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AMIODARONE USE IN PATIENTS LISTED FOR HEART TRANSPLANT IS ASSOCIATED WITH INCREASED ONE-YEAR POST-TRANSPLANT MORTALITY

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Abstract

Introduction—Pre-transplant amiodarone use has been postulated as a risk factor for morbidity and mortality after orthotopic heart transplant (OHT). We assessed pre-OHT amiodarone use and tested the hypothesis that it is associated with impaired post-OHT outcomes.

Methods—We performed a retrospective cohort analysis of adult OHT recipients in the ISHLT registry transplanted between 2005 and 2013, stratified by pre-OHT amiodarone use. We derived propensity scores using logistic regression with amiodarone use as the dependent variable, and assessed the associations between amiodarone use and outcomes with Kaplan-Meier analysis after matching patients 1:1 based on propensity score, and with Cox regression with adjustment for propensity score.

Results—Of 14,944 OHT patients in the analysis cohort, 32% (N=4,752) received pre-OHT amiodarone. Amiodarone use was higher in recent years (29% in 2005-07, 32% in 2008-10, and

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35% in 2011-13). Amiodarone-treated patients were older and more frequently had a history of sudden cardiac death (27% vs 13%) and pre-OHT mechanical circulatory support. Key donor characteristics and allograft ischemic time were similar between groups. In propensity-matched analyses, amiodarone-treated patients experienced higher rates of cardiac reoperation (15% vs 13%) and permanent pacemaker (5% vs 3%) after OHT and prior to discharge. Amiodarone-treated patients also had higher 1-year mortality (HR 1.15, 95% CI: 1.02, 1.30), but the risks of early graft failure, retransplantation, and rehospitalization were similar between groups.

Conclusions—Amiodarone use before OHT was independently associated with increased 1-year mortality. The need for amiodarone therapy should be carefully and continuously assessed in patients awaiting OHT.

Introduction

Survival after heart transplantation in the current era is substantially better than survival in the early years of heart transplantation, and continues to improve.^{1,2} This is mostly due to improved survival in the first year after transplant; however, the risk of mortality remains highest early after transplant. While early post-transplant mortality is affected by the transplant procedure and post-transplant care, it is increasingly recognized that donor and recipient characteristics and pre-transplant management also play an important role in in-hospital and post-discharge outcomes.

Some investigations suggested that pre-transplant anti-arrhythmic therapy with amiodarone results in increased risk of primary graft dysfunction (PGD), early graft failure, and increased mortality^{3,4}, while other studies found no difference in peri-operative morbidity or mortality in those treated with amiodarone and those not receiving this therapy.⁵⁻⁷ However, these investigations included small numbers of patients, were mostly based on single-center experience, and reported on patients transplanted more than a decade ago. No large multi-center studies in the contemporary era have addressed this question.

We examined the data available in the International Society for Heart and Lung Transplantation (ISHLT) scientific transplant registry (ISHLT Registry) to assess the prevalence of amiodarone use before heart transplantation and clinical characteristics of patients treated with amiodarone, and tested the hypothesis that pre-transplant amiodarone therapy is independently associated with increased post-transplant morbidity and mortality.

Methods

Data Source

The ISHLT Registry was the data source in this study. This database is populated by participating national and international organ transplant registries and collectives, and by individual transplant centers globally.⁸ History of taking amiodarone prior to transplant is reported (yes/no) in the registry.

Study Population

The study population included adult (age ≥ 18 years) recipients of OHT included in the ISHLT Registry with pre-transplant amiodarone use reported. Prior amiodarone use was defined as history of taking amiodarone prior to transplant. In order to study a contemporary cohort of transplant recipients in the current era of mechanical circulatory support and pre- and post-transplant management, we limited the study population to those who underwent transplantation from January 2005 to December 2013. We excluded patients with no information regarding pre-transplant amiodarone use, and patients with prior heart transplants, multi-organ transplants, heterotopic transplants, or domino transplants. The Duke University Institutional Review Board granted an exemption from review for this study.

Outcomes

The primary outcome was time to all-cause death within 1-year after transplant. Secondary outcomes included early post-transplant outcomes such as post-transplant time on inotropes, need for reoperation, length of hospital stay, graft failure, and pacemaker implant prior to hospital discharge. Post-transplant time on inotropes was defined as the number of days that inotropes were used after transplantation prior to discharge, and length of stay as number of days between transplant and hospital discharge among those who were discharged alive. Need for reoperation or permanent pacemaker between transplant and hospital discharge were categorized as yes, no, or unknown. We examined both graft failure at hospital discharge and 30-day death or retransplant due to graft failure. Graft failure at hospital discharge was based on a report by treating centers. The outcome of 30-day death or retransplant due to graft failure was termed “early graft failure” in the ISHLT 32nd Adult Heart Transplant Report on early graft failure.¹ This definition is stricter than most definitions of primary graft dysfunction, which may include graft dysfunction after 30 days. We also examined 1-year rehospitalization, retransplant, or need for permanent pacemaker.

Statistical Analyses

Groups were stratified by prior amiodarone use. We described baseline characteristics of heart transplant recipients and organ donors using frequencies and percentages for categorical variables and median and 25th, 75th percentiles (inter-quartile range) for continuous variables. Categorical variables were compared using the Pearson chi-square test or Fisher’s exact test and continuous variables were compared using Wilcoxon rank-sum test. We calculated the prevalence of pre-transplant amiodarone use by year of transplant, and assessed for trend using the Cochran-Armitage test.

Given the non-randomized use of amiodarone, propensity score methodology was used to assess the association between amiodarone use and post-transplant clinical outcomes. The propensity score is the propensity from 0 to 1 of receiving a treatment (in this case amiodarone) given a set of known variables (in this case other baseline characteristics included in the ISHLT registry database) and is used to adjust for potential selection bias, confounding and differences between treatment groups in observational studies.⁹ A propensity analysis was performed using a logistic regression model, with amiodarone use as the outcome of interest. Candidate variables used to construct the logistic model included

are marked in Table 1. Using a backwards selection cutoff alpha level of 0.20, prior malignancy, drug-treated hypertension, and angina were removed from the model. Based on this final model, a propensity score was computed for each transplant recipient. For each transplant recipient with amiodarone use, a transplant recipient with no amiodarone use was selected, using a greedy 5 → 1 digit matching algorithm. This algorithm matches recipients from the two amiodarone groups who have similar propensity scores, first matching on five digits of the propensity score, then four digits for cases that did not match, and so on to one digit matching. Of the 4,752 amiodarone transplant recipients, 4,633 were propensity-matched to a non-amiodarone transplant recipients. This resulted in a total propensity-matched cohort of 9,266 transplants. Covariates used in the calculation of the propensity scores after matching were assessed for balance between amiodarone groups.

The Kaplan-Meier method was used to produce estimates of patient survival stratified by amiodarone use for the entire cohort (unadjusted), and also for the propensity-matched cohort. In addition, Cox proportional hazards regression was used to assess the relationship between amiodarone use and mortality and morbidity outcomes, adjusting for recipient, donor, and transplant procedure characteristics. Continuous risk factors were included in the models using a restricted cubic spline.

For multivariable analyses, missing data was handled by imputing the overall median value for continuous variables and imputing the most frequent category for categorical variables. P-values of <0.05 were considered statistically significant.

Results

Baseline characteristics

Of the 14,944 adult patients who underwent heart transplantation and had documentation of amiodarone use, 4,752 (31.8%) were treated with amiodarone prior to heart transplant. Amiodarone use increased over time and was highest in the most recent era (29.1% in 2005-07, 31.9% in 2008-10, and 34.6% in 2011-13; $p<0.001$) (**Figure 1**). History of sudden cardiac death had an opposite trend, being highest in the early eras and lowest in the most recent era (18.6% in 2005-07, 16.9% in 2008-10, 15.9% in 2011-13; $p<0.001$). Patients with prior amiodarone use before transplant, compared to those without prior amiodarone use, were older (mean [SD] age 54.5 [11.3] vs 51.2 [13.1]; $p<0.001$) and more frequently had history of sudden cardiac death (26.5% vs 12.9%; $p<0.001$) and implantable defibrillator in place (87.2% vs 76.3%; $p<0.001$) (**Table 1**). They also had higher rates of pre-transplant intra-aortic balloon pump (6.4% vs 5.3%) and left ventricular assist device (31.4% vs 25.5%) use, and lower rates of intravenous inotrope use (38.4% vs 40.9%; $p=0.004$) compared to those who did not receive amiodarone. Key donor characteristics were similar between groups, and both groups had similar median allograft ischemic time (**Table 2**).

Outcomes

For the full (unmatched) cohort, amiodarone-treated patients had longer post-transplant length of hospital stay (15 vs 14 days; $p<0.001$), higher rates of cardiac reoperation (14.5% vs 12.6%; $p=0.003$) and permanent pacemaker implant (4.6% vs 3.3%; $p=0.001$) prior to

discharge (**Table 3a**). Patients treated with amiodarone had higher rates of graft failure at discharge (7.6% vs 6.1%), 30-day death or retransplant due to graft failure (2.7% vs 2.1%; $p=0.02$), and 1-year post-transplant mortality (12.0% vs 10.4%). Among patients discharged alive after transplant, rates of hospitalization and re-transplant in the first year were similar.

The propensity score matched cohort yielded 4,633 matched pairs. Similar to the full cohort, amiodarone-treated patients had higher rates of cardiac reoperation (14.5% vs 12.6%; $p=0.01$) or permanent pacemaker implant (4.7% vs 3.4%; $p=0.002$) prior to discharge (**Table 3b**). Amiodarone treated patients had higher 1-year mortality (12.0% vs 10.4%; $p=0.01$), but similar rates of rehospitalization between transplant and 1-year for those surviving to discharge (40.8% vs 41.7%; $p=0.42$). After propensity matching, those treated with amiodarone still had higher rates of graft failure at hospital discharge (7.6% vs 5.9%), but rates of 30-day death or retransplant due to graft failure were no longer statistically different between groups (2.7% vs 2.2%; $p=0.20$). Characteristics of early graft function and early graft failure are detailed in the Supplemental Tables.

There was a statistically significant difference in survival rates between the groups, with those without prior amiodarone use having better Kaplan-Meier survival up to 1 year (unadjusted $p<0.01$ for the full cohort and $p=0.01$ for the propensity-matched cohort [**Figure 2A and 2B**, respectively]). Primary cause of death is depicted in the Supplemental Figures. Infection, graft failure, and other organ system failure were the leading causes of death in the first year for patients with and without prior amiodarone use. In adjusted Cox regression, amiodarone use was similarly associated with higher risk of mortality up to 1 year (HR 1.15, 95% CI 1.02, 1.30; $p=0.03$) (**Table 4**). In contrast, prior amiodarone use was not significantly associated with risk of 30-day death or retransplant due to graft failure (HR 1.19, 95% CI 0.92, 1.54; $p=0.19$), or risk of 1-year retransplantation, rehospitalization, or need for permanent pacemaker.

Discussion

Using data from the ISHLT Registry, we examined amiodarone use prior to heart transplantation, and its association with post-transplant morbidity and mortality. First, we observed that pre-transplant amiodarone was used in 1/3 of patients and its use has increased over time. Second, patients treated with amiodarone were older, had higher rates of temporary and durable mechanical circulatory support prior to transplant, and more commonly had a history of sudden cardiac death, but not coronary artery disease. Third, pre-transplant amiodarone use was independently associated with a clinically significant 15% increased risk of death during the first year post-transplant.

Numerous mechanisms by which pre-transplant amiodarone use can affect post-transplant outcomes as a direct risk factor have been suggested. Given the rapid distribution of amiodarone into tissues and the long half-life, the effects of amiodarone can persist for months after the drug is discontinued.^{10,11} Specific pharmacologic properties of amiodarone, including calcium channel blockage and alpha- and beta-receptor blockade, result in negative chronotropic and inotropic effects of the drug.¹²⁻¹⁴ In addition, amiodarone has vasodilatory effects.¹⁴⁻¹⁶ Post-transplant vasoplegia, characterized by refractory

hypotension, low systemic vascular resistance, and acidosis is associated with greater risk of early post-transplant mortality.^{17,18} While a direct association between amiodarone and vasoplegia has not been detected, data are limited. Furthermore, calcineurin inhibitors are primarily metabolized by the CYP3A4 enzyme system, and amiodarone is a potent CYP3A4 inhibitor which causes notable drug interactions.^{13,19} Due to the long half-life of amiodarone, these interactions can occur even after amiodarone is discontinued.

Amiodarone use over time and patient characteristics

Pre-transplant amiodarone use has increased in recent eras; however, it is unclear if the increased use is justified. The increased use of amiodarone parallels the increasing age of transplant recipients, along with a decreased history of sudden cardiac death.¹ Indeed, we found that patients treated with amiodarone were older and had higher rates of temporary and durable mechanical circulatory support prior to transplant, consistent with prior reports.²⁰ Amiodarone-treated patients may have been more hemodynamically unstable and required mechanical circulatory support, or patients with a history of arrhythmia requiring antiarrhythmic therapy may not have been able to be safely bridged to transplant with inotropic agents. Despite the differences in recipient characteristics between the groups, donor characteristics were similar between groups, suggesting that amiodarone use does not directly or indirectly relate to other variables affecting donor-recipient matching.

Outcomes

Mortality—Prior smaller studies had conflicting results with respect to the association of amiodarone use with post-transplant mortality.³⁻⁷ Our study included a large and geographically and clinically diverse patient population. We identified statistically significant and clinically meaningful 15% increased risk of death in patients with a history of amiodarone therapy before transplant, which is concerning.

Permanent Pacing—Given the negative chronotropic effects of amiodarone, one could hypothesize that patients with prior amiodarone use would have an increased risk for needing a permanent pacemaker after transplant and that this may contribute to additional adverse events. Previously published data regarding the effect of pre-transplant amiodarone on post-transplant conduction and need for permanent pacemaker use are conflicting.²¹⁻²⁵ Our results show a higher frequency of requiring permanent pacemaker prior to discharge, but no difference in the rate of permanent pacemaker implant from discharge to 1 year post-transplant, which is consistent with the half-life of and exposure to amiodarone, with no significant residual net effect.

Graft Dysfunction and Graft Failure—It is unknown whether pre-transplant amiodarone use is associated with PGD. In recent years, heart transplant centers have noticed an increased incidence of PGD immediately after the transplant procedure. There continues to be considerable variability in the incidence of PGD among centers, with rates ranging from 2.3% to 28.2%, likely related, in part, to different definitions for PGD among centers.^{1,26} A recent consensus statement proposed an updated definition of PGD, incorporating information about cardiac function, mechanical support, and inotropes used. These updated criteria are yet to be incorporated to data collection in the ISHLT Registry.²⁶

Information regarding graft dysfunction and early graft failure, defined as death or retransplant within the first 30 days after transplant, is available, however.¹ Amiodarone treated patients had higher rates of graft failure at hospital discharge. Using the definition of early graft failure which captures the most severe cases of graft dysfunction leading to death within 30 days of transplant, amiodarone treated patients had higher unadjusted rates of early graft failure, consistent with prior reports; however, after multivariable adjustment, we found that rates of early graft failure were similar between the groups.¹ While amiodarone use was not associated with early graft failure, the higher frequency of early graft failure and in-hospital graft dysfunction among patients treated with amiodarone suggests that pre-transplant treatment with amiodarone may play a role in early post-transplant outcomes.

Clinical implications—The common use of amiodarone, along with the associated increased risk suggests that the decision to initiate and continue use of amiodarone in patients listed for heart transplant should be carefully considered. A significant proportion of amiodarone-treated patients had a history of sudden cardiac death and pre-transplant mechanical circulatory support, primarily in the form of implantable continuous-flow left ventricular assist devices. The use of these devices has increased dramatically in recent years and pre-OHT mechanical circulatory support has been shown to be associated with worse post-OHT outcomes.²⁷ While there are some clinical scenarios where they may elevate the risk of ventricular arrhythmias, they often also reduce such risk. Certainly, left ventricular assist devices can sustain circulation in the presence of ventricular arrhythmias.^{28,29} We therefore believe that assessment of continued indication for amiodarone use should be standard in the changing clinical picture of patients with advanced heart failure awaiting heart transplant. Repeated assessment of the daily dose of amiodarone needed should also be routinely performed in patients identified as requiring amiodarone. Furthermore, increased attention should be paid to identifying risk of post-transplant graft dysfunction in patients with prior amiodarone use, and strategies should be developed to detect and manage graft dysfunction in these patients.^{30,31}

Limitations—Our results should be taken in the context of several limitations. First, it is possible that pre-transplant amiodarone use is merely a risk marker for higher risk patients, though this possibility was addressed by thorough statistical adjustment. We adjusted for selection bias and confounding by using propensity scores derived from known baseline confounders, but we were not able to account for potential unmeasured confounders not reported to the registry. While the Registry has broad and generalizable coverage providing for good external validity, we are limited by the accuracy and completeness of the data entered into the registry and the lack of certain potentially important variables such as drug formulation, duration, dose or indication for amiodarone therapy, which relate to the internal validity of our results. Furthermore, the registry does not include specific data to correspond to components of a consensus definition of PGD, thus in-hospital graft dysfunction and the ISHLT Registry Report definition of early graft failure were used to examine early post-transplant graft dysfunction.^{1,26}

Conclusions—Use of amiodarone prior to heart transplantation has been increasing. Patients treated with amiodarone were older with higher rates of comorbidities and

mechanical circulatory support prior to transplant. Pre-transplant amiodarone use was independently associated with higher rates of in-hospital graft dysfunction and 1-year mortality. These findings, in the context of continued increase in amiodarone use in heart transplant candidates, strongly suggest that indications for amiodarone therapy should be carefully and continuously assessed in patients awaiting heart transplant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Frequency of Pre-Transplant Amiodarone Use by Year of Transplant from 2005 to 2013.

Cochran-Armitage trend test statistic=-5.89, $p<.0001$.

Figure 2.
Survival Rates from Kaplan-Meier Estimates Among Heart Transplant Recipients by Pre-Transplant Amiodarone Use

Panel A shows the survival curves for the full cohort

Panel B shows the survival curves for the propensity-matched cohort

Table 1

Pre-transplant recipient characteristics by pre-transplant amiodarone use

	N	% Missing	No Amiodarone (N=10192)	N	% Missing	Amiodarone (N=4752)	p value
Age, years, Median (IQR) ^a	10192	--	54.0 (44.0 - 61.0)	4752	--	57.0 (49.0 - 63.0)	<0.001
Gender, Male, No (%) ^a	10192	--	7466 (73.3%)	4752	--	3883 (81.7%)	<0.001
Weight kg, Median (IQR) ^a	10180	0.12	79.8 (68.0 - 92.1)	4752	--	82.1 (70.5 - 93.9)	<0.001
Primary Diagnosis for Transplant, No (%) ^a	10192	--		4752	--		<0.001
Dilated Myopathy			4830 (47.4%)			2241 (47.2%)	
Coronary Artery Disease			4033 (39.6%)			1989 (41.9%)	
Congenital Heart Disease			335 (3.3%)			103 (2.2%)	
Restrictive Myopathy			275 (2.7%)			81 (1.7%)	
Hypertrophic Cardiomyopathy			255 (2.5%)			106 (2.2%)	
Valvular Heart Disease			221 (2.2%)			106 (2.2%)	
Other			243 (2.4%)			126 (2.7%)	
Condition at time of transplant, No (%)	10185	0.07		4752	--		0.02
Not hospitalized			2929 (28.8%)			1474 (31.0%)	
Hospitalized, not in ICU			1573 (15.4%)			722 (15.2%)	
In ICU			5683 (55.8%)			2556 (53.8%)	
Support at time of transplant, No (%)							
Intravenous Inotropes	10191	0.01	4170 (40.9%)	4751	0.02	1825 (38.4%)	0.004
Intra-Aortic Balloon Pump	10191	0.01	539 (5.3%)	4751	0.02	302 (6.4%)	0.01
Ventilator	10191	0.01	227 (2.2%)	4751	0.02	117 (2.5%)	0.37
ECMO	10191	0.01	80 (0.8%)	4751	0.02	32 (0.7%)	0.46
Inhaled Nitric Oxide	10191	0.01	27 (0.3%)	4751	0.02	29 (0.6%)	0.001
Prostaglandins	10191	0.01	27 (0.3%)	4751	0.02	16 (0.3%)	0.45
Other	10191	0.01	638 (6.3%)	4751	0.02	388 (8.2%)	<0.001
Ventricular Assist Device, No (%)	10150	0.41		4741	0.23		<0.001
Left Ventricular Assist Device			2584 (25.5%)			1488 (31.4%)	
Right Ventricular Assist Device			32 (0.3%)			8 (0.2%)	
Total Artificial Heart			92 (0.9%)			49 (1.0%)	
Left + Right Ventricular Assist Device			344 (3.4%)			166 (3.5%)	
None			7098 (69.9%)			3030 (63.9%)	
Medical History, No (%)							
Hypertension ^a	10008	1.81	4615 (46.1%)	4646	2.23	2327 (50.1%)	<0.001
Diabetes ^a	10142	0.49	2609 (25.7%)	4734	0.38	1256 (26.5%)	0.30
Angina ^a	8946	12.23	1327 (14.8%)	4012	15.57	619 (15.4%)	0.38
Cerebrovascular Disease ^a	10130	0.61	471 (4.6%)	4716	0.76	255 (5.4%)	0.05

	N	% Missing	No Amiodarone (N=10192)	N	% Missing	Amiodarone (N=4752)	p value
Peripheral Vascular Disease ^a	9963	2.25	315 (3.2%)	4577	3.68	143 (3.1%)	0.90
Prior Cardiac Surgery ^a	10145	0.46	4572 (45.1%)	4738	0.29	2365 (49.9%)	<0.001
History of Sudden Cardiac Death ^a	9951	2.36	1284 (12.9%)	4547	4.31	1207 (26.5%)	<0.001
Implantable Defibrillator ^a	9868	3.18	7528 (76.3%)	4662	1.89	4063 (87.2%)	<0.001
COPD ^a	9970	2.18	412 (4.1%)	4588	3.45	251 (5.5%)	<0.001
Prior Malignancy ^a	10173	0.19	661 (6.5%)	4750	0.04	317 (6.7%)	0.69
Hemodialysis ^a	9944	2.43	83 (0.8%)	4617	2.84	53 (1.1%)	0.07
Dialysis	10098	0.92	241 (2.4%)	4709	0.90	147 (3.1%)	0.01
Serum Laboratory Values, Median (IQR)							
Creatinine, mg/dL	9994	1.94	1.1 (0.9 - 1.4)	4678	1.56	1.3 (1.0 - 1.6)	<0.001
Serum Total Bilirubin, mg/dL	9576	6.04	0.8 (0.5 - 1.3)	4510	2.37	0.8 (0.5 - 1.2)	0.03
Serum Albumin, g/dL	9244	9.30	3.8 (3.3 - 4.2)	4260	10.35	3.7 (3.2 - 4.1)	<0.001
Hemodynamics, Median (IQR)							
Mean PA pressure, mmHg	9074	11.00	28.0 (21.0 - 36.0)	4246	11.10	28.0 (21.0 - 35.0)	0.02
PCWP, mmHg	8632	15.31	19.0 (12.0 - 25.0)	4058	14.60	18.0 (12.0 - 25.0)	0.15
Cardiac Output, L/min	9020	11.50	4.2 (3.3 - 5.2)	4233	10.92	4.4 (3.5 - 5.3)	<0.001
Cardiac Index, L/min/m ²	9019	11.51	2.2 (1.8 - 2.7)	4232	10.94	2.2 (1.8 - 2.7)	0.13

Abbreviations: COPD: chronic obstructive pulmonary disease; ECMO: extra corporeal membrane oxygenation; ICU: intensive care unit; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure

^aVariables used to derive propensity score

Table 2

Donor and transplant procedure characteristics by recipient pre-transplant amiodarone use

	N	No Amiodarone (N=10192)	N	Amiodarone Use (N=4752)	p value
Age, years, Median (IQR)	10192	30.0 (21.0 - 42.0)	4751	30.0 (22.0 - 42.0)	0.50
Gender, Male, No (%)	10192	7202 (70.7%)	4752	3554 (74.8%)	<0.001
Weight, kg, Median (IQR)	10115	79.2 (69.0 - 90.7)	4735	80.3 (70.0 - 93.0)	<0.001
Primary Cause of Death, No (%)	9878		4613		0.65
Head Trauma		5827 (59.0%)		2749 (59.6%)	
Cerebrovascular/Stroke		2415 (24.4%)		1087 (23.6%)	
Anoxia		1543 (15.6%)		737 (16.0%)	
Other		93 (0.9%)		40 (0.9%)	
Left Ventricular Ejection Fraction (%), Median (IQR)	9671	60.0 (55.0 - 65.0)	4562	60.0 (55.0 - 65.0)	0.81
Cardiac Abnormalities, No (%) ^a	10192	9415 (92.4%)	4752	4438 (93.4%)	0.03
Catheterization, No (%)	9697	1722 (17.8%)	4573	803 (17.6%)	0.77
Cardiac Arrest with Downtime, No (%)	9557	518 (5.4%)	4506	274 (6.1%)	0.11
CPR Time following Downtime, Median (IQR)	518	15.0 (8.0 - 28.0)	274	16.0 (8.0 - 30.0)	0.50
Ischemic Time, hours, Median (IQR)	9962	3.3 (2.5 - 3.9)	4648	3.3 (2.5 - 3.9)	0.65
Inotrope Use, No (%)	10192		4752		
Dopamine		2155 (21.1%)		1051 (22.1%)	0.18
Dobutamine		146 (1.4%)		45 (0.9%)	0.01
Epinephrine		93 (0.9%)		35 (0.7%)	0.28
Levophed		983 (9.6%)		464 (9.8%)	0.82
Neosynephrine		1864 (18.3%)		972 (20.5%)	0.002
3+ Inotropic Agents at Time of Incision		136 (1.4%)		76 (1.7%)	0.25
Initial Hemodynamics, Median (IQR)					
Mean arterial pressure, mmHg	1078	83.0 (72.0 - 95.0)	512	83.0 (73.0 - 96.0)	0.37
Central venous pressure, mmHg	1682	8.0 (6.0 - 11.0)	790	8.0 (6.0 - 11.0)	0.88
Mean PA pressure, mmHg	1405	20.0 (16.0 - 24.0)	662	20.0 (16.0 - 24.0)	0.60
PCWP, mmHg	1178	12.0 (8.0 - 16.0)	562	12.0 (9.0 - 15.0)	0.73
Cardiac Output, L/min	1364	7.2 (5.7 - 8.9)	643	7.2 (5.7 - 9.0)	0.57
Cardiac Index, L/min/m ²	1364	3.7 (2.9 - 4.5)	643	3.6 (2.9 - 4.5)	0.82
Final Hemodynamics, Median (IQR)					
Mean arterial pressure, mmHg	1056	83.0 (74.0 - 95.0)	509	84.0 (76.0 - 98.0)	0.17
Central venous pressure, mmHg	1627	9.0 (7.0 - 11.0)	780	9.0 (7.0 - 11.0)	0.96
Mean PA pressure, mean, mmHg	1376	20.0 (17.0 - 24.0)	637	20.0 (17.0 - 24.0)	0.39
PCWP, mmHg	1077	12.0 (9.0 - 15.0)	506	12.0 (9.0 - 14.0)	0.09
Cardiac Output, L/min	1278	8.1 (6.7 - 10.0)	605	8.1 (6.7 - 10.1)	0.94
Cardiac Index, L/min/m ²	1278	4.2 (3.5 - 5.0)	605	4.1 (3.4 - 5.1)	0.77

Abbreviations: CPR: cardiopulmonary resuscitation; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure

^a Donor cardiac abnormalities include congenital structural and/or left ventricular hypertrophy structural and/or valve structural and/or wall abnormalities or any vessels with ≥ 50% stenosis or left ventricular ejection fraction < 50%

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Table 3a

Outcomes for full cohort by pre-transplant amiodarone use

	N	No Amiodarone (N=10192)	N	Amiodarone (N=4752)	p value
Post-Transplant Outcomes Prior to Discharge					
Time on Inotropes (days), Median (IQR) ^a	6885	5.0 (3.0 - 7.0)	3329	5.0 (3.0 - 8.0)	<0.001
Cardiac Reoperation, No (%)	9354	1183 (12.6%)	4355	632 (14.5%)	0.003
Length of Stay, Median (IQR) ^b	9427	14.0 (10.0 - 21.0)	4360	15.0 (11.0 - 22.0)	<0.001
Graft Function at Discharge	10180		4748		0.004
Graft Still Functioning		9559 (93.9%)		4389 (92.4%)	
Graft Failure		621 (6.1%)		359 (7.6%)	
Primary Non-function		206 (2.0%)		126 (2.7%)	
Acute Rejection		29 (0.3%)		7 (0.1%)	
Chronic Rejection/Atherosclerosis		1 (0.0%)		0 (0.0%)	
Other Graft Failure		26 (0.3%)		18 (0.4%)	
Patient Death (Graft Failure Not Reported)		359 (3.5%)		208 (4.4%)	
Permanent Pacemaker Prior to Discharge	10053	331 (3.3%)	4535	217 (4.6%)	0.001
Early Graft Failure^c	10183	211 (2.1%)	4752	127 (2.7%)	0.02
Time from OHT to EGF, days, Median (IQR)	211	5.0 (1.0 - 12.0)	127	4.0 (1.0 - 10.0)	0.60
Post-Transplant Outcomes from Discharge to 1 Year^d					
Hospitalization	9501	3740 (42.1%)	4491	1689 (40.9%)	0.19
Pacemaker	9903	289 (3.3%)	4445	144 (3.5%)	0.51
Outcomes 1 Year Post-Transplant^d					
Death within 1 Year Post-Transplant	10192	1058 (10.4%)	4752	568 (12.0%)	0.004
Retransplanted within 1 Year Post-Transplant	10192	30 (0.3%)	4752	13 (0.3%)	0.83

Abbreviations: EGF: early graft failure; OHT: orthotopic heart transplant

^aTime on inotropes excludes Isoproterenol^bLength of stay calculated for those discharged alive^cEarly graft failure defined as 30-day death or retransplant due to graft failure^dAnalysis of events between discharge and 1 year was limited to patients surviving discharge

Table 3b

Outcomes for propensity score matched cohort

	N	No Amiodarone (N=4633)	N	Amiodarone (N=4633)	p value
Post-Transplant Outcomes Prior to Discharge					
Time on Inotropes (days), Median (IQR) ^a	3102	5.0 (3.0 - 7.0)	3242	5.0 (3.0 - 8.0)	<0.001
Cardiac Re-operation, No (%)	4215	533 (12.6%)	4241	616 (14.5%)	0.01
Length of Stay, Median (IQR) ^b	4302	14.0 (10.0 - 21.0)	4248	15.0 (11.0 - 22.0)	<0.001
Graft Dysfunction at Discharge	4628		4629		0.01
Graft Still Functioning		4353 (94.1%)		4277 (92.4%)	
Graft Failure		275 (5.9%)		352 (7.6%)	
Primary Non-function		99 (2.1%)		122 (2.6%)	
Acute Rejection		11 (0.2%)		6 (0.1%)	
Chronic Rejection/Atherosclerosis		1 (0.0%)		0 (0.0%)	
Other Graft Failure		15 (0.3%)		18 (0.4%)	
Patient Death (Graft Failure Not Reported)		149 (3.2%)		206 (4.5%)	
Permanent Pacemaker Prior to Discharge	4571	156 (3.4%)	4569	213 (4.7%)	0.002
Early Graft Failure^c	4632	104 (2.2%)	4633	123 (2.7%)	0.20
Time from OHT to EGF, days, Median (IQR)	104	6.0 (1.0 - 16.0)	123	4.0 (1.0 - 10.0)	0.18
Post-Transplant Outcomes from Discharge to 1 Year^d					
Hospitalization	4347	1699 (41.7%)	4378	1644 (40.8%)	0.42
Pacemaker	4295	134 (3.3%)	4334	142 (3.6%)	0.57
Outcomes 1 Year Post-Transplant^d					
Death within 1 Year Post-Transplant	4633	480 (10.4%)	4633	554 (12.0%)	0.01
Retransplanted within 1 Year Post-Transplant	4633	13 (0.3%)	4633	12 (0.3%)	0.84

Abbreviations: EGF: early graft failure; OHT: orthotopic heart transplant

^aTime on inotropes excludes Isoproterenol^bLength of stay calculated for those discharged alive^cEarly graft failure defined as 30-day death or retransplant due to graft failure^dAnalysis of events between discharge and 1 year was limited to patients surviving discharge

Table 4

Associations between amiodarone use and outcomes up to 1 year in propensity-matched cohort

One Year Outcome	Adjusted Hazard Ratio (95% CI)	p value
Death (N=9,266)	1.15 (1.02, 1.30)	0.03
Retransplant (N=9,266) ^a	0.92 (0.42, 2.01)	0.83
Rehospitalization ^{a,b} (N=8,103)	1.00 (0.93, 1.07)	0.94
Pacemaker ^{a,b} (N=8,007)	1.11 (0.88, 1.41)	0.38
Early Graft Failure ^{a,c} (N=9,265)	1.19 (0.92, 1.54)	0.19

^aFor analyses of non-fatal events, patients were censored at time of death^bThe rehospitalization and pacemaker models were limited to events occurring between discharge and 1 year, so only patients surviving to transplant discharge were included in the analyses^cEarly graft failure defined as 30-day death or retransplant due to graft failure