Optimization of Preoperative Amiodarone Therapy for Survival and Primary Graft Dysfunction in Patients undergoing Heart Transplantation

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Introduction

Many patients on the waitlist or under evaluation for heart transplantation (HT) develop life-threatening arrhythmias.

Amiodarone (AMIO) is the preferred antiarrhythmic agent, used in ~35% of patients pre-HT.

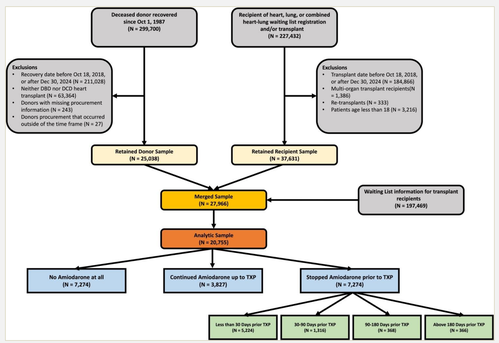
However, AMIO use in HT candidates remains debated due to the spectrum of adverse effects, i.e. pulmonary toxicity, sinus bradycardia, thyrotoxicosis, AV block, ventricular arrhythmias, and hepatotoxicity.

Building on single center studies completed before the 2018 UNOS heart allocation change, we provide a contemporary evaluation of the impact of pre-HT AMIO therapy on the long-term mortality, graft failure, and primary graft dysfunction (PGD).

We test the hypothesis that the time at which AMIO is discontinued may have a significant role in balancing the therapeutic effects with the risk of PGD.

Methods

Identified adult patients (≥ 18yo) listed for first-time HT in the US from 10/18/2018 – 12/30/2024.



Baseline recipient + donor characteristics were compared.

30-days, 6-months, 1-, 3-, and 5-years survival, PGD at 24 hours, acute rejection, LOS, reintubation, dialysis, stroke, and permanent pacemaker implantation compared.

Restricted cubit spline curve to assess the association between time of amiodarone discontinuation and risk of PGD.

Multivariate Cox proportional hazard models for mortality and PGD risk based on recipient pre-HT AMIO status.

Results

20,755 HT recipients identified: 46.5% never used AMIO, 18.4% continued AMIO, 35.1% stopped AMIO at least 5 days before HT.

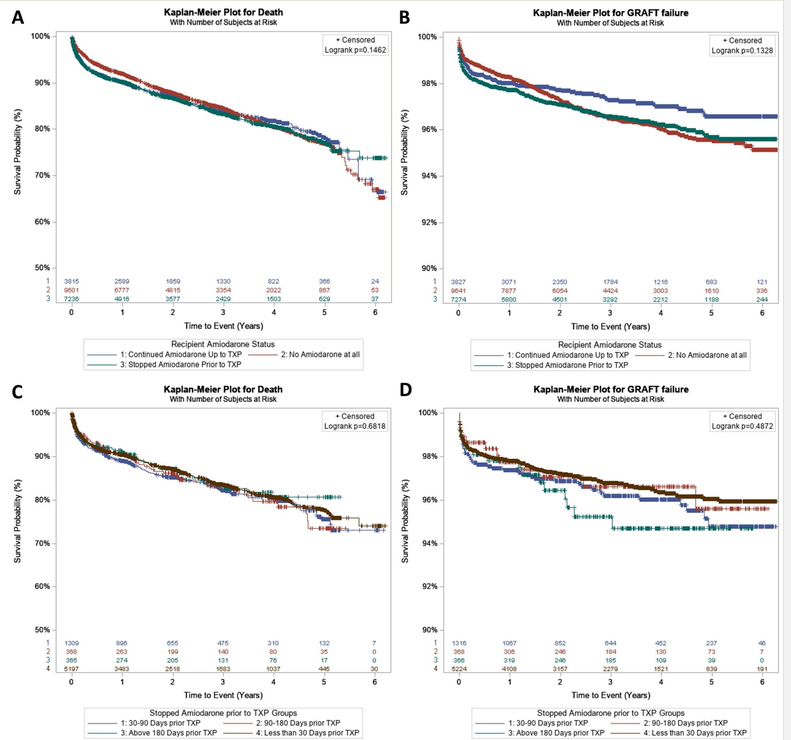


Figure 1. Kaplan-Meier survival analysis based on recipient pre-transplant amiodarone use.

There were no differences in 6-year recipient (**A; *p*=0.15**) and graft (**B; *p*=0.13**) survival by AMIO use. There were no differences in recipient (**C; *p*=0.68**) and graft (**D, *p*=0.49**) survival by timing of AMIO discontinuation.

Outcomes	Total (N=20,755)	No Amiodarone (N=9,654)	Continued Amiodarone up to TXP (N=3,827)	Stopped Amiodarone prior to TXP (N=7,274)	*P-Value*
Primary Graft Dysfunction					
At 24 hours, N (%)	685	266 (2.8%)	162 (4.2%)	289 (3.9%)	***0.019***
Postoperative Complications					
Length of Hospital Stay, days, mean (SD)	25.03 (28.59)	23.66 (26.55)	26.79 (31.08)	25.95 (29.74)	***<0001***
Stroke, N (%)	810	363 (3.8%)	169 (4.4%)	278 (3.8%)	*0.188*
Pacemaker, N (%)	323	132 (1.4%)	107 (2.8%)	122 (1.7%)	***0.011***
Dialysis, N (%)	3682	1444 (15%)	830 (21.7%)	1408 (19.4%)	***<0001***
Acute Rejection, N (%)	1831	921 (9.5%)	299 (7.8%)	611 (8.4%)	***0.002***
Treated for Rejection within 1 year, N (%)	2140	1060 (11%)	358 (9.4%)	722 (9.9%)	***0.008***
Reintubation, N (%)	76	38 (0.4%)	14 (0.4%)	24 (0.3%)	*0.794*

Results

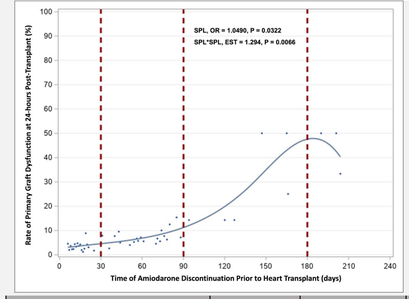


Figure 2. Spline plot of PGD rates based on time of AMIO discontinuation.

As the AMIO cessation period extends beyond 30 days before OHT, the PGD risk continues to rise until reaching a peak at 180 days. Stopping within 30-days is associated with the lowest risk of PGD.

Outcomes	Total (N=7,274)	5-30 days prior TXP (N=5,244)	30-90 days prior TXP (N=1,316)	90-180 days prior TXP (N=368)	> 180 days prior TXP (N=366)	*P-Value*
Primary Graft Dysfunction						
At 24 hours, N (%)	213	141 (2.7%)	40 (3.0%)	11 (3%)	21 (5.7%)	***0.012***
Postoperative Complications						
Length of Hospital Stay, days, mean (SD)	25.95 (29.74)	25.77 (30.57)	26.35 (28.38)	25.44 (24.01)	31.46 (19.77)	***0.034***
Stroke, N (%)	278	184 (3.5%)	62 (4.7%)	13 (3.5%)	19 (5.2%)	*0.108*
Pacemaker, N (%)	102	61 (1.2%)	24 (1.8%)	5 (1.4%)	12 (3.3%)	***0.028***
Dialysis, N (%)	1408	1031 (19.7%)	235 (17.9%)	72 (19.6%)	70 (19.1%)	*0.493*
Acute Rejection, N (%)	611	421 (8.1%)	125 (9.5%)	30 (8.2%)	35 (9.6%)	*0.317*
Treated for Rejection within 1 year, N (%)	722	499 (9.6%)	133 (10.1%)	38 (10.3%)	52 (14.2%)	***0.038***
Reintubation, N (%)	24	15 (0.3%)	7 (0.5%)	1 (0.3%)	1 (0.3%)	*0.573*

Variable	Hazard Ratio	95% Confidence Interval	*P-Value*
Multivariate Analysis			
Recipient Amiodarone Status			
No Amiodarone at all	REF		
Continued Amiodarone Up to TXP	1.63	[1.31 - 2.01]	***<0001***
Stopped Amiodarone Prior to TXP	1.31	[1.09 - 1.58]	***0.004***
Timing of Amiodarone Discontinuation			
5-30 Days prior TXP	REF		
30-90 Days prior TXP	1.54	[0.70 - 3.37]	*0.283*
90-180 Days prior TXP	1.40	[0.54 - 3.61]	*0.487*
>180 Days prior TXP	2.13	[1.02 - 4.44]	***0.035***

AMIO use (both continuation + stopping) was associated with increased PGD risk.

Stopping AMIO >180 days before HT was associated with increased PGD risk.

Conclusions

Pre-HT AMIO use (regardless of stopping) is associated with increased risk of short-term mortality and PGD → AMIO toxicity may carry over to the transplanted heart allograft.

However, pre-HT AMIO use has little impact on long-term mortality.

Stopping AMIO as close to HT as possible offers a 'window of opportunity' to withdraw or reduce the doses.

As patients move up the waitlist, HT candidates' AMIO regimen should be closely monitored and adjusted to balance the anti-arrhythmic benefits and minimize the early complications associated with AMIO.