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Mortality in status 2 patients listed for heart transplantation in the United States: Will understanding cause of death help justify implantation of left ventricular assist devices into less sick patients?

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ABSTRACT

Objective: It remains unclear whether left ventricular assist device (LVAD) implantation in non-inotrope dependent patients is of clinical benefit. This study sought to evaluate cause of death in patients listed for heart transplant (HT) to determine the relative risks and benefits of implanting LVAD into patients who are less sick than those included in the original clinical trials.

Methods: We examined death as the primary outcome in 23,098 patients listed for HT from 2006 to 2014 using proportional subdistribution hazards modeling. Cause of death was examined as a secondary outcome using χ^2 tests.

Results: 1859 (8.1%) patients were removed from the wait list for death, including 229 (2.7%) status 1A, 349 (4.6%) status 1B, 246 (13.2%) status 2, and 1035 (26.0%) status 7 patients ($P < 0.0001$). Status 2 patients who received LVAD while listed had a higher risk of death compared to those who did not (adjusted HR 1.68; 95% CI 1.09–2.59; $P = 0.02$), while there was no increased risk of death in status 1A (HR 1.02; 95% CI 0.68–1.51; $P = 0.9$) and status 1B (HR 0.89; 95% CI 0.65–1.23; $P = 0.5$) who received LVAD. Status 2 patients who received LVAD were more likely to die cerebrovascular causes (0.6% vs. 0.1%, $P = 0.009$) and organ failure (70.6% vs. 29.4%, $P = 0.003$).

Conclusions: LVAD implantation in status 2 patients listed for HT is associated with a higher risk of death. More research is needed to determine the impact LVAD implantation will have on mortality in patients with ambulatory, non-inotrope dependent HF.

1. Introduction

More than 100,000 Americans with stage D heart failure (HF) are refractory to optimal medical therapy, with a 1-year survival of only 10% to 25% [1,2]. Although heart transplantation (HT) remains the therapy of choice for stage D HF, the demand for HT far outpaces the supply of donor organs [3]. Mechanical circulatory support with a durable left ventricular assist device (LVAD) is increasingly used for the clinical stabilization of patients with stage D HF who are listed for HT, in addition to those who are not transplant eligible [4].

LVAD therapy has demonstrated consistent improvements in mortality, quality of life, and functional status compared to optimal medical therapy for stage D HF [1,5]. The favorable clinical outcomes associated with the use of LVAD therapy in the past decade have encouraged rapid uptake of this technology, as well as a movement to pursue device intervention earlier in the HF disease spectrum. Patients included in the landmark LVAD clinical trials were often critically ill, with cardiogenic shock and end-organ dysfunction despite treatment with either inotropic or intra-aortic balloon pump support. Implanting LVADs into these critically ill patients was justified, since any morbidity associated with device implantation was balanced against the high mortality associated with medical management of cardiogenic shock [1,2].

Despite significant advances with LVAD therapy, however, device-related morbidity remains high. Approximately 70% of patients experience a major adverse event by one year including driveline infection, stroke, bleeding, and device malfunction [4]. Since the morbidity associated with these devices is not trivial, the idea of implanting LVADs into "less sick" patients has come with some criticism. Most experts would agree that more research is needed to determine whether the benefits of LVAD therapy outweigh the risks of LVAD-related complications before these devices can be routinely implanted into patients who are less sick than the patients studied in the pivotal clinical trials.

Recent clinical trials, including the Randomized Evaluation of Ventricular assist device InterVEntion before Inotropic Therapy (REVIVE-IT) and the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management (ROADMAP),

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have attempted to answer these questions by investigating implantation of LVADs into ambulatory HF who are not yet inotrope dependent and not listed for HT [6,7]. Non-inotrope dependent patients who are listed for HT may have similar clinical characteristics to those who would have enrolled in these clinical trials. Thus, we performed a retrospective cohort analysis utilizing the Scientific Registry of Transplant Recipients (SRTR) database to examine cause of death in patients listed for HT, in an effort to investigate whether LVAD implantation in non-inotrope dependent patients impacts wait list morbidity and mortality.

2. Methods

2.1. Study population

All subjects ≥18 years of age listed for HT from January 1, 2006 (the year of the last major HT allocation change) to March 25, 2014 were identified in the SRTR database, which includes deidentified data on all patients listed for a HT in the United States (US). SRTR maintains separate thoracic candidate and mechanical circulatory support files, which were combined for the purpose of this analysis. Since all data is deidentified, formal review was deemed unnecessary by the Emory University Institutional Review Board.

2.2. Listing status

Upon listing for HT, patients are designated as United Network of Organ Sharing (UNOS) status 1A, 1B, 2, or 7 based on their degree of hemodynamic compromise. UNOS status 1A is the highest priority status, and includes patients requiring extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), mechanical ventilation, high-dose continuous intravenous inotropes, or an exemption for critical illness such as ventricular tachycardia or complications with mechanical circulatory support including VAD and total artificial heart (TAH). UNOS status 1B is the next highest priority status, and includes patients receiving moderate dose continuous intravenous inotropes as well as stable VAD or TAH patients. UNOS status 2 is the lowest priority status, and includes patients who are hemodynamically stable and do not require continuous intravenous inotropes or mechanical circulatory support. UNOS status 7 patients are temporarily inactive due to a change in clinical condition that prohibits transplantation.

2.3. Study outcomes

We examined death as the primary outcome, taking into account the hazards from the competing risk of transplantation. Follow-up time started on the day of listing for HT, and continued until the day of removal from the wait list for transplantation, death, or other reason. Patients were censored if they were withdrawn from the list for another reason (i.e. improvement in clinical status), or if they were still waiting for HT on the last day of follow-up on March 25, 2014.

The cause of death was examined as a secondary outcome. Cause of death is submitted by the transplant centers, and verified by the SRTR using the Social Security Death Master File and Centers for Medicare & Medicaid Services data sources to provide additional death ascertainment [8].

2.4. Study covariates

Demographic and clinical covariates are defined by the transplant centers at the time of listing for HT. None of the subjects had missing data for the following variables: age, sex, race/ethnicity, ABO blood group, cardiac diagnosis, history of diabetes, body mass index (BMI), estimated glomerular filtration rate (eGFR), presence of defibrillator (ICD), ventilator, ECMO, IABP, inotrope support, insurance status, and listing status. There was significant missingness for albumin (18.5%), hypertension (17.7%), cardiac output (9.3%), and pulmonary capillary wedge pressure (PCWP, 12.4%), which we addressed using multiple imputation to allow these patients to contribute their available risk factors in multivariable models. Data for pulmonary wedge pressure was missing in 23.8%, 10.9%, and 6.8% of status 1A, 1B, and 2 patients respectively ($P < 0.0001$). Data for cardiac output was missing in 15.0%, 7.4%, and 7.8% of status 1A, 1B, and 2 patients respectively ($P < 0.0001$). Data for hypertension was missing in 18.7%, 16.0%, and 19.1% of status 1A, 1B, and 2 patients respectively ($P < 0.0001$). Data for albumin was missing in 20.3%, 16.9%, and 19.2% of status 1A, 1B, and 2 patients respectively ($P < 0.0001$).

2.5. Statistical analysis

Data are presented as mean ± standard deviation (SD) or *N* (%) of patients. Baseline characteristics were compared between patients according to initial listing status using the χ^2 or Fisher's exact test for categorical variables, and analysis of variance test for continuous variables. The primary and secondary outcomes were determined according to status at the time the patient was removed from the waiting list (last status). If a patient was listed status 7 just prior to wait list removal, their listing status (1A, 1B, or 2) just prior to being made status 7 was used for analysis. To estimate the association of last waitlist status with the risk of death, we used the Fine and Gray model of competing

Table 1
Clinical characteristics of 23,098 patients listed for heart transplant from 2006 to 2014 according to initial listing status.

	Total $N = 23,098$	Status 1A $N = 5359$	Status 1B $N = 9233$	Status 2 $N = 8506$	*P*
Age, years	52.0 ± 12.7	50.9 ± 13.2	52.0 ± 12.8	52.8 ± 12.2	<0.0001
Female	5892 (25.5)	1376 (25.7)	2300 (24.9)	2216 (26.1)	0.2
Nonwhite race	7292 (31.7)	1848 (34.6)	3343 (36.3)	2101 (24.9)	<0.0001
Cardiac diagnosis					<0.0001
• Ischemic	8729 (37.8)	2016 (37.6)	3336 (36.1)	3377 (39.7)	
• Dilated	10,895 (47.2)	2626 (49.0)	4960 (53.7)	3309 (38.9)	
• Valvular	430 (1.9)	98 (1.8)	148 (1.6)	184 (2.2)	
• Restrictive	658 (2.9)	123 (2.3)	171 (1.9)	364 (4.3)	
• Congenital	720 (3.1)	83 (1.6)	202 (2.2)	434 (5.1)	
• Hypertrophic	474 (2.1)	76 (1.4)	137 (1.5)	261 (3.1)	
• Other	1192 (5.2)	337 (6.3)	279 (3.0)	576 (6.8)	
Hypertension[a]	9598 (50.5)	2064 (47.4)	3906 (50.3)	3628 (52.7)	<0.0001
Diabetes	6413 (27.8)	1421 (26.5)	2717 (29.4)	2275 (26.8)	<0.0001
ICD	17,323 (75.9)	3513 (66.4)	7274 (79.9)	6536 (77.6)	<0.0001
BMI, kg/m^2	27.5 ± 5.1	26.8 ± 5.2	27.5 ± 5.1	27.8 ± 5.0	<0.0001
ECMO	225 (1.0)	208 (3.9)	9 (0.1)	8 (0.1)	<0.0001
Ventilator	584 (2.5)	439 (8.2)	103 (1.1)	42 (0.5)	<0.0001
IABP	1093 (4.7)	851 (15.9)	168 (1.8)	74 (0.9)	<0.0001
Inotropes	7232 (31.3)	2172 (40.5)	4620 (50.0)	440 (5.2)	<0.0001
eGFR[a], mL/min/1.73 m^2	68.7 ± 37.4	70.9 ± 42.4	69.2 ± 37.3	66.7 ± 34.0	<0.0001
eGFR categories, mL/min/1.73 m^2					<0.0001
• ≥60	12,347 (53.5)	2911 (54.3)	5087 (55.1)	4349 (51.1)	
• 30–59	9271 (40.1)	2034 (38.0)	3622 (39.2)	3615 (42.5)	
• <30	1480 (6.4)	414 (7.7)	524 (5.7)	542 (6.4)	
Albumin[a], mg/dL	3.7 ± 0.7	3.4 ± 0.7	3.6 ± 0.7	3.9 ± 0.6	<0.0001
PCWP[a], mm Hg	20.2 ± 8.7	21.9 ± 9.2	21.0 ± 8.8	18.7 ± 8.1	<0.0001
CO[a], L/min	4.3 ± 1.4	4.2 ± 1.5	4.3 ± 1.4	4.4 ± 1.3	<0.0001
Prior cardiac surgery	8981 (39.3)	2197 (41.5)	3523 (38.7)	3261 (38.7)	<0.001
Total days active	208.6 ± 310.3	88.2 ± 173.2	161.4 ± 223.7	335.8 ± 400.6	<0.0001

Values are mean ± SD, or *N* (%). BMI, body mass index; CO, cardiac output; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intraaortic balloon pump; ICD, defibrillator; PCWP, pulmonary capillary wedge pressure.

[a] Missing data was present for the following variables: albumin ($N = 18,819$), hypertension ($N = 19,002$), PCWP ($N = 20,237$), and CO (N = 20,950).

risks (with transplant being treated as a competing event), which extends the Cox model to competing risks data by considering the proportional subdistribution hazard [9]. The proportional hazards assumption was tested and verified for all risk factors using Schoenfeld residual correlation analysis. All variables in Table 1 were considered for inclusion in the multivariable models.

In order to further characterize the impact of LVAD implantation on the risk of death, we examined mortality in patients who received an LVAD after being listed for HT compared to those who did not. Using the date of implant, we determined the last waitlist status within 5 days of LVAD implant. Because LVADs were not randomly assigned in this patient cohort, potential confounding and selection biases were accounted for by developing a propensity score. The propensity for LVAD placement was determined using a multivariable logistic regression model that included variables at the time of initial listing that may have increased the propensity for LVAD implantation (age, gender, cardiac diagnosis, ABO blood group, BMI, eGFR, albumin, PCWP, ventilator, ECMO, IABP, and inotrope support). This model yielded a concordance statistic of 0.66 indicating reasonably good discrimination. A propensity score was then calculated from the logistic equation for each patient, representing the probability that a patient would receive an LVAD while listed. Subsequently, using a publicly available macro [10], we used the propensity scores to match each patient who received an LVAD while listed to patients ($N = 1$) who did not based on the listing status 5 days prior to implant for those patients who received an LVAD, or based on the initial listing status for those patients who did not receive an LVAD. Our final model adjusted for the presence of LVAD while listed in addition to the propensity score itself. Due to the potential for misclassification of patients who required circulatory support (i.e. inotropes, IABP, ECMO, or ventilator) at initial listing or while listed as status 2, we performed a sensitivity analysis that excluded those patients.

All tests of statistical significance were two-tailed, and P values < 0.05 were considered significant. Data were analyzed with the use of SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Study population

During the study period, 23,993 patients ≥18 years of age were listed for HT in the United States. Of these, 895 patients were initially listed as status 7, and were excluded from the current analysis (Fig. 1). The remaining 23,098 patients formed the study cohort.

3.2. Baseline characteristics at HT listing

The clinical characteristics of the 23,098 HT candidates who formed our analytic cohort are shown in Table 1. Compared to patients initially listed as status 1A or 1B, status 2 patients were older, more likely to be White, had a lower GFR, a similar rate of diabetes, less likely to have dilated cardiomyopathy, and had a greater number of active days on the wait list. Compared to status 1A patients, Status 2 patients were more likely to have an ICD, and were less likely to require circulatory support with ECMO, mechanical ventilation, IABP, or intravenous inotropes.

3.3. Clinical factors associated with wait list removal for death

During the study period, 1859 (8.1%) patients were removed from the wait list for death, including 658 (12.2%) status 1A, 744 (8.1%) status

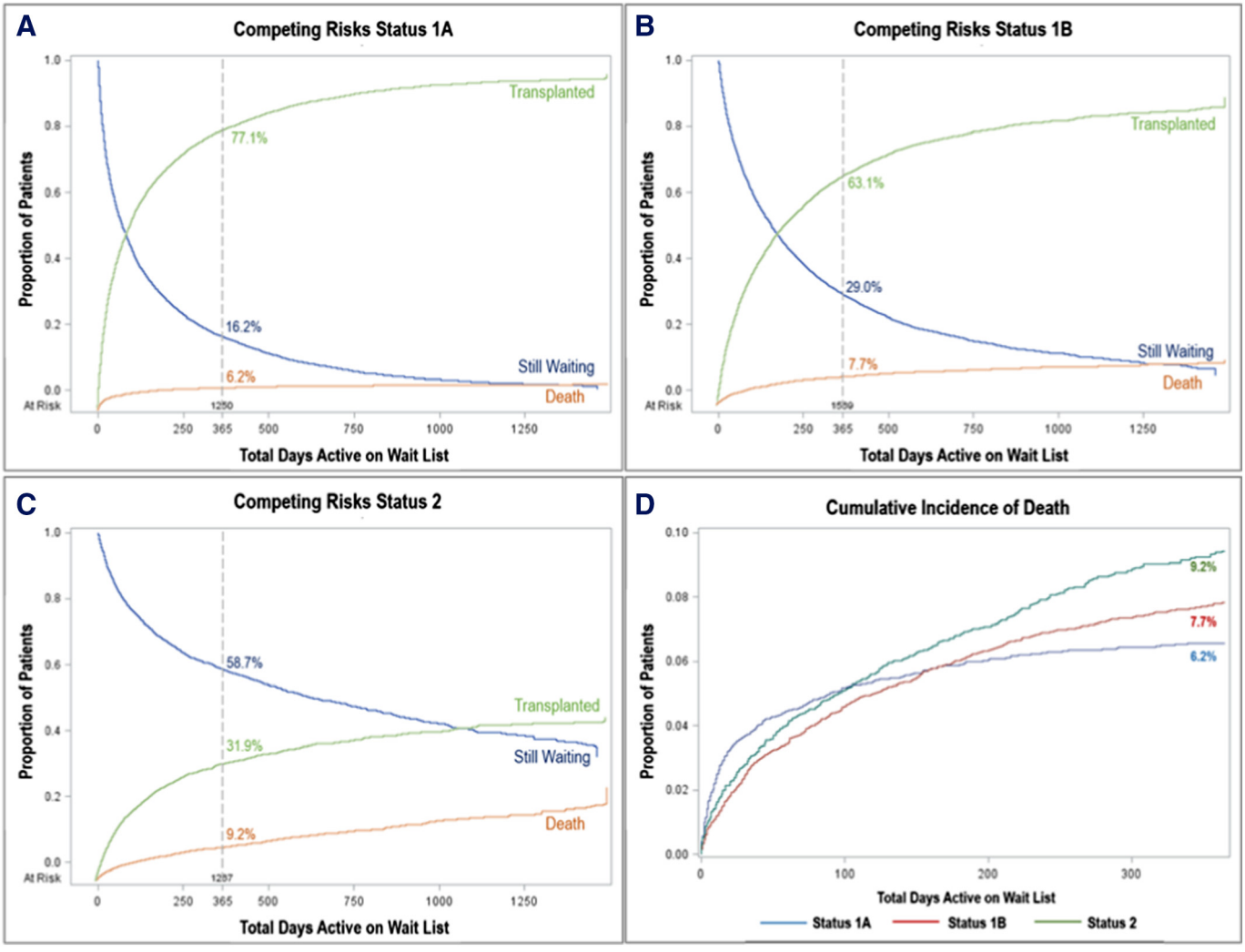

Fig. 1. Competing outcomes for patients listed for heart transplant in the US from 2006 to 2014 in status 1A (A), 1B (B), and 2 (C) at the time of wait list removal. The cumulative percentage of those who died on the wait list at 365 days is shown in D.

Table 2
Causes of death in patients listed for heart transplant from 2006 to 2014 according to last status prior to wait list removal.

	Status 1A $N = 658$	Status 1B $N = 744$	Status 2 $N = 457$	P
Cardiovascular				<0.0001
• Cardiac arrest	103 (15.9)	139 (19.1)	117 (26.0)	
• Ventricular failure	88 (13.4)	57 (7.7)	20 (4.4)	
• CAD/MI	2 (0.3)	10 (1.3)	11 (2.4)	
• Other	51 (7.8)	26 (3.5)	20 (4.4)	
Renal, liver, or MSOF	152 (23.1)	117 (15.7)	62 (13.6)	<0.0001
Infection	68 (10.3)	72 (9.7)	26 (5.7)	0.02
Cerebrovascular	73 (11.1)	96 (12.9)	27 (5.9)	0.0005
Respiratory	20 (3.0)	31 (4.2)	13 (2.8)	0.4
Hemorrhage	28 (4.3)	18 (2.4)	4 (0.9)	0.002
Other	43 (6.5)	52 (7.0)	42 (9.2)	0.2
Unknown	29 (4.4)	126 (16.9)	115 (25.2)	<0.0001

CAD, coronary artery disease; MI, myocardial infarction; MSOF, multi-organ system failure.

1B, and 457 (5.4%) status 2 ($P < 0.0001$) based on last status. The incidence rate of death on the wait-list was 15.8 per 100 patient-years in status 1A, 14.2 per 100 patient-years in status 1B, and 12.0 per 100 patient-years in status 2 based on last status. Fig. 1 illustrates competing outcomes for listed patients, and the cumulative percentage of patients who died on the wait-list at 365 days based on listing status at the time of wait list removal.

3.4. Cause of death at wait list removal

The causes of death according to listing status at the time of wait list removal are shown in Table 2. Cardiovascular (CV) death was the most common cause of death in all groups. Specifically, ventricular failure and cardiac arrest were the most common causes of CV death in status 1A patients, while cardiac arrest was the most common cause of CV death in status 1B and 2 patients. Other causes of CV death included arterial embolism and aortic aneurysm. Cause of death in status 2 patients did not differ based on ischemic vs. nonischemic HF etiology ($P = 0.3$) or presence of an ICD ($P = 0.4$). Compared to status 1, status 2 patients were less likely to be removed for cerebrovascular causes of death, as well as non-CV causes of death such as organ failure, infection, or hemorrhage.

3.5. Impact of LVAD implantation on risk of death using propensity matching

During the study period, 2096 (9.1%) patients went on to receive an LVAD after listing, including 673 (7.9%) patients initially listed as status 2, compared to 533 (10.0%) status 1A and 890 (9.7%) status 1B patients ($P < 0.0001$). A total of 332 (15.8%) patients who received a LVAD while listed died. In the peri-operative period defined as within 30 days post-implant, 109 patients died (5.2%) which were evenly distributed across status 1A ($n = 47$, 6.2%), 1B ($n = 29$, 5.3%), and status 2 ($n = 29$, 4.3%) ($P = 0.34$). Overall, those patients who received an LVAD while listed had a higher unadjusted risk of death compared to those patients who did not (Fig. 2), and were more likely to die of a stroke ($P < 0.001$).

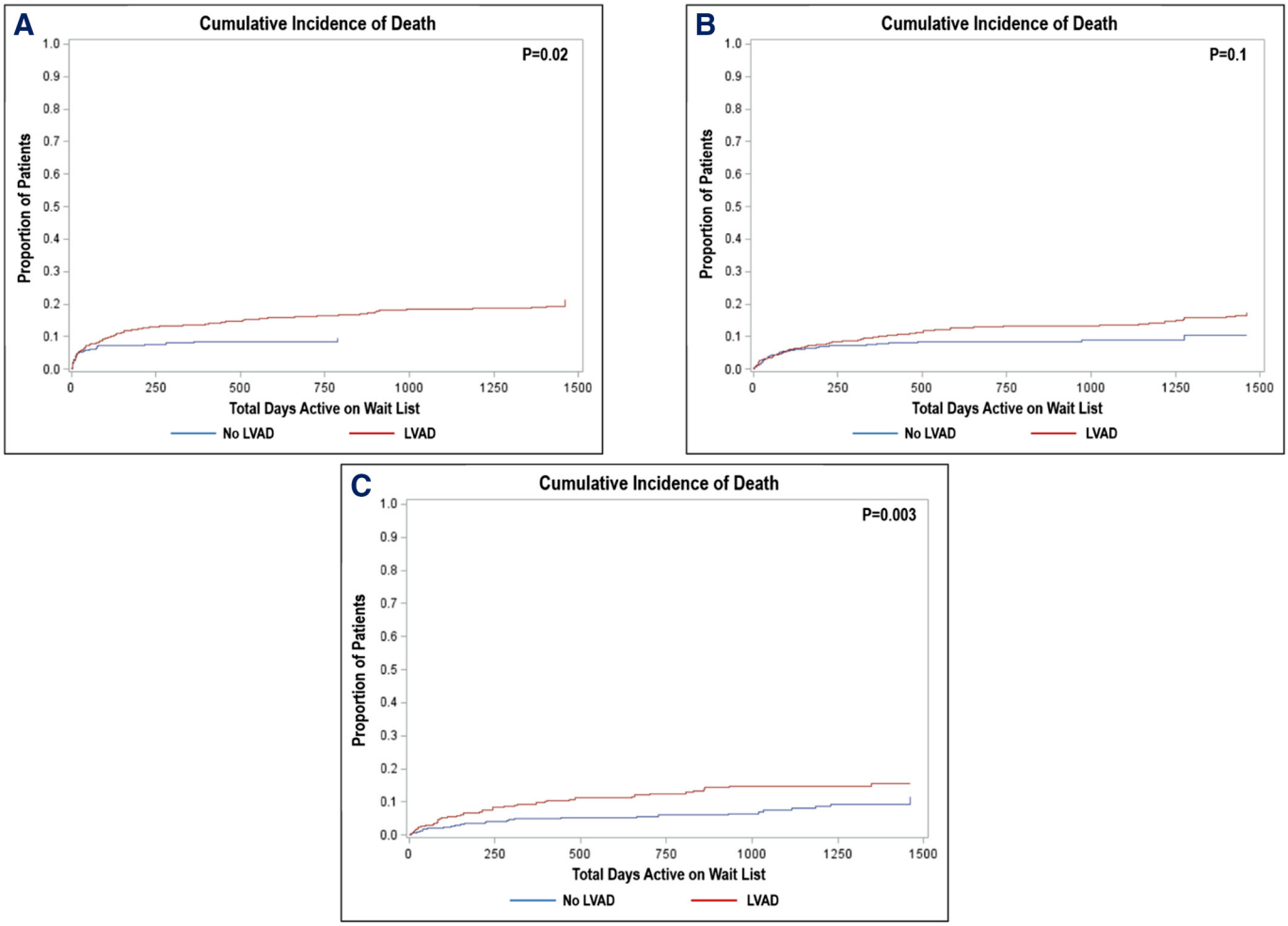

Fig. 2. Cumulative unadjusted incidence of death in status 1A (A), 1B (B), and 2 (C) patients who received an LVAD while listed vs. those who did not (propensity matched cohort). In comparison to status 2 patients who did not receive LVAD, status 2 patients who received LVAD were less likely to die of cardiac arrest, but more likely to die of cerebrovascular causes and organ failure.

However, after adjustment for propensity scores in the matched cohorts, the risk of death was only higher in those status 2 patients who received an LVAD (HR 1.68; 95% CI 1.09–2.59; $P = 0.02$) compared to those who did not, while there was no impact of LVAD on the risk of death in status 1A (HR 1.02; 95% CI 0.68–1.51; $P = 0.9$) and status 1B (HR 0.89; 95% CI 0.65–1.23; $P = 0.5$) patients. Compared to status 2 patients who did not receive an LVAD while listed, Status 2 patients who received an LVAD were less likely to die of cardiac arrest (20.0% vs 2.4%, $P < 0.0001$), but were more likely to die of cerebrovascular causes (0.6% vs. 0.1%, $P = 0.009$) and organ failure (70.6% vs. 29.4%, $P = 0.003$). There was no difference in other causes of death, including respiratory, infection, and hemorrhage. A sensitivity analysis including only the status 2 patients who did not require circulatory support ($N = 867$) did not alter the findings (HR 1.55; 95% CI 1.12–2.16; $P = 0.008$).

4. Discussion

In the present study, we analyzed incidence and cause of death in 23,098 patients listed for HT from 2006 to 2014 to determine if LVAD implantation in non-inotrope dependent patients might improve wait list morbidity and mortality. Although CV death was the most common cause of death in all groups, status 1B and 2 patients were most likely to die of cardiac arrest while status 1A patients were most likely to die of cardiac arrest and ventricular failure. Those patients listed as status 2 who went on to receive an LVAD while listed had a higher risk of death than those status 2 patients who did not receive an LVAD, while LVAD was not associated with an increased risk of death in patients listed as status 1A and 1B. These results suggest that survival in patients who are not yet inotrope dependent may be influenced to a greater extent by sudden cardiac arrest than by progressive ventricular failure, such that earlier LVAD implantation may not have as great an impact on mortality in this patient population.

Similar to our findings, prior studies have identified the most common causes of CV death in stage D HF patients to be sudden cardiac arrest and progressive ventricular failure [11–13]. Recent studies in ambulatory HF populations suggest that the proportion of patient deaths due to sudden cardiac arrest has been decreasing, likely due to the survival benefit associated with use of ICDs in patients with chronic HF [12,13]. Accordingly, there has been a concomitant increase in the contribution of deaths due to progressive ventricular failure and/or non-CV deaths [13]. The mechanism of sudden death in stage D HF patients is typically due to ventricular tachycardia/fibrillation, or bradycardia and/or electromechanical dissociation [14]. VT is common in patients with LVADs, however it remains unclear whether ICDs confer a survival benefit in this population [15,16]. Currently, there is little published data regarding how well bradycardic episodes are tolerated in patients with LVADs. Although LVADs will clearly alleviate progressive ventricular failure, this was not the primary cause of death in status 2 patients in our cohort.

Our analysis is unique because we observed a higher risk of death in patients listed as status 2 just prior to wait list removal when taking into account the competing risk of transplant. Our status 2 population was older, had a higher BMI, and lower GFR than the 1A population, which is a partial explanation for the higher risk of death. Other analyses that have examined wait list outcomes in patients listed for HT have typically found the highest risk of death in status 1A patients, however most of these analyses used the initial listing status to determine clinical outcomes, and were limited to Cox models that did not take into account the competing risk of transplantation [17–19]. Although patients listed as status 1A just prior to wait list removal had the highest incidence rate of death in our cohort, status 2 patients had a higher risk of death when taking into account the fact that they are less likely to be transplanted. Although recent data suggest that ~95% of transplants occur in status 1A/B patients and that the number of status 2 wait-list registrants continues to decline [17,20], our findings confirm that the risk of death in status 2 patients is still relatively high. Dardas et al. examined wait list outcomes in patients listed for HT from 2003 to 2008, and found that the unadjusted risk of death among status 2 patients was 9% at 1 year and 13% at 2 years [17]. Our analysis shows a similar degree of wait list mortality, as status 2 patients in our cohort had a 9.2% risk of death at 1 year. Still, our findings underscore the need to identify an intervention in HF patients with characteristics similar to those who are listed as status 2 that will decrease the high risk of mortality in this population.

Currently, there are few clinical trials that have examined the benefit of implanting LVADs into less sick patients. The recently completed ROADMAP trial was a prospective observational study that compared HeartMate II LVAD vs. optimal medical management (OMM) in ambulatory, non-inotrope dependent, NYHA IIIB and IV ambulatory HF patients considered INTERMACS profile 4–7 [21]. Importantly, these patients were not listed (or planned to be listed) for HT, and otherwise met FDA criteria for destination therapy. Despite more symptomatic HF in the LVAD group, 1-year survival on original therapy favored the LVAD group vs. OMM (80 ± 4 vs. $64 \pm 5\%$, $P = 0.03$). Moreover, secondary endpoints including improvements in 6 min walk distance, health-related quality of life, and depression scores favored LVAD therapy. Despite these benefits, adverse events including bleeding, stroke, arrhythmias and rehospitalizations were all more common in the LVAD group. Similarly, we found that LVAD-related complications such as infection, organ failure, cerebrovascular events, and hemorrhage were more common causes of death in status 2 patients who received an LVAD while listed compared to those that did not.

More recently, the REVIVE-IT randomized trial aimed to compare HeartMate II vs. OMM in NYHA class III HF patients, attempting to provide more scientific evidence regarding the potential advantages of LVAD therapy in treating earlier-stage, less ill HF patients. Due to multiple reports of increased incidence of pump thrombosis in HeartMate II patients [22,23], the trial's data and safety monitoring board felt there was a lack of equipoise directly related to concerns of using LVAD as an intervention in the target population. Thus, the REVIVE-IT study was closed due to lack of clinical equipoise and futility in timely enrollment. The fate of REVIVE-IT highlights the need to balance the survival benefit of LVAD with the risk of adverse events. It is unclear whether another attempt of a trial of LVAD therapy in patients with less advanced HF will ever be completed, as many "thought experts assert that the data necessary to offer LVAD therapy to patients with less advanced HF can be obtained from registry data or nonrandomized observations trials" [24]. Indeed, as mechanical circulatory support moves into the less sick patient profiles, decision making will be increasingly influenced by factors beyond survival, including functional and quality of life data, with ongoing attention paid to the heavy burden of adverse events.

Our study has several important limitations. Although SRTR data is validated at the time of entry, and internally verified when outliers exist, there may still be database errors that affect the internal validity of the data as well as our research findings. Moreover, many clinical variables known to be associated with mortality in stage D HF (i.e. sodium, blood pressure, heart rate, etc.) are lacking in this database. Still, the use of registry data allows access to large numbers of patients with "real-world" outcomes, and is an important resource for research since it gives a large-scale view of clinical outcomes for large numbers of patients. Accordingly, in our dataset there were patients who required circulatory support (i.e. inotropes, IABP) who were classified as status 2 at initial listing. This small number of patients did not impact the findings of our study, however this is a real example of possible misclassification error that is inherent to working with registry data. Although wait list deaths are verified by SRTR using the SSMDF, there may be some inaccuracies in the reported cause of death. More importantly, cause of death was unknown in almost 21% of patients listed status 2 at the time of wait list removal. In addition to cause of death, we had significant missingness of a portion of our baseline data in the

status 1A patients, which could be a source of bias in our multivariable models. Finally, status 2 patients who received LVAD while listed would likely have had this done due to clinical deterioration, with associated status change to either 1A or 1B. Since information on covariates was only available at the time of initial listing, it is possible that characteristics changed by the time of LVAD implantation. Thus, using propensity scores which were developed based on covariates at the time of initial listing may have introduced some bias in our multivariable models.

In conclusion, our analysis has confirmed that status 2 patients have a relatively high risk of death on the HT waiting list, with a low likelihood of transplantation. As the number of transplants in status 2 patients continues to decline, finding other interventions besides currently approved medical and device therapies that improve survival and quality of life in this population will become a key priority. Our data confirm that LVAD implantation in patients who were not inotrope-dependent when initially listed for HT was associated with higher mortality. However, this increased risk of mortality must be balanced with the mortality risk of continued medical therapy in a patient whose HF may be progressing. What risk of death or adverse event a patient is willing to accept for potential improvement in functional status and quality of life is a personal choice. Thus, more data is needed to precisely determine the risk and benefits of LVAD for the 'less sick', such that patients can truly provide informed consent for earlier LVAD placement.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.015.

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