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Benefits of Neurohormonal Therapy in Patients with Continuous-Flow Left Ventricular Assist Devices

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Abstract

Left ventricular assist devices (LVADs) have dramatically improved short-term outcomes among patients with advanced heart failure. While neurohormonal blockade (NHB) is the cornerstone of treatment for patients with heart failure with reduced ejection fraction, its effect after LVAD placement has not been established. We reviewed medical records of 307 patients who underwent primary LVAD implantation from January 2006 to September 2015 at two institutions in the United States. Patients were followed for at least two years post LVAD implantation or until explantation, heart transplantation, or death. Cox regression analysis stratifying on center was used to assess associations with mortality. NHB use was treated as a time-dependent predictor. Stepwise selection indicated treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs) (HR=0.53 (0.30–0.95), $P = 0.03$), age at the time of implantation (HR = 1.28 (1.05–1.56) per decade, $P = 0.02$), length of stay post implantation (HR = 1.16 (1.11–1.21) per week, $P < 0.01$) and INTERMACS profile of 1 or 2 (HR = 1.86 (1.17–2.97), $P < 0.01$) were independent predictors of mortality. In this large, retrospective study, treatment with ACEIs or ARBs was an independent factor associated with decreased mortality post LVAD placement.

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Introduction

Continuous-flow left ventricular assist devices (LVADs) have ushered in a new era of management for patients with advanced heart failure.[1] LVADs have been approved for bridge-to-transplantation (BTT) and destination therapy (DT); however, mortality after LVAD implantation remains high at 30% at 2 years.[1] Because the availability of donor hearts is finite, stagnant, and unlikely to change in the foreseeable future,[2] there is a need to establish effective strategies to improve outcomes in patients after LVAD implantation.

Neurohormonal modulation is the cornerstone of medical management of heart failure;[3,4] however, the benefit of using neurohormonal agents in the unloaded post-LVAD heart has not been established. Neurohormonal blockade (NHB) has been speculated to promote left ventricular recovery in LVAD patients.[5–7] Although it is possible that NHB therapy—angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs)—might mitigate arrhythmias, right heart failure, renal dysfunction, persistent pulmonary hypertension, and other complications in LVAD patients,[8–11] more information demonstrating the efficacy of these agents in the post-LVAD population is needed before this approach can be widely advocated. Given the lack of proven benefit, it is not surprising that the recent Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis, as well as larger datasets, demonstrated the use of NHB therapy was low and highly variable among LVAD patients.[12,13] To help determine the value of NHB therapy in LVAD patients, we sought to investigate the benefits of these agents using a large database of patients from two LVAD centers in the United States.

Methods

Study Population

We retrospectively reviewed medical charts of patients age 18 years or older who had been implanted with primary LVAD at the University of California San Diego Medical Center, San Diego, CA and Aurora St. Luke's Medical Center, Milwaukee, WI between January 2006 and September 2015. We excluded patients who had received total artificial hearts and biventricular assist devices. The final study cohort consisted of 307 subjects. The decision to start patients on NHB had been made based on clinical judgment by a multidisciplinary team that included heart failure cardiologists. Patients had been followed from the time of LVAD implantation until explantation, heart transplantation, death, or last follow-up available. All records were reviewed for demographic characteristics, laboratory test results, medications, and clinical events. Specific medication information was collected monthly through 12 months post-LVAD implantation.

Statistical Analysis

Categorical baseline variables were described using frequency and percentage. The Shapiro-Wilk test was used to determine normality. Continuous variables identified as non-normal were described using median and interquartile range. Continuous variables identified as normal were described using mean and standard deviation. Competing risks, which uses a

proportional subdistribution function, was utilized to describe the probability of competing events of explantation, heart transplantation, or death post LVAD implantation. A Cox regression analysis was used to identify predictors associated with all-cause mortality post LVAD. To account for any potential differences, all models were stratified on center. The final multivariable model was developed through stepwise selection with all predictors examined for univariate associations included in the model-building process. A P value <0.05 was required for entry into the model and to remain in the model. Because the NHB medications were collected in the post-LVAD timeframe, they were set up as time-dependent predictors to account for any changes in medication regimen over time. All other variables examined were collected as of the time of implant. Time-dependent predictors incorporate the most recent indication for treatment for each patient into the Cox regression framework. Thereby, at each event time, the number of subjects at risk and their most recent treatment status are identified. Not only does this analysis reflect the true clinical nature of the patient, it also avoids immortal time bias.[14] Patients were indicated as being on or off an NHB medication at each monthly interval with the indication carried forward until the next month's information was available. At 12 months, the final indications collected for each medication were carried forward until the end of follow-up in the modeling. Competing risks regression analysis, which fits the proportional subdistribution hazards regression model described in Fine and Gray,[15] was utilized to assess the effect of covariates on the subdistribution of a particular type of failure in a competing risks setting. Each cause of death group with at least 8 events was modeled separately while allowing the other causes of death to be adjusted for as competing events. ACEI/ARB indication is treated as time-dependent as it was in all other models and thus is allowed to change through a patient's follow-up time. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). This study, including a waiver of informed consent, was approved by the local institutional review board at both participating institutions.

Results

Baseline patient characteristics prior to LVAD implantation are shown in Table I. The median age was 60 [52–67] years, and 76.5% of subjects were male. At the time of implantation, the INTERMACS profile included 37.8% of patients in INTERMACS class 1 or 2. The majority of patients were implanted as BTT (n = 228, 74.3%) receiving either HeartMate II (Abbott, Abbott Park, IL) (n=244, 79.5%) or HeartWare (Medtronic, Minneapolis, MN) (n=63, 20.5%). Table II describes the number of patients on each medication alone and in combination with other medications at 3, 6, 9, and 12 months.

The probability of receiving a heart transplant (n = 159) at 3, 6, 12, and 24 months post LVAD was 4%, 25%, 42%, and 53%, respectively (Figure 1). The probability of all-cause mortality (n = 79) at 3, 6, 12, and 24 months post LVAD was 8%, 13%, 20%, and 27%, respectively (Figure 1). The causes of death are shown in Supplemental Table I as a group and sub-divided into more specific causes of death. Each cause of death group with at least 8 events was modeled separately while allowing the other causes of death to be adjusted for as competing events. Supplemental Table II shows the association between being on ACEI/ARB and the described cause of death. Due to a low number of events, there is limited power to assess associations and thus none of the *P* values reach statistical significance.

However, all hazard ratios indicate the direction of the association as showing reduced risk for those on ACEI/ARB. Additionally, when causes of death due to heart failure and respiratory are combined, and thus the power increased, the association between ACEI/ARB and those causes shifts into a trend (HR = 0.4 (0.14–1.17), P=0.09), and when neurologic causes of death are included, the association becomes statistically significant (HR=0.38 (0.16–0.094), P=0.037). These models indicate that heart failure, respiratory, and neurologic deaths are most likely the main items driving the association between ACEI/ARB and overall mortality.

A univariate Cox regression analysis found that each decade increase in age was associated with a 28% increased risk of mortality (hazard ratio [HR] = 1.28 (1.07–1.55), P <0.01), each week increase in length of stay in the hospital post LVAD implantation was associated with a 15% increased risk of mortality (HR = 1.15 (1.10–1.20), P <0.01), and INTERMACS profile 1 or 2 was associated with a 79% increase in the risk of mortality compared with INTERMACS profiles 3–5 (HR = 1.79 (1.14–2.82), P = 0.01) (Supplemental Table III).

The time-dependent evaluation of the effect of NHB medications on mortality post LVAD implantation in univariate analysis revealed that use of ACEIs or ARBs, regardless of any additional medication, was associated with a 50% decreased risk of mortality (HR = 0.50 (0.29–0.86), P = 0.01). Statistically, beta-blockers (HR = 0.70 (0.43–1.14), P = 0.15), MRAs (HR = 1.00 (0.55–1.81), P = 0.99), hydralazine (HR = 0.87 (0.43–1.77), P = 0.71) and nitroglycerin (HR = 1.10 (0.48–2.56), P = 0.82) were not significantly associated with a decreased risk of mortality in this patient population (Supplemental Table III). Multivariable analysis showed that ACEI/ARB use (HR = 0.53 (0.30–0.95), P = 0.03); age at time of implantation (HR = 1.28 per decade (1.05–1.56), P = 0.02), length of stay post implantation (HR = 1.16 per week (1.11–1.21), P <0.01) and INTERMACS profile of 1 or 2 (HR = 1.86 (1.17–2.97), P <0.01) were independent predictors of mortality (Table III).

Next, we investigated the effect of a combination of medications in comparison with no NHB on mortality. Univariate analysis demonstrated a mortality advantage to being on ACEI/ARB alone, BB alone, or ACEI/ARB+BB in comparison to being on no NHB therapy (Table IV). In a multivariate model, taking ACEI/ARB only, ACEI/ARB+BB, or BB only, compared with no NHB, were independently associated with decreased mortality after adjusting for post LVAD length of stay, age at implantation, and INTERMACS profile 1 or 2 (Table V).

In order to assess baseline factors and initial ACEI/ARB indication, patients who were alive with their LVAD in place at 1 month post-implantation were included and split based on whether they were on ACEI/ARB at 1 month [126 (42%)] vs. not on ACEI/ARB at 1 month [173 (58%)] (Supplemental Table IV). The group of patients who were on ACEI/ARB vs. the group of those who were not on ACEI/ARB was younger (57 [48–64] vs. 61 [55–690, respectively, P<0.01), had a higher percentage of African-American individuals (42 [33.3%] vs. 30 [17.3%], respectively, P<0.01), had a lower percentage of Hispanic individuals (5 [4%] vs. 18 [10.4%], P=0.04), had more non-ischemic cardiomyopathy (64 [50.8%] vs. 63 [36.4%], P=0.03), had less coronary artery disease (72 [57.1%] vs. 130 [75.1%], P<0.01) and had lower percentage to hypertension (79 [62.7%] vs. 128 [74%], P=0.04).

Discussion

In this observational study of LVAD patients, use of an ACEI or ARB following LVAD placement was associated with a reduction in mortality risk by 47%. This association was statistically significant even when adjusted for relevant comorbidities and INTERMACS profile.

This is the largest study to date to show an association between ACEI or ARB use and mortality in LVAD patients. The strengths of our conclusions are based on a well-delineated dataset from two, varied clinical practice institutions with a follow-up period of 24 months. The survival rate at 24 months was 73%, which is consistent with an INTERMACS report with a survival rate between 68% and 73%, with improvement in the more recent era.[1] Additionally, monthly medication information was collected for the first 12 months after LVAD implantation and incorporated into the Cox regression as a time-dependent predictor in order to avoid immortal biases created when either baseline or time point specific data on medication are used.[14]

NHB therapy is the cornerstone for the treatment of patients with heart failure with reduced ejection fraction.[16–21] Although the role of NHB in LVAD patients remains unclear, there are several small clinical investigations that have demonstrated benefit. Basic science investigations offered mechanistic credence to NHB therapy in LVAD-supported patients who demonstrated reverse remodeling and beneficial improvements of molecular markers. Birks *et al.*[5] demonstrated that 12 out of 19 selected patients initiated on protocol-driven NHB therapy had myocardium recovery resulting in sustained LVAD explanation. Patel *et al.*[6] implemented an aggressive protocol to up-titrate NHB among 21 LVAD-supported patients and found significant improvements in several echocardiographic parameters, with one quarter of patients achieving complete recovery of cardiac function by left ventricular ejection fraction. Concordant data by Grupper *et al.*[7] demonstrated the consistent improvement of various echocardiographic measures (left ventricular ejection fraction, left ventricular volume and mass) as well as improvements in clinical parameters (New York Heart Association class, 6-minute walk distance) and the combined endpoint of cardiovascular death or heart failure hospitalization. These studies in aggregate comprise less than 120 patients, took place in single centers, and were not powered to demonstrate NHB category-specific or mortality outcomes.

Even though the mechanism of benefit is unknown at this time, the effect of ACEIs/ARBs in LVAD patients may be related to afterload reduction, cardiac reverse remodeling, effects on peripheral adrenergic receptors, reverse electrical remodeling, and anti-fibrotic properties.[22–26] Elevated blood pressure in LVAD patients is associated with significant adverse events, including stroke, pump thrombosis, and aortic insufficiency; therefore, the blood pressure reduction associated with ACEIs or ARBs has theoretical benefit. More recently it has been shown that ACEI or ARB therapy is associated with a reduced risk of gastrointestinal bleeding.[26]

Theoretically, beta-adrenergic blockade also should be beneficial in LVAD patients. Basic scientific investigation suggests that the reverse remodeling seen with beta-adrenergic

blockade could be particularly effective in the unloaded heart.[27,28] Several small trials[29,30] suggest that BBs can lead to myocardial recovery, but this has yet to be supported by randomized trials. Given the frequency and morbidity of arrhythmia in LVAD patients, the use of BBs seems advantageous.[31] Nonetheless, no randomized data support their use in this patient population. Furthermore, our study showed mortality benefit among patients using BB alone or BB in combination with ACEI/ARB compared with patients who are not on any NHB therapy. When looking at medication details, it is apparent that use of ACEI/ARB alone had the strongest association with reduction in mortality as compared with other medication combinations. Use of a BB alone has a mortality advantage compared with patients who are not on any NHB therapy; however, when a BB is combined with other medications, the association is not as strong. Use of an ACEI/ARB alone or in combination with other medications remains associated with a reduction in mortality compared with anyone who is not on an ACEI/ARB.

Our study has several limitations. First, as in all retrospective clinical datasets, our patients were not randomized to treatment NHB strategy and therefore selection bias may influence the observed outcomes; some but not all of this bias can be mitigated with multi-regression modeling. Second, neither titration strategies nor dose of NHB medication were explored as part of this analysis because the group numbers were small and we could not account for variability in practice patterns of medication adjustments. Third, although patients were followed up to 24 months, we collected data on NHB until 12 months post LVAD implantation as chronic medications at 1-year post LVAD implantation are unlikely to change at the second year follow-up. To support this assumption, we performed a sensitivity analysis that confirmed consistency of NHB therapy in over 80% of the study population between 6 and 12 months post implantation. Fourth, the effects of other pharmacological agents, such as clenbuterol,[32] and different treatment strategies, including LVAD speed change, were not considered. The retrospective nature of this dataset did not allow systematic collection of echocardiographic information, hemodynamic data, and right ventricle functional parameters; therefore, we chose not to introduce this information in the manuscript. Finally, we were not able to assess true patient compliance with NHB therapy; however, noncompliance would only underestimate the true benefit of NHB.

In conclusion, we found the use of ACEIs/ARBs to be significantly associated with lower mortality in a cohort of LVAD patients. We believe that a sufficiently powered, randomized study of ACEIs/ARBs in LVAD patients is warranted to validate our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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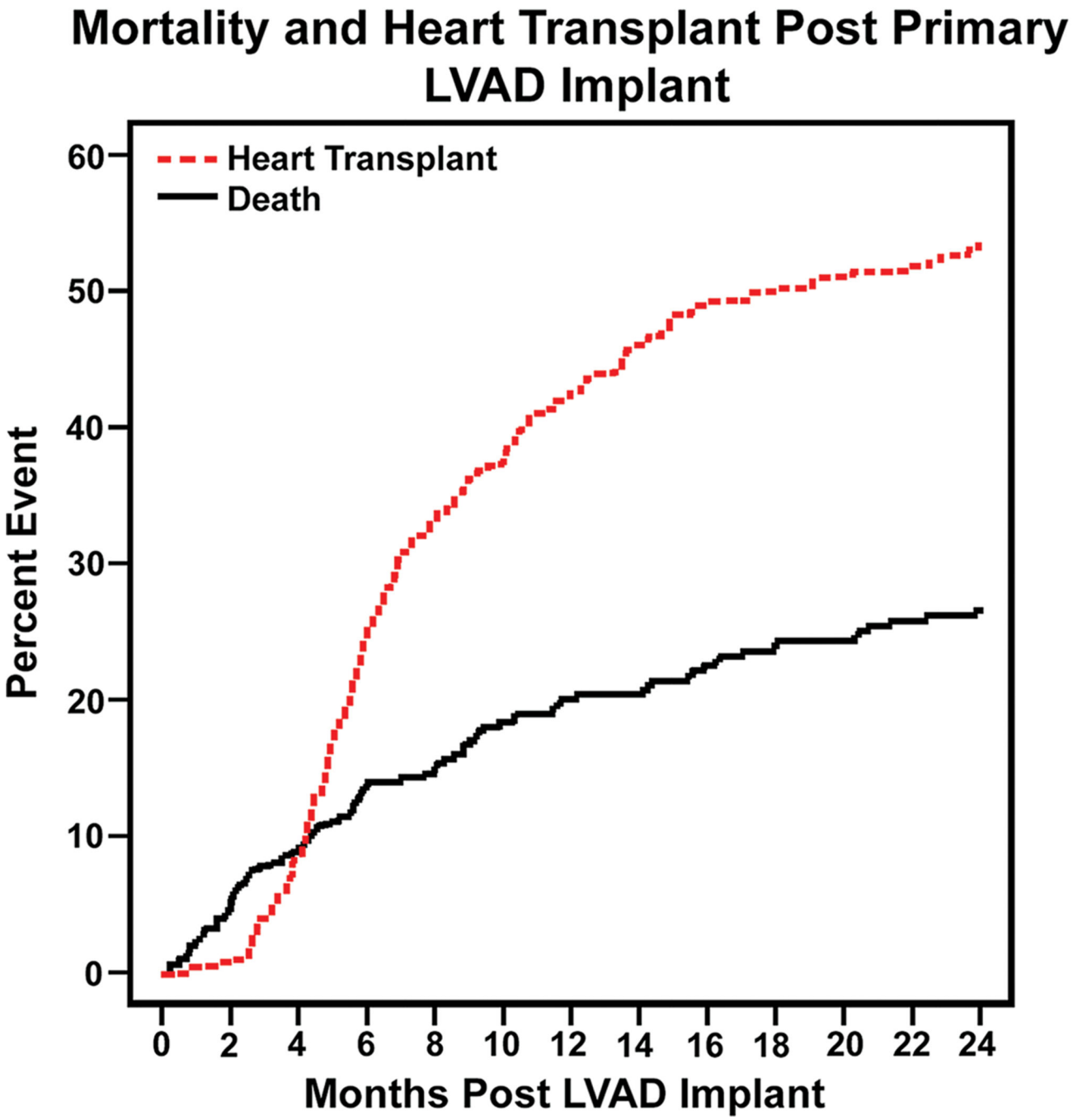

Figure 1.
Heart transplantation vs. all-cause mortality. Competing risk curve for mortality and heart transplantation after continuous-flow left ventricular assist device (LVAD) implantation.

Table I.

Pre-implant Characteristics of Patients Collected at Time of Implantation or Closest to Implantation Date Within 60 Days Pre-implant

Characteristic	All patients (n = 307)
Age at implant	60.0 [52.0–67.0]
Male sex, n (%)	235 (76.5%)
LOS post-implant, days	16 [12–24]
INTERMACS profile, n (%)	
1	27 (8.8%)
2	89 (29.0%)
3	64 (20.9%)
4	99 (32.3%)
5	14 (4.6%)
Missing	14 (4.6%)
Race, n (%)	
Caucasian	195 (63.5%)
African-American	76 (24.8%)
Hispanic	23 (7.5%)
Asian/Pacific Islands	3 (1%)
Other	10 (3.2%)
Implant strategy, n (%)	
DT	79 (25.7%)
BTT	228 (74.3%)
Type of LVAD, n (%)	
HeartMate II	244 (79.5%)
HeartWare	63 (20.5%)
Body mass index, kg/m^2	28.1 [24.1–33.1]
Smoking status, n (%)	
Never smoker	115 (37.5%)
Former smoker	187 (60.9%)
Current smoker	5 (1.6%)
Heart rate, bpm	82.0 [73.0–96.0]
Systolic blood pressure, mmHg	102.0 [92.0–117.0]
Diastolic blood pressure, mmHg	65.0 [59.0–72.0]
Non-ischemic cardiomyopathy, n (%)	132 (43%)
New York Heart Class	
I or II	2 (0.6%)
III or IV	282 (91.9%)
Class missing	23 (7.5%)
Serum sodium, mEq/L	136.0 [133.0–139.0]
Blood urea nitrogen, mg/dL	30.0 [19.0–43.0]
Serum creatinine, mg/dL	1.5 [1.2–1.9]

Characteristic	All patients (n = 307)
Hemoglobin, g/dL	11.3 ± 2.1
Coronary artery disease, n (%)	205 (66.8%)
History of hypertension, n (%)	210 (68.4%)
Diabetes mellitus, n (%)	154 (50.2%)
History of CVA, n (%)	92 (30%)
Atrial arrhythmia, n (%)	149 (48.5%)
Chronic kidney disease, n (%)	173 (56.4%)
COPD, n (%)	58 (18.9%)
Prior PCI, n (%)	139 (45.9%)
Prior CABG, n (%)	95 (31%)

Data presented as number (%), mean ± standard deviation, or median with interquartile range.

BTT, bridge to transplant; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LOS, length of stay; PCI, percutaneous coronary intervention.

Chronic renal disease is defined by glomerular filtration rate <60 mL/min/1.73 m^2 present over 3 months.

Table II.

Number of Patients Taking Neurohormonal Therapy at Different Time Points

Drug Combination	3 months n = 271 (alive with implant)	6 months n = 188 (alive with implant)	9 months n = 140 (alive with implant)	12 months n = 110 (alive with implant)
ACEI/ARB only	36 (13.3%)	25 (13.3%)	14 (10.0%)	12 (10.9%)
ACEI/ARB + BB	38 (14.0%)	19 (10.1%)	15 (10.7%)	5 (4.6%)
ACEI/ARB + MRA	13 (4.8%)	7 (3.7%)	7 (5.0%)	6 (5.5%)
BB only	40 (14.8%)	35 (18.6%)	23 (16.4%)	16 (14.5%)
BB + MRA	29 (10.7%)	22 (11.7%)	10 (7.1%)	10 (9.1%)
MRA only	32 (11.8%)	22 (11.7%)	15 (10.7%)	13 (11.8%)
ACEI/ARB + BB + MRA	19 (7.0%)	8 (4.3%)	8 (5.7%)	11 (10.0%)
Other	64 (23.6%)	50 (26.6%)	48 (34.3%)	37 (33.6%)

Data presented as n (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker (70% carvedilol and 30% metoprolol succinate); MRA, mineralocorticoid receptor antagonist; Other, hydralazine and nitroglycerin.

Table III.

Multivariable Cox Regression Models for 2-year Mortality

Predictor	Hazard ratio (95% CI)	*P* value
Age at implant (decades)	1.28 (1.05–1.56)	0.02
LOS post-implant (weeks)	1.16 (1.11–1.21)	<0.01
ACEI/ARB (time-dependent)	0.53 (0.30–0.95)	0.03
INTERMACS profile		
1–2, reference 3–5	1.86 (1.17–2.97)	<0.01
Missing, reference 3–5	0.62 (0.19–2.08)	0.44

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LOS, length of stay.

Table IV.

Univariate Cox Regression Analysis of the Breakdown of Neurohormonal Therapy Combinations (2-year Mortality)

Predictor	Hazard ratio (95% CI)	*P* value
ACEI/ARB only	0.19 (0.06–0.62)	<0.01
ACEI/ARB + BB	0.34 (0.13–0.87)	0.02
ACEI/ARB + MRA	0.38 (0.09–1.65)	0.20
BB only	0.43 (0.20–0.94)	0.03
BB + MRA	0.60 (0.22–1.64)	0.32
MRA only	0.60 (0.24–1.54)	0.29
ACEI/ARB + BB + MRA	0.74 (0.32–1.70)	0.48

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CI, confidence interval; MRA, mineralocorticoid receptor antagonist. All drugs treated as time-dependent variables in model.

Table V.

Multivariable Cox Regression Models Including the Breakdown of Neurohormonal Therapy Combinations (2-year Mortality)

Predictor	Hazard ratio (95% CI)	*P* value
Age at implantation (per decade)	1.30 (1.06–1.61)	0.01
LOS post implantation (per week)	1.14 (1.09–1.20)	<0.01
INTERMACS profile		
1–2, ref: 3–5	1.89 (1.18–3.02)	<0.01
Missing, ref: 3–5	0.54 (0.16–1.81)	0.32
ACEI/ARB only (ref: no NHB)	0.22 (0.07–0.73)	0.01
ACEI/ARB + BB (ref: no NHB)	0.37 (0.14–0.97)	0.04
ACEI/ARB + MRA (ref: no NHB)	0.53 (0.12–2.39)	0.41
BB only (ref: no NHB)	0.45 (0.21–0.97)	0.04
ACEI/ARB + BB + MRA (ref: no NHB)	0.82 (0.34–2.01)	0.67
BB + MRA (ref: no NHB)	0.82 (0.29–2.31)	0.70
MRA only (ref: no NHB)	0.65 (0.26–1.64)	0.36

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CI, confidence interval; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LOS, length of stay; MRA, mineralocorticoid receptor antagonist; NHB, neurohormonal blockade. All NHB drugs treated as time-dependent in model.