAD HbA1c was not associated with the risk of all-cause mortality by 3 years on LVAD support. Patients with a higher HbA1c before LVAD support, however, had a higher chance of developing intracerebral hemorrhage, LVAD-related infection, or device thrombosis by 3 years on LVAD support.

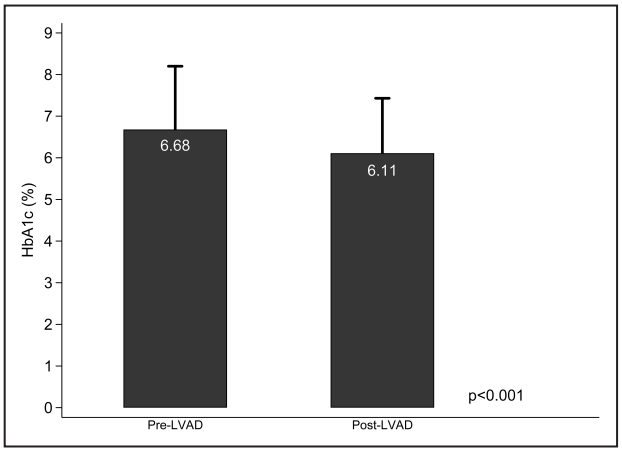


Figure 4. HbA1c values pre- and post-LVAD support.
The bars represent mean values and the caps the SD. HbA1c indicates glycated hemoglobin; and LVAD, left ventricular assist device.

Last, we found that in patients with available HbA1c measurements before and following LVAD implantation, HbA1c decreased from 6.69±1.54% pre-LVAD to 6.10±1.35% post-LVAD support (*P*<0.001). It should be acknowledged, however, that only a small proportion of patients were included in the analysis (127 out of

375), with the small sample size potentially affecting this finding. It has been reported that glycemic control improves following LVAD implantation with decreased fasting blood glucose and HbA1c levels, as well as antidiabetic medical therapy requirements.[44,47,50–52] Multiple physiologic factors might be driving these findings, stemming from improved hemodynamics, cardiac output, and tissue perfusion. Low cardiac output in advanced HF leads to upregulation of the renin-angiotensin-aldosterone system, and increases cortisol and catecholamine levels, which in turn lead to insulin resistance.[53] MCS helps correct these metabolic disturbances by increasing cardiac output and enhancing blood flow to peripheral tissues. It has also been shown that LVAD support reduces inflammation, which might also contribute to ameliorate insulin resistance.[54,55] Improved physical activity, more frequent follow-up, and better care coordination and medication optimization could also play a role.[51] Last, it should be noted that red blood cell lifespan and turnover rate are affecting HbA1c levels and might be contributing to decreased levels on LVAD support. MCS devices can lead to mechanical damage and destruction of red blood cells, leading to reduced hemoglobin and increased reticulocyte counts,[56,57] potentially overestimating a favorable glycemic control.

Limitations of the current study include the potential selection bias introduced by the inclusion of patients with available HbA1c measurements before LVAD implantation and at least 3 months echocardiographic follow-up on LVAD support, excluding patients who died or underwent heart transplantation before this time point. Additional limitations to be mentioned are the relatively small sample size and the inclusion of data from patients treated across a consortium of collaborating sites (ie, Utah Cardiac Recovery Program). Although the collaborating environment and research infrastructure allows for the rigorous, prospective follow-up of patients, it poses limitations on the generalizability of our findings. Additional limitations include the use of only 1 modality to assess cardiac functional improvement and the absence of information on micro- and macrovascular complications of T2D that could affect the study outcomes, as well as the limited number of patients treated with sodium-glucose cotransporter-2 inhibitors, which did not allow us to examine the impact of these medications on our results. Moreover, HF and T2D pharmacotherapy is presented for the 3-month post-LVAD time point. We acknowledge that pharmacologic regimen might have changed in subsequent time points. Last, the inclusion of available HbA1c values within the 1-year period preceding LVAD implantation does not allow for the assessment of longer-term glycemia and its potential effect on study outcomes.

The findings of our study suggest that T2D and pre-LVAD glycemia might affect the potential for functional cardiac improvement in patients with advanced HF supported with a durable LVAD. Moreover, it seems that glycemia before LVAD support does not affect all-cause mortality rates, but it affects the risk for the development of LVAD-related adverse events by 3 years on MCS. The degree and duration of glycemic control optimization before LVAD implantation to potentially promote and sustain cardiac functional improvement and improve outcomes warrants further investigation. Findings from the advanced HF/MCS investigational setting could inform the care of patients with earlier-stage HF and concomitant T2D or prediabetes, and follow-up studies in this patient population are warranted.

ARTICLE INFORMATION

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Disclosures

Dr Fang serves on the steering committee of the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial and on the data and safety monitoring board of the Dapagliflozin in Preserved Ejection Fraction Heart Failure (PRESERVED-HF) trial for AstraZeneca. Dr Drakos serves as a consultant for Abbott Laboratories and Pfizer and has received research support from Novartis and Merck. The remaining authors have nothing to disclose.

Supplemental Material

Tables S1–S2
Figures S1–S2

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