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The Interaction of Amiodarone and Continuous-flow Left Ventricular Assist Device Use in Risk of Severe Primary Graft Dysfunction Following Heart Transplantation

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Background. Primary graft dysfunction (PGD) increases morbidity and mortality after heart transplant. Here we investigated (1) the association of continuous-flow left ventricular assist device (CF-LVAD), amiodarone, and severe PGD and (2) the safety of amiodarone discontinuation in CF-LVAD patients. **Methods.** Retrospective, single-center study of heart transplant recipients was conducted to investigate the association of risk factors and severe PGD. Patients were grouped into 4 groups based on the presence (denoted +) or absence (denoted –) of amiodarone and CF-LVAD. Prospective amiodarone discontinuation was undertaken to investigate its safety in a cohort of CF-LVAD patients. Study endpoints were severe PGD and recurrence of arrhythmia. **Results.** Severe PGD was strongly associated with CF-LVAD and amiodarone use, and its prevalence is highest if both risk factors were present (CF-LVAD–/amiodarone– 1.5%, CF-LVAD–/amiodarone+ 4.5%, CF-LVAD+/amiodarone– 7.1%, CF-LVAD+/amiodarone+ 21.8%; $P<0.01$). The product of every 1-y additional CF-LVAD support by every 100 mg amiodarone was associated with severe PGD (adjusted odds ratio, 1.43; 95% confidence interval, 1.15-1.78; $P<0.01$). Amiodarone was prospectively discontinued in 28 CF-LVAD patients. Of them, 6 patients had recurrence of arrhythmia requiring treatment or heart failure admission. There were no deaths. Nine patients in whom amiodarone had been discontinued had heart transplants with no severe PGD. **Conclusions.** Amiodarone and CF-LVAD were independently associated with severe PGD. The combination of both risk factors was associated with a higher prevalence of severe PGD. Amiodarone discontinuation was associated with recurrence of arrhythmia in 6 CF-LVAD patients. There was no mortality associated with amiodarone discontinuation.

(*Transplantation Direct* 2022;8: e1281; doi: 10.1097/TXD.0000000000001281).

INTRODUCTION

Primary graft dysfunction (PGD) following orthotopic heart transplantation is associated with increased risk of early mortality. Its reported prevalence ranges from 2.3% to 28.2%.[1] An increasing number of recent analyses have found an association between pretransplant amiodarone use and PGD.[2-5] It is postulated that severe PGD was affected by means of a dose-dependent relationship with amiodarone.[2]

Received 8 September 2021. Revision received 1 December 2021.

Accepted 2 December 2021.

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This study is supported by the Division of Cardiology, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY. M.R.-L. received a personal grant Magda Heras from Sociedad Española de Cardiología.

D.G. is a consultant for Abbott, Medtronic, and Abiomed. U.P.J. is a consultant for Abbott. The other authors declare no conflicts of interest.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001281

This finding is especially concerning given that amiodarone use exceeded 30% of heart transplant waitlisted patients in the modern era and it was associated with increased 1 y posttransplant mortality.[6]

Of note, the association of amiodarone and severe PGD was equally observed in heart transplant recipients bridged from continuous-flow left ventricular assist devices (CF-LVADs).[7] In the United States, >30% of heart transplant waitlisted patients are supported by a CF-LVAD because of its superior survival benefits,[8] thus rendering CF-LVAD an essential and unmodifiable component of end-stage heart failure treatment. CF-LVAD patients often tolerate even sustained ventricular arrhythmias with sufficient hemodynamic support[9] and could permit the safe discontinuation of amiodarone to reduce the risk of PGD following heart transplantation. Here, we sought to (1) investigate the association of CF-LVAD, amiodarone, and severe PGD and (2) evaluate the safety of prospective amiodarone discontinuation in CF-LVAD patients.

MATERIALS AND METHODS

A retrospective chart review was conducted of all adult heart transplant recipients (age >18 y) between June 2006 and December 2017. Baseline characteristics, intraoperative data, and postoperative outcomes were collected. Donor heart data were retrieved from the United Network for Organ Sharing (UNOS) database. Patients were grouped into 4 groups based on the presence (denoted +) or absence (denoted –) of amiodarone and CF-LVAD at the time of transplant. Primary endpoint was severe PGD. Severe PGD was defined as severe left, right, or biventricular function requiring mechanical circulatory support other than intra-aortic balloon pump (IABP) within 24 h posttransplantation in the absence of surgical causes, known pulmonary hypertension, or hyperacute rejection.[1]

Beginning July 2017, prospective amiodarone discontinuation in stable outpatient CF-LVAD patients was undertaken. The decision to discontinue amiodarone in these patients was based on the emerging knowledge of its association with severe PGD and increased 1-y mortality post–heart transplant.[2,6] CF-LVAD patients were screened by a ventricular assist device coordinator or an advanced heart failure/transplant cardiologist for suitability for amiodarone discontinuation. Baseline characteristics were collected before amiodarone cessation. Amiodarone was either immediately stopped or weaned off in a tapered fashion under the supervision of an advanced heart failure/transplant cardiologist and guided by serial defibrillator interrogation as needed. Patients were followed in clinic until heart transplantation or end of study. The primary endpoints were recurrence of arrhythmia requiring implanted cardioverter defibrillator therapies or antiarrhythmic therapy, heart failure hospitalization, or death. Secondary endpoint was severe PGD. The institutional review board of Albert Einstein College of Medicine provided a waiver of consent for both cohorts.

Statistical Analysis

Continuous variables were summarized as mean ± SD and categorical variables as frequency and percentages. Categorical variables were analyzed with chi-square test, and continuous variables were analyzed with analysis of variance or independent Student *t* test as appropriate. Univariate logistic regression analysis was used to identify preoperative risk factors of severe PGD. Univariate variables with a *P* value <0.2 were subsequently entered into a multivariate logistic regression model. A *P* value <0.05 was considered statistically significant. All data analyses were performed with IBM SPSS Statistics for Macintosh version 26.0 (IBM Corp, Armonk, NY).

RESULTS

A total of 250 adults were transplanted between June 2006 and December 2017. Seven patients with pulsatile LVADs

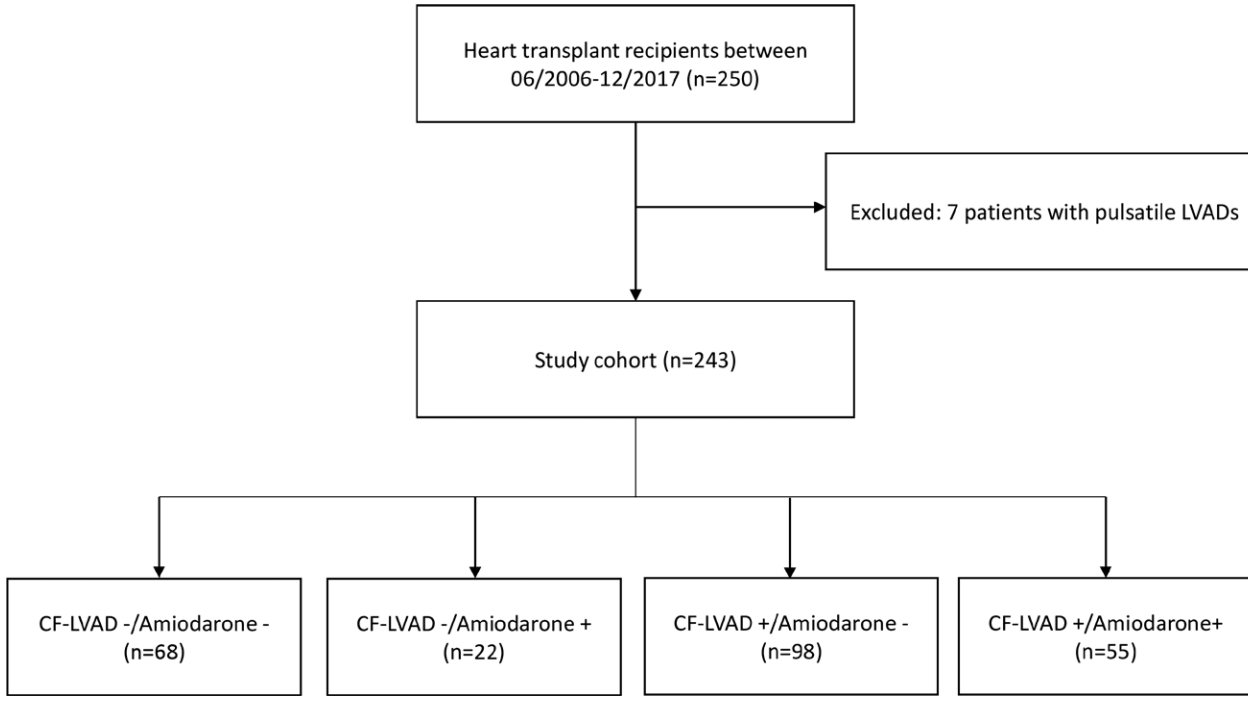

FIGURE 1. Flowchart of retrospective analyses of heart transplant recipients between June 2006 and December 2017. CF-LVAD, continuous-flow left ventricular assist device; +, presence; -, absence.

were excluded from the analysis. Two hundred forty-three patients formed the final study cohort and were grouped according to the presence (denoted +) or absence (denoted –) of amiodarone and CF-LVAD (Figure 1).

The mean age of the cohort was 53.6 ± 13.2 y, 29.6% were female, 59.7% were with nonischemic cardiomyopathy, and 63.0% were bridged with a CF-LVAD. Baseline recipient characteristics, pretransplant medications, and donor and perioperative data of each group are listed in Table 1. The prevalence of amiodarone use in the cohort was 31.7%.

Amiodarone, CF-LVAD, and Severe PGD

A stepwise increase in severe PGD prevalence was observed across the 4 groups (CF-LVAD–/amiodarone– 1.5% versus CF-LVAD–/amiodarone+ 4.5% versus CF-LVAD+/amiodarone– 7.1% versus CF-LVAD+/amiodarone+ 21.8%; $P < 0.01$; Figure 2).

In univariate analysis, recipient diabetes, hypertension, UNOS status 1A at transplant, CF-LVAD, amiodarone, beta-blocker, sildenafil, anoxia as donor cause of death, donor cardiopulmonary resuscitation time (per 1 min), donor–recipient size mismatch, and intraoperative red blood cell transfusion (per 100 mL) were associated with severe PGD at a P value <0.2 (**Table S1**, SDC, http://links.lww.com/TXD/A399) and were chosen for the multivariate analysis. A multivariate logistic regression analysis found that CF-LVAD (adjusted odds ratio [aOR], 5.18; 95% confidence interval [CI], 1.08-24.85; $P = 0.04$) and preoperative amiodarone use (aOR, 3.37; 95% CI, 1.22-9.29; $P = 0.02$) were independently associated with severe PGD.

A subsequent multivariate model identified every 1 y of CF-LVAD support was associated with an aOR 1.81 (95% CI, 1.16-2.81; $P = 0.01$) for severe PGD, and every 100 mg of preoperative amiodarone dose at heart transplant was associated

TABLE 1.

Baseline recipient, donor, and perioperative characteristics of retrospective cohort according to the presence or absence of CF-LVAD and amiodarone

Baseline characteristics	CF-LVAD–/amiodarone– (n = 68)	CF-LVAD–/amiodarone+ (n = 22)	CF-LVAD+/amiodarone– (n = 98)	CF-LVAD–/amiodarone+ (n = 55)	P
Age (y)	50.4 ± 15.9	56.0 ± 12.2	54.0 ± 12.5	55.9 ± 9.9	0.09
Female sex (%)	26 (38.2)	10 (45.5)	24 (24.5)	12 (21.8)	<0.05
BMI (kg/m^2)	25.1 ± 5.4	24.6 ± 4.5	27.6 ± 4.6	29.1 ± 4.5	<0.01
UNOS status 1A at heart transplant (%)	55 (80.9)	20 (90.9)	77 (78.6)	49 (89.1)	0.27
NICM (%)	46 (67.6)	15 (68.2)	50 (51.0)	34 (61.8)	0.13
Diabetes (%)	23 (33.8)	7 (31.8)	42 (42.9)	29 (52.7)	0.14
Hypertension (%)	36 (52.9)	12 (54.5)	69 (70.4)	37 (67.3)	0.10
CKD (%)	16 (23.5)	10 (45.5)	25 (25.8)	17 (30.9)	0.21
Duration of CF-LVAD support (mo)	–	–	12.6 ± 12.6	11.7 ± 9.9	0.65
Amiodarone total dose (mg)	–	372.7 ± 198.0	–	300.0 ± 140.1	0.07
Aspirin (%)	32 (47.1)	13 (59.1)	75 (76.5)	40 (72.7)	<0.01
ACE inhibitor/ARB (%)	32 (47.1)	9 (40.9)	57 (59.2)	29 (52.7)	0.29
Beta-blocker (%)	53 (77.9)	20 (90.9)	86 (87.8)	47 (85.5)	0.28
Aldosterone antagonist (%)	43 (63.2)	18 (81.8)	30 (30.6)	18 (32.7)	<0.01
Hydralazine (%)	14 (20.6)	8 (36.4)	31 (31.6)	13 (23.6)	0.29
Nitrate (%)	15 (22.1)	7 (31.8)	15 (15.3)	9 (16.4)	0.27
Sildenafil (%)	3 (4.4)	0 (0.0)	19 (19.2)	11 (20.0)	<0.01
Inotrope (%)	60 (88.2)	20 (90.9)	0 (0.0)	2 (3.6)	<0.01
Presurgery IABP (%)	6 (8.8)	7 (31.8)	0 (0.0)	0 (0.0)	<0.01
Presurgery ECMO (%)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.46
Baseline donor data					
Age (y)	30.2 ± 12.2	30.6 ± 10.9	32.5± 10.8	30.9 ± 9.0	0.56
Anoxia as cause of death (%)	28 (43.8)	11 (52.4)	44 (45.4)	32 (60.4)	0.26
CPR time (min)	16.6 ± 23.0	23.7 ± 29.7	15.3 ± 19.1	19.6 ± 22.4	0.38
LVEF (%)	61.4 ± 6.2	63.0 ± 6.4	59.7 ± 6.9	60.3 ± 5.5	0.13
Donor–recipient size mismatch[a] (%)	7 (10.9)	3 (14.3)	15 (15.5)	15 (28.3)	0.08
Improved donor LVSD[b] (%)	10 (15.6)	2 (10.0)	13 (13.5)	3 (5.7)	0.38
Perioperative data					
Dual organ transplant (%)	9 (13.2)	2 (9.1)	3 (3.1)	1 (1.8)	0.02
Total ischemic time (min)	207.4 ± 51.3	237.2 ± 58.1	213.9 ± 52.6	214.0 ± 55.8	0.18
Total CPB time (min)	173.3 ± 61.3	178.4 ± 77.6	201.1 ± 58.9	213.4 ± 75.8	0.01
Intraoperative RBC transfusion (mL)	434.6 ± 928.8	231.8 ± 381.0	659.8 ± 748.7	741.4 ± 790.3	0.02
Intraoperative FFP transfusion (mL)	335.6 ± 650.7	195.2 ± 294.2	578.5 ± 643.0	540.0 ± 579.7	0.01
Intraoperative platelet transfusion (mL)	289.1 ± 462.4	182.5 ± 273.9	433.4 ± 394.4	447.9 ± 428.3	0.01

[a]Donor–recipient size mismatch defined as donor-to-recipient predicted heart mass ratio <0.86.[10]
[b]Improved donor LVSD defined as LVEF ≤40% on initial TTE that resolved (LVEF ≥50%) during donor management on a subsequent TTE.[11]
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CF-LVAD, continuous-flow left ventricular assist device; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NICM, nonischemic cardiomyopathy; RBC, red blood cell; TTE, transthoracic echocardiogram; UNOS, United Network for Organ Sharing; +, presence; –, absence.

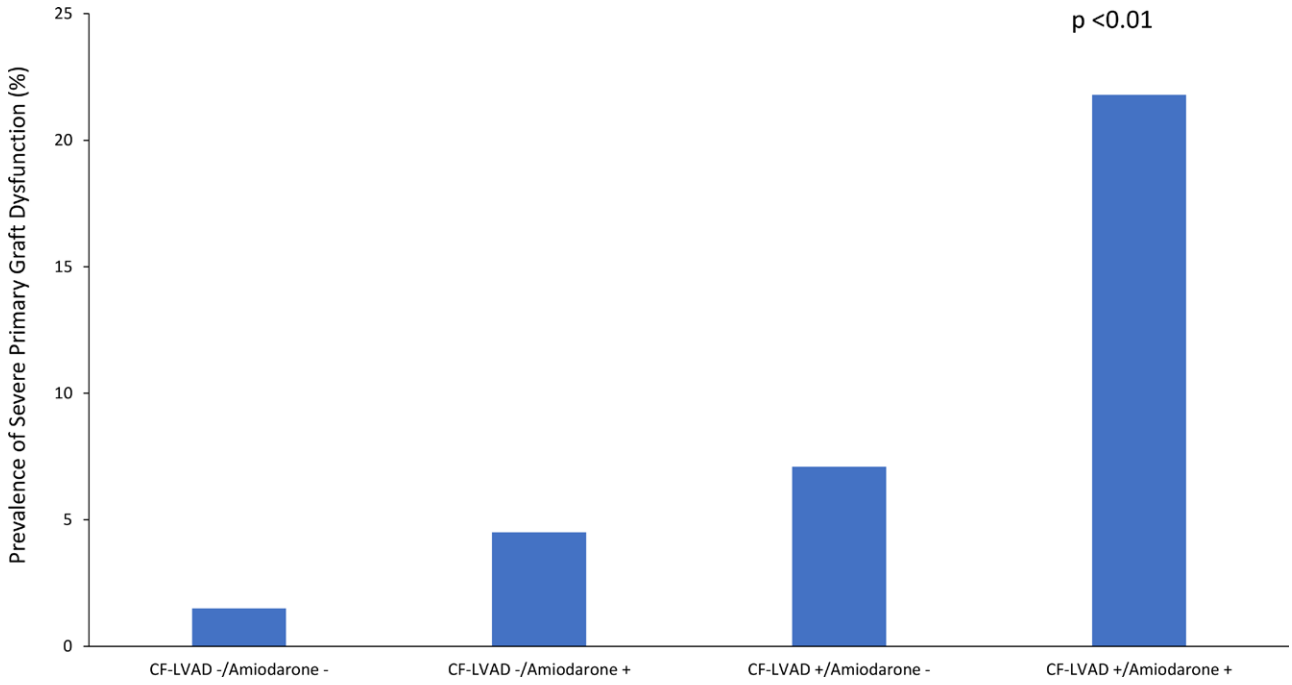

FIGURE 2. The prevalence of severe PGD based on the presence or absence of CF-LVAD and amiodarone. CF-LVAD, continuous-flow left ventricular assist device; PGD, primary graft dysfunction; ; +, presence; –, absence.

with an aOR 1.35 (95% CI, 1.05-1.71; $P=0.02$) for severe PGD (Table 2).

Additionally, recipient diabetes was associated with severe PGD (aOR, 4.90; 95% CI, 1.60-15.00; $P=0.01$) and every 100 mL of intraoperative red blood cell transfusion was associated with an aOR 1.08 (95% CI, 1.03-1.14; $P<0.01$) for severe PGD. Recipient hypertension was associated with an aOR of 0.16 (95% CI, 0.05-0.49; $P<0.01$) for severe PGD (Table 2).

Further analysis of the multivariate model found an interaction between the duration of CF-LVAD support (per 1 y) by preoperative amiodarone dose at heart transplant (per 100 mg) was associated with severe PGD (aOR, 1.43; 95% CI, 1.15-1.78; $P<0.01$; Table 3).

Clinical Risk Factors, Urgency for Heart Transplantation Listing, and Severe PGD During 2006–2017

In the period of 2006–2017, there was an observed nonsignificant increase of heart transplant recipients bridged from a CF-LVAD device, that is, 50% (2006–2009) versus 60.0% (2010–2013) versus 67.1% (2014–2017), $P=0.19$. The incidence of pretransplant amiodarone doubled from 2006–2009 (17.9%) to 2010–2013 (36.0%) and plateaued in 2014–2017 (32.1%) ($P=0.21$). In the same period, a trend of increased severe PGD incidence was observed, that is, 3.6% (2006–2009) versus 5.3% (2010–2013) versus 11.4% (2014–2017) ($P=0.19$) (**Figure S1,** SDC, http://links.lww.com/TXD/A399).

CF-LVAD patients were more frequently listed for UNOS status 1A because of LVAD-related complications, that is, 10.7% (2006–2009) versus 26.7% (2010–2013) versus 32.9% (2014–2017) ($P=0.06$). On the other hand, a decrease in CF-LVAD patients being listed for UNOS status 1A because of elective 30-d time was observed over the same period, that is, 35.7% (2006–2009) versus 21.3% (2010–2013) versus 19.3% (2014–2017) ($P=0.16$) (**Figure S2,** SDC, http://links.lww.com/TXD/A399).

TABLE 2.

Multivariate logistic regression model of clinical risk factors for severe PGD[a]

Risk factors	OR (95% CI)	*P*
Duration of CF-LVAD support (per 1 y)	1.81 (1.16-2.81)	0.01
Amiodarone (per 100 mg)	1.35 (1.06-1.71)	0.02
Recipient diabetes	4.90 (1.60-15.00)	0.01
Recipient hypertension	0.16 (0.05-0.49)	<0.01
Intraoperative RBC transfusion (per 100 mL)	1.08 (1.03-1.14)	<0.01

[a]Adjusted for recipient diabetes, recipient hypertension, UNOS status 1A at transplant, duration of CF-LVAD support (per 1 y), beta-blocker, sildenafil, amiodarone dose (per 100 mg), donor CPR time (per 1 min), anoxia as donor cause of death, donor–recipient size mismatch, and intraoperative RBC transfusion (per 100 mL).

CF-LVAD, continuous-flow left ventricular assist device; CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; PGD, primary graft dysfunction; RBC, red blood cell; UNOS, United Network for Organ Sharing.

TABLE 3.

Multivariate logistic regression model of multiplicative interaction between duration of CF-LVAD support and amiodarone dose[a]

Risk factors	OR (95% CI)	*P*
Duration of CF-LVAD support (per 1 y) × amiodarone (per 100 mg)	1.43 (1.15-1.78)	<0.01
Recipient diabetes	4.45 (1.48-13.38)	0.01
Recipient hypertension	0.19 (0.06-0.55)	<0.01
Intraoperative RBC transfusion (per 100 mL)	1.07 (1.02-1.13)	0.01

[a]Adjusted for recipient diabetes, recipient hypertension, UNOS status 1A at transplant, duration of CF-LVAD support (per 1 y), beta-blocker, sildenafil, amiodarone dose (per 100 mg), donor CPR time (per 1 min), anoxia as donor cause of death, donor–recipient size mismatch, intraoperative RBC transfusion (per 100 mL), and duration of CF-LVAD support (per 1 y) × amiodarone dose (per 100 mg).

CF-LVAD, continuous-flow left ventricular assist device; CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; RBC, red blood cell; UNOS, United Network for Organ Sharing.

A sensitivity analysis was performed to assess the clinical risk factors for severe PGD in the setting of era and urgency of heart transplantation. Heart transplantation urgency was stratified on the basis of UNOS status 1A justification wherein ill patients were grouped from those hospitalized with inotropes (status 1A), nondischargeable VAD, extracorporeal membrane oxygenation, IABP (status 1A), mechanical ventilation (status 1A), CF-LVADs with complications (status 1A), and those listed for exception (status 1A); meanwhile, stable patients were grouped from CF-LVAD listed at UNOS status 1A based on elective 30-d time and patients on status 1B and status 2.

A multivariate model of recipient diabetes, hypertension, urgency for heart transplantation (ill versus stable patients), era of heart transplantation, duration of CF-LVAD (per 1 y), amiodarone dose (per 100 mg), beta-blocker, sildenafil, anoxia as donor cause of death, donor cardiopulmonary resuscitation time (per 1 min), donor–recipient size mismatch, and intraoperative red blood cell transfusion (per 100 mL) that found every 1 y of CF-LVAD support was associated with an aOR 1.81 (95% CI, 1.16-2.81; $P = 0.01$) for severe PGD, and every 100 mg of preoperative amiodarone dose at heart transplant was associated with an aOR 1.35 (95% CI, 1.05-1.71; $P = 0.02$) for severe PGD (**Table S2a,** SDC, http://links.lww.com/TXD/A399).

Similarly, subsequent analysis of the multivariate model found that an interaction between the duration of CF-LVAD support (per 1 y) and preoperative amiodarone dose at heart transplant (per 100 mg) was associated with severe PGD (aOR, 1.43; 95% CI, 1.15-1.78; $P < 0.01$; **Table S2b,** SDC, http://links.lww.com/TXD/A399).

Prospective Amiodarone Discontinuation in CF-LVADs

A total of 49 CF-LVAD patients with active amiodarone use were screened and considered for amiodarone discontinuation between July 2017 and February 2020. Twenty-eight patients who underwent amiodarone discontinuation formed the cohort (Figure 3).

The mean age of the cohort was 55.9 ± 10.3 y, 10.7% were female, 78.6% were with nonischemic cardiomyopathy, and 89.3% had an implantable cardioverter defibrillator or cardiac resynchronization therapy-defibrillator device. Table 4 lists the baseline characteristics of the cohort.

Six out of 28 patients had an arrhythmia recurrence. Among them, 3 patients were hospitalized or reported implantable cardioverter defibrillator (ICD) shocks in the setting of ventricular tachyarrhythmia and restarted on amiodarone, 2 patients were asymptomatic but found to have an episode of ventricular tachyarrhythmia that was detected on routine ICD interrogation (1 patient had antitachycardia pacing and another patient received ICD shock), and 1 patient was hospitalized for acute heart failure because of recurrence of atrial fibrillation with rapid ventricular response that was treated with beta-blockers. None of the patients died.

Among all patients who were discontinued off amiodarone, there was no difference in ischemic cardiomyopathy cause between patients with arrhythmia recurrence compared with those without arrhythmia recurrence (2/6 [33.3%] versus 4/22 [18.2%]; $P = 0.42$). However, patients with arrhythmia recurrence had a nonstatistically significant higher mean 6-mo cumulative amiodarone dose before discontinuation

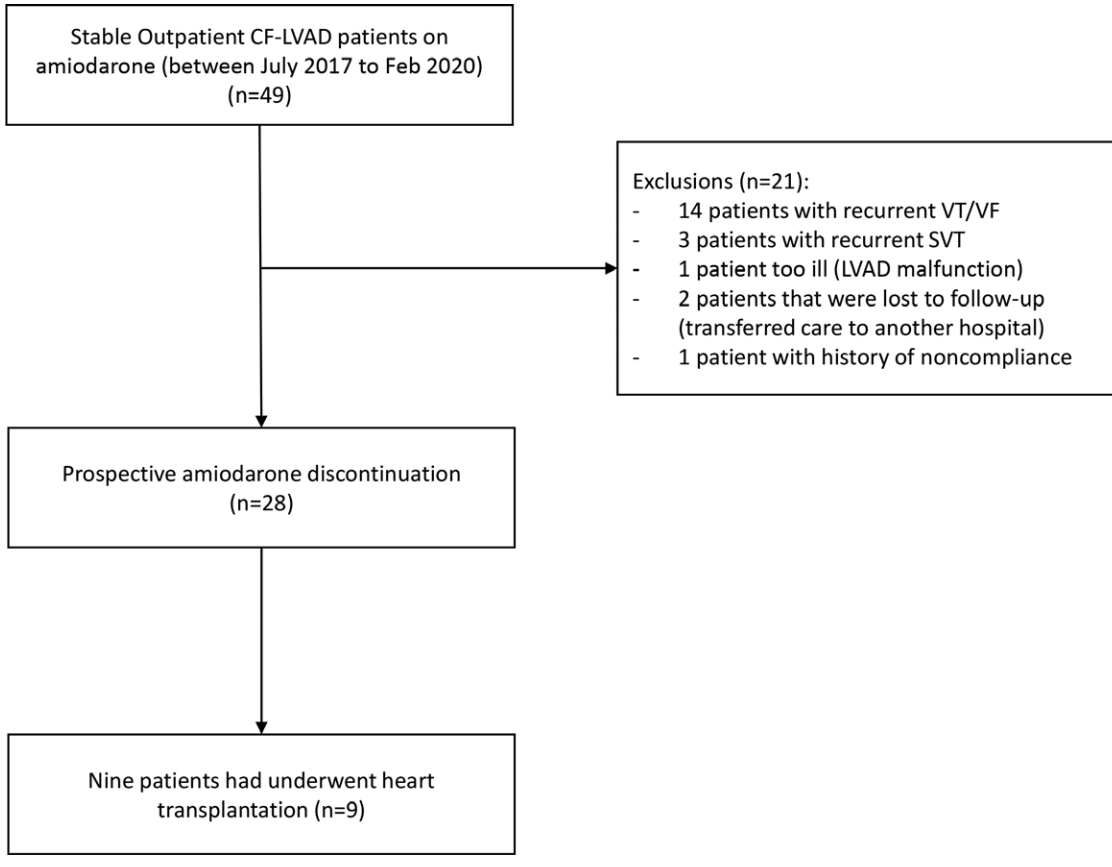

FIGURE 3. Flowchart of prospective amiodarone discontinuation in stable CF-LVAD patients. CF-LVAD, continuous-flow left ventricular assist device; SVT, supraventricular tachycardia; VT/VF, ventricular tachycardia/ventricular fibrillation.

TABLE 4.

Baseline recipient, donor, and perioperative characteristics of prospective amiodarone discontinuation cohort

Baseline recipient characteristics	Prospective amiodarone discontinuation cohort (n = 28)
Age (y)	55.9 ± 10.3
Female sex (%)	3 (10.7)
NICM (%)	22 (78.6)
Diabetes (%)	11 (39.3)
Hypertension (%)	20 (71.4)
CKD (%)	13 (46.4)
BMI (kg/m^2)	29.9 ± 7.3
ICD/CRT-D (%)	25 (89.3)
Duration of CF-LVAD support (m)	27.7 ± 15.7
Aspirin (%)	19 (67.9)
ACE-I/ARB (%)	10 (35.7)
Beta-blocker (%)	24 (85.7)
Aldosterone antagonist (%)	7 (25.0)
Sildenafil (%)	8 (28.6)
Coumadin (%)	27 (96.4)
Amiodarone total dose (mg/d)	250.0 ± 79.3
Indication for amiodarone	
Atrial fibrillation (%)	10 (35.7)
Ventricular tachyarrhythmia (%)	17 (60.7)
Frequent premature ventricular ectopy (%)	1 (3.6)
Duration of amiodarone use (d)	534.5 ± 673.3
Baseline donor data characteristics	**Prospective amiodarone discontinuation cohort (n = 9)**
Age (y)	36.3 ± 10.4
Female sex (%)	3 (33.3)
BMI (kg/m^2)	29.2 ± 7.5
Anoxia as cause of death (%)	6 (66.7)
CPR time (min)	28.3 ± 32.4
LVEF (%)	57.2 ± 2.6
Perioperative data characteristics	**Prospective amiodarone discontinuation cohort (n = 9)**
Dual organ transplant (%)	1 (11.1)
Total ischemic time (min)	205.1 ± 40.6
Total CPB time (min)	194.3 ± 76.2
Intraoperative RBC transfusion (mL)	500.0 ± 580.9
Intraoperative FFP transfusion (mL)	506.2 ± 581.6
Intraoperative platelet transfusion (mL)	343.4 ± 291.2

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CF-LVAD, continuous-flow left ventricular assist device; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; CRT-D, cardiac resynchronization therapy defibrillator; FFP, fresh frozen plasma; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; RBC, red blood cell.

(32 784.2 ± 8856.0 versus 29 264.8 ± 10 650.8 mg; $P = 0.47$) compared with patients without arrhythmia recurrence. The mean duration of amiodarone use among patients with a recurrence of arrhythmia was lower compared with patients without arrhythmia recurrence (320.7 ± 155.2 d versus 592.8 ± 748.7 d; $P = 0.39$).

Nine of the 28 patients had heart transplantation. The median length of time after amiodarone discontinuation to heart transplant was 189 d (interquartile range, 90.5–371.5 d). There were no severe PGD events observed.

DISCUSSION

In this study, we investigated (1) the association of CF-LVAD, amiodarone, and severe PGD and (2) the safety of prospective amiodarone discontinuation in CF-LVAD patients. The principal findings of our study are as follows. First, a stepwise increase in prevalence of severe PGD was observed across 4 groups comprising patients without CF-LVAD and amiodarone use followed by groups with either 1 or both risk factors. Second, pretransplant amiodarone and CF-LVAD were independently associated with severe PGD (**Figure S3,** SDC, http://links.lww.com/TXD/A399). Furthermore, the length of CF-LVAD support and pretransplant amiodarone dose was independently associated with severe PGD. Third, an interaction between pretransplant amiodarone dose, length of CF-LVAD support, and severe PGD was observed. Fourth, recipient diabetes and intraoperative red blood cell (RBC) transfusion were independently associated with severe PGD, and recipient hypertension was associated with lower odds for severe PGD. Finally, prospective amiodarone discontinuation in CF-LVAD patients was associated with 21.4% composite adverse outcomes because of arrhythmia recurrence. There was no mortality observed following amiodarone discontinuation. In the small subset of CF-LVAD patients who were discontinued off amiodarone and subsequently received a heart transplant, there were no reported severe PGD.

In this longitudinal cohort at our center, we found that the prevalence of severe PGD was highest in the group with both CF-LVAD and amiodarone at approximately 22% as compared to groups with either 1 or no risk factors. The use of CF-LVAD as a bridge to transplant in our center was notably higher than reported incidence of 49.4% among all heart transplant recipients in the United States in 2017.[12] Nevertheless, the utilization of CF-LVAD before transplant in our center was comparable with the higher end range of 8.1% to 77.4% observed in a recent analysis of UNOS transplant centers.[13] Similarly, pretransplant exposure to amiodarone accounted for nearly one-third of all patients in our center, mirroring the trend seen in a large international registry of heart transplant waitlisted patients.[6] Here, this study found that both CF-LVAD and amiodarone were both independently associated as risk factors for severe PGD in keeping with the results of recent contemporary analyses.[2-5,7] More importantly, we found a statistically significant interaction between the length of CF-LVAD support, pretransplant amiodarone dose, and severe PGD.

The pathophysiology of CF-LVAD and pretransplant amiodarone leading to PGD is currently not well understood, and it is equally unclear if both risk factors cause PGD through a common or separate pathway. In several animal model studies, amiodarone reduced myocardial contractility and cardiac output and worsen diastolic function that is suggestive of a negative inotropic and lusitropic effect.[14,15] Although the negative inotropic effect was previously demonstrated in human studies involving intravenous amiodarone loading, it has not been observed with chronic oral amiodarone consumption.[16-18] In contrast, a study by See et al postulated an immunologic response in recipients of prior ventricular assist device as a mechanism for PGD following heart transplantation. The authors found that pretransplant ventricular assist device patients had elevated levels of polyreactive natural antibody immunoglobulin G that was reactive to apoptotic cells and was associated with PGD.[19]

Additionally, this study found that recipient diabetes was associated with a 5-fold increase in odds for severe PGD. This finding was similarly seen in the RADIAL study and a recent large PGD study in the United Kingdom.[5,20] An analysis by

Sabatino et al[21] identified that recipient diabetes was a predictor for adverse outcomes among patients with PGD. This study also found that every 100 mL of RBC transfusion during the intraoperative period was associated with 1.1 increase in odds for severe PGD. This observation was echoed in a study by Subramaniam et al,[22] which found that RBC transfusion during the intraoperative and first 24 h after heart transplantation was associated with increased odds for graft dysfunction requiring mechanical circulatory support, renal dysfunction requiring renal replacement therapy, and 30-d mortality. An analysis by Howard-Quijano et al[23] found a dose-dependent relationship between RBC transfusion and postoperative inotrope score among a group of pediatric heart transplant recipients. In the same analysis, patients who received >60 mL/kg of total RBC transfusion within the first 48 h of heart transplant were more likely to have a major adverse event of post-transplant extracorporeal membrane oxygenation, sepsis, open chest, acute kidney injury requiring dialysis, and graft failure.[23] Interestingly, recipient hypertension was associated with 6 times lower odds for severe PGD. Although the mechanism of recipient hypertension in reducing severe PGD risk is unclear, it could be related to a lower incidence of vasoplegia. In an analysis by Tsiouris et al, recipient hypertension trended more commonly among patients without vasoplegia after cardiac surgery. The univariate analysis found that recipient hypertension was associated with an odds of 0.77 (95% CI, 0.58-1.02; $P = 0.07$) for vasoplegia.[24] Similarly, a study by van Vessem et al[25] identified that prior hypertension was associated with reduced risk for vasoplegia (aOR, 0.28; (95% CI, 0.08-0.91; $P = 0.034$) in heart failure patients who had underwent mitral valve repair.

This study observed that 21.4% (n = 6) of stable outpatient CF-LVAD patients had a composite adverse event because of recurrence of arrhythmia following prospective amiodarone discontinuation. One patient had a heart failure hospitalization because of recurrence of atrial fibrillation, which was treated with rate control strategy, whereas the other 5 patients had ventricular tachyarrhythmias requiring antitachycardia therapies or antiarrhythmic therapy. There were no deaths reported in the prospective amiodarone discontinuation cohort. Nine patients from this group had heart transplantation and none of them had severe PGD. A retrospective study by Hoemann et al[3] had reported that 28.6% patients had hospital readmissions because of non-arrhythmic causes following amiodarone discontinuation and 9.5% incidence of severe PGD. The reported incidence

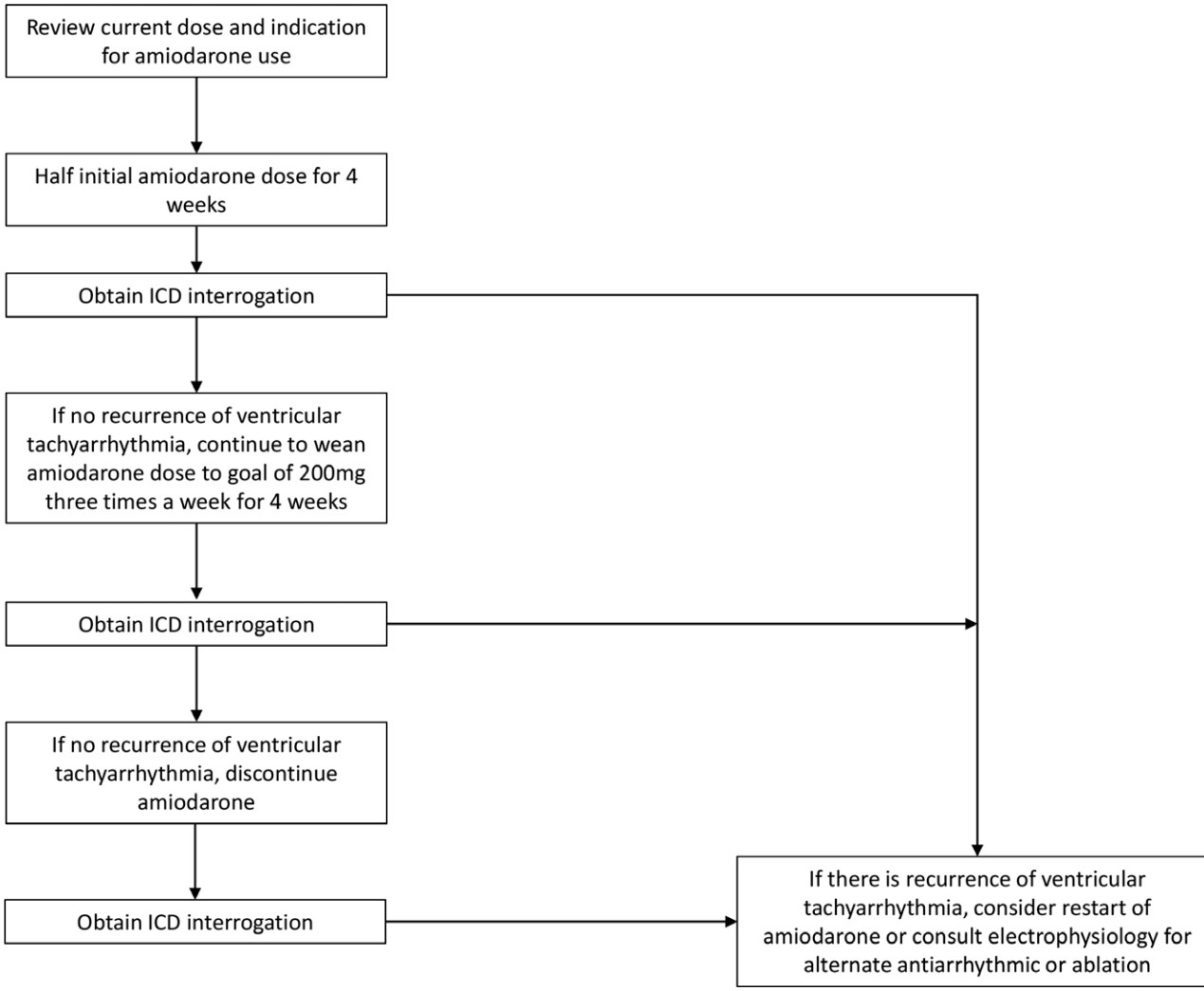

FIGURE 4. Proposed algorithm for amiodarone discontinuation in CF-LVAD patients. CF-LVAD, continuous-flow left ventricular assist device; ICD, implantable cardioverter defibrillator.

of severe PGD being higher compared with this study could be related to the possibility of incomplete amiodarone washout before heart transplant because of a shorter time of amiodarone discontinuation to transplant as reported by the authors with the median of 74 d (interquartile range, 37–174 d), whereas the median length of time after amiodarone discontinuation to heart transplant in the current study was 189 d.[3] Our data suggest that the reduction of severe PGD can be achieved in CF-LVAD patients by removing amiodarone as an exposure before transplant. A proposed algorithm of amiodarone discontinuation in CF-LVADs is provided in Figure 4.

Limitations

This study has several limitations. First, the study of clinical risk factors and severe PGD was retrospective in design and represented data from a single transplant center. Second, the retrospective analysis of clinical risk factors was limited in the evaluation of serum creatinine, glomerular filtration rate, peripheral vascular disease, chronic liver disease, and cumulative amiodarone doses for the retrospective data analysis as the medical record keeping from 2006 to 2017 had transitioned from hand-written records to 2 different electronic medical records with challenges to the availability of the data in the medical records for analysis. Third, the prospective amiodarone discontinuation consisted of a single study group with a lack of control group. Fourth, the prospective amiodarone cohort had a small sample size and only 9 patients from the cohort had heart transplant by the end of the study. This was because of fewer patients in the later years being placed on amiodarone as a choice of antiarrhythmic agent in CF-LVADs leading to a challenge of recruiting newer patients. Fifth, the current study was limited by study design to assess clinical outcomes including intensive care unit duration of stay and survival outcomes. Thus, future studies would be needed to evaluate these important clinical outcomes especially after severe PGD. Sixth, the present study was not able to evaluate the mechanism of amiodarone leading to severe PGD, and therefore, limited conclusions could be derived. Future studies are required to evaluate the causal relationship between amiodarone and severe PGD.

CONCLUSIONS

In summary, pretransplant amiodarone and CF-LVAD were independently associated with severe PGD. The combination of both risk factors was associated with a higher prevalence of severe PGD. This small pilot study of prospective amiodarone discontinuation was associated with arrhythmia recurrence in 6 out of 28 patients and no observed mortality. There was an absence of severe PGD in a subset of heart transplant recipients of the pilot study. Future studies are needed to evaluate for safety and benefit of amiodarone discontinuation in pretransplant patients.

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