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# Implantable cardioverter defibrillators in patients with orthotopic heart transplant: A multicenter case series

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## Abstract

**Background:** Sudden cardiac death (SCD) is common after orthotopic heart transplant (OHT). No clear guidelines for implantable cardioverter defibrillator (ICD) implantation in OHT patients at high risk for SCD currently exist.

**Objectives:** To assess the safety, efficacy, and benefit of ICDs and resynchronization therapy post-OHT. We also provide a systematic review of previous reports.

**Methods:** A retrospective multicenter cohort study within the United States. Patients with ICD post-OHT between 2000 and 2020 were identified.

**Results:** We analyzed 16 patients from 4 centers. The mean standard-deviation (*SD*) age was 43 (18) years at OHT and 51 (20) years at ICD implantation. The mean (*SD*) duration from OHT to ICD implantation was 9 (5) years. The mean (*SD*) left ventricular ejection fraction (LVEF) was 35% (17%). There were 2 (13%) postprocedural complications: 1 hematoma and 1 death. Mean (*SD*) follow-up was 24 (23) months. Survival rate was 63% (10/16) at 1 year and 56% (9/16) at 2 years, with 6/7 of those who died having LVEF < 35% at the time of the ICD implantation. Patients were more likely to receive appropriate therapy if their ICD was implanted for secondary (5/8) rather than primary (0/8) prevention ($p = .007$). Of those who did, 4 patients survived to 30 days post-ICD therapy. Severe CAV was not associated with the rate of appropriate therapy.

**Conclusions:** Beneficial outcomes were observed when ICDs were implanted for secondary prevention only, and in patients with higher baseline LVEF. We also observed benefits with resynchronization therapy.

KEYWORDS

advanced heart failure, appropriate therapy, heart transplantation, implantable cardioverter defibrillator, sudden cardiac death

**Abbreviations:** BiV, biventricular; CAV, cardiac allograft vasculopathy; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; OHT, orthotopic heart transplant; RBBB, right bundle branch block; SCD, sudden cardiac death.

#ICD utilization is safe and more beneficial when implanted for secondary prevention and in those with less severe cardiomyopathy in patients post #OHT who at risk for #SCD.

#CardioTwitter #EPeeps #Transplant

Waddah Maskoun and Mohamad Raad have co-first authorship.

Both Waddah Maskoun and Mohamad Raad contributed equally to this manuscript.

  

## 1 | INTRODUCTION

Sudden cardiac death (SCD) accounts for around 10% of post-orthotopic heart transplant (OHT) mortality.[1] The exact etiology and pathology leading to SCD are unknown. One study suggested that the main findings at the time of SCD in OHT patients were asystole and pulseless electrical activity.[2]

The current guidelines designate a class IIb recommendation for implantable cardioverter defibrillator (ICD) implantation in post-OHT patients "with a heart transplant and severe allograft vasculopathy with [left ventricle] LV dysfunction, an ICD may be reasonable if meaningful survival of greater than 1 year is expected."[3] It is unclear whether other regular guideline criteria for ICD implantation can be extrapolated from the general heart failure population to patients with OHT. In a national survey of 59 medical directors of heart transplant programs (response rate 56%), there was no explicit agreement on indications for ICDs in patients with OHT.[4]

The benefit of primary or secondary prevention with ICDs in post-OHT patients who are at high risk of SCD is yet to be validated. In this multicenter case series, we assessed the safety, efficacy, and benefit of ICDs and resynchronization therapy in patients at high risk of SCD post-OHT, and we provide a systematic review of previous reports.

## 2 | METHODS

This is a multicenter retrospective cohort study. We analyzed the electronic health records of adult patients who received OHT at Henry Ford Hospital, Indiana University, Mayo Clinic, and The Ohio State University. Patients were included if they had a post-OHT ICD implantation between 2000 and 2020. The Institutional Review Boards at all participating institutions approved the study.

Patients were considered at high risk for SCD based on the physicians' discretion at the time of ICD implantation. The indications for ICD implantation included primary prevention due to graft dysfunction with a depressed left ventricular ejection fraction (LVEF) ≤ 35% or secondary prevention due to known ventricular arrhythmia or high-risk syncope attributed to an arrhythmic etiology.

Patient demographics, comorbid conditions, medications, transplantation, and post-OHT ICD implantation data were collected. Transplantation data included the cause of transplantation, patient age at time of transplantation, and the date of surgery. ICD implantation data included graft LVEF, electrocardiogram data before ICD implantation, and cardiac allograft vasculopathy (CAV) at the time of implantation. CAV criteria was based on the International Society for Heart and Lung Transplantation.[5] Significant CAV was defined as ≥50% stenosis in ≥1 epicardial artery. Severe CAV was defined as ≥70% stenosis in the proximal left main or proximal left anterior descending artery, ≥70% stenosis in ≥2 epicardial vessels, or severe diffuse CAV.[5] Significant valvular disease was defined by any valvular disease (stenosis/regurgitation) assessed as contributing to the observed cardiomyopathy. Procedural data included the indication and year the ICD was implanted, type of ICD, side of implantation, defibrillation threshold testing, and procedural complications (hematoma, infection, lead dislodgment, perforation, tamponade, or death). Long-term outcomes included ICD therapies delivered (both appropriate and inappropriate), follow-up to the response of the cardiac resynchronization therapy, device-related complications, and mortality.

Statistical Package for Social Sciences (SPSS, version 27; IBM) was used for data analysis. Descriptive statistical analyses were obtained for all included study variables. Categorical variables are expressed as frequency or percentage, whereas continuous variables are presented as mean and standard deviation. Univariate analysis was performed by using $\chi^2$ test or Fisher exact test for categorical variables and *t* test or the Mann–Whitney *U* test for continuous variables.

A review of the literature was performed using Medline and PubMed databases between January 1990 and December 2020. Studies that addressed the safety, efficacy, and benefit of ICD implantation in post-OHT patients were included. Abstracts and studies published in non-English language were excluded. If a case series was published more than once, we included the more recent study with the larger number of patients.

## 3 | RESULTS

### 3.1 | Patient baseline characteristics

A total of 16 patients were included from 4 transplant centers (4 from Henry Ford Hospital, 7 from Indiana University, 4 from Mayo Clinic, and 1 from Ohio State University). The mean age (standard deviation [*SD*]) at OHT was 43 ± 18 years (range: 12–67 years). Of 16 patients, 4 were female (25%), 12 were male (75%), 13 were White, and 3 were African American. The indication for transplantation was ischemic cardiomyopathy in 6 patients, while the other 10 patients had nonischemic cardiomyopathy. Other medical comorbidities are listed in Table 1. There were 6 patients who had a device before transplantation (5 ICD and 1 permanent pacemaker). Those devices were explanted during or after OHT.

### 3.2 | Patient characteristics at implantation

The mean (*SD*) age at ICD implantation was 51 ± 20 years, and the mean (*SD*) duration from OHT to implantation was 9 ± 5 years (range: 0.1–16 years). Table S1 includes the characteristics of every patient included in this study.

At the time of implantation, 9 patients had significant CAV, 8 of which were considered severe. The average LVEF was 35% ± 17%. None of the patients had any significant valvular disease. All the patients were in sinus rhythm and 1 patient was atrial paced. The mean (*SD*) QRS duration was 137 ± 34 ms, and 4 patients had a wide QRS duration >150 ms—two with left bundle branch block (LBBB) and two with right bundle branch block (RBBB).

**TABLE 1** Baseline characteristics

| Variable | Results (*N* = 16) |
|---|---|
| Sex, no. (%) | |
| Female | 4 (25%) |
| Male | 12 (75%) |
| Indication for OHT, no. (%) | |
| Ischemic cardiomyopathy | 6 (38%) |
| Nonischemic cardiomyopathy | 10 (42%) |
| Age at OHT, mean ± *SD*, years | 43 ± 18 |
| Age at ICD implantation post-OHT, mean ± *SD* | 51 ± 20 |
| Duration from OHT to ICD implantation, mean ± *SD*, years | 9 ± 5 |
| Left ventricular ejection fraction, mean% ± *SD* | 35% ± 17% |
| Comorbid Conditions, no. (%) | |
| Hypertension | 15 (94%) |
| Diabetes mellitus | 3 (19%) |
| Significant CAV | 9 (56%) |
| Severe CAV | 8 (50%) |
| Coronary artery disease | 11 (69%) |
| Atrial fibrillation | 2 (13%) |
| Cerebrovascular disease | 0 (0%) |
| Obstructive sleep apnea | 4 (25%) |
| Chronic kidney disease | 8 (50%) |
| ECG characteristics at ICD implantation | |
| Sinus rhythm | 15 (94%) |
| Atrial paced rhythm | 1 (6%) |
| QRS duration, mean ± *SD*, ms | 137 ± 34 |
| Left anterior fascicular block, no. (%) | 3 (19%) |
| Incomplete right bundle branch block, no. (%) | 4 (25%) |
| Complete right bundle branch block, no. (%) | 8 (50%) |
| Left bundle branch block, no. (%) | 2 (13%) |
| Medications, no. (%) | |
| Beta-blocker | 13 (81%) |
| ACEi, ARB, ARNi | 9 (56%) |
| Anticoagulation | 3 (19%) |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor neprilysin inhibitor; CAV, cardiac allograft vasculopathy; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; OHT, orthotopic heart transplantation, *SD*, standard deviation.

The indication for ICD implantation was primary prevention in the 8 patients assessed as having an increased risk of SCD (7 with LVEF ≤ 35% and 1 patient with severe CAV and rejection with LVEF = 60%) and for secondary prevention in the remaining 8 patients.

Six single-chamber, 6 dual-chamber, and 3 biventricular (BiV) devices were implanted. One additional His-pacing approach was used after an unsuccessful BiV attempt. All but 2 patients had their device implanted on the left side (the 2 exceptions because of left-sided venous stenosis and extreme tortuosity from devices before OHT). Defibrillation threshold testing was performed in 2/8 and 7/8 patients in which the indication for implantation was for primary and secondary prevention, respectively. There were 2 procedural complications, including 1 hematoma that required evacuation, and 1 death. The patient who developed a hematoma was on home subcutaneous enoxaparin for deep vein thrombosis treatment. The patient who died had end-stage heart failure and the CRT device was considered as a last salvage attempt. He developed pulseless electrical activity arrest peri-procedure that was attributed to advanced cardiomyopathy (LVEF 19%, RBBB with QRS duration 167 ms). The device had normal function, and there were no signs of effusion or other signs of perforation postprocedure.

### 3.3 | Long-term follow-up

The survival rate for all patients was 63% (10/16) at 1 year and 56% (9/16) at 2 years. The mean (*SD*) follow-up was 24 ± 23 months with 6 of 16 patients alive at the time of data collection.

Five patients received appropriate ICD therapies for ventricular arrhythmias. Of these, 4 patients survived for 30 days post-ICD therapy (median [*SD*] 77 ± 67 months, range: 1–142 months), whereas 1 patient was hospitalized and died within 24 h of the first ICD therapy from advanced cardiomyopathy and cardiogenic shock (LVEF was 19%). The mean (*SD*) time from first appropriate ICD therapy to the last follow-up date available was 48 ± 64 months (range: 0–142 months). Patients were more likely to receive appropriate ICD therapy if the ICD device was implanted for secondary prevention (5/8) rather than for primary prevention (0/8) ($p = .007$). No other comorbid conditions were significantly associated with appropriate therapy. To note, severe CAV was not associated with the rate of appropriate therapy (odds ratio: 0.56, 95% confidence interval: 0.07–4.76, $p = .59$).

The mean (*SD*) follow-up from ICD implantation to last follow-up for patients who did not receive any appropriate device therapy was 26 ± 27 months. Three patients received inappropriate shocks for supraventricular arrhythmias (1 atrial tachycardia) at a rate above the therapy threshold, and 1 patient developed a pocket infection 4 years after implantation that required extraction and reimplantation of a new device.

Excluding the cardiac resynchronization patients, patients with an LVEF ≤ 35% were less likely to receive appropriate ICD therapy or survive at 1 year post-ICD implantation (Table 2). As noted above, 1 patient with severely reduced LVEF received appropriate ICD therapy and died within 7 months of ICD therapy. Patient characteristics and outcomes according to the indication for ICD implantation are listed in Table 3.

**TABLE 2** Characteristics of patients according to left ventricular ejection fraction excluding patients who received resynchronization therapy (biventricular or His-Pacing therapy)

| | Ejection fraction ≤35% Total *n* = 6 | Ejection fraction >35% Total *n* = 6 |
|---|---|---|
| Age, mean ± *SD*, years | 44 ± 15 | 35 ± 18 |
| Duration from OHT to ICD, years | 10 ± 4 | 9 ± 6 |
| Age at ICD Implantation, mean ± *SD*, years | 54 ± 15 | 44 ± 21 |
| Hypertension | 6 (100%) | 5 (83%) |
| Diabetes mellitus | 0 (0%) | 1 (17%) |
| Significant CAV | 5 (83%) | 2 (33%) |
| Severe CAV | 5 (83%) | 1 (17%) |
| Coronary artery disease | 4 (67%) | 4 (67%) |
| Atrial fibrillation | 1 (17%) | 0 (0%) |
| Cerebrovascular disease | 0 (0%) | 0 (0%) |
| Obstructive sleep apnea | 1 (17%) | 3 (50%) |
| Chronic kidney disease | 3 (50%) | 2 (33%) |
| Survival at 1 year post-ICD implantation, no. (%) | 2 (33%)[a] | 5 (83%) |
| Survival at 2 years post-ICD implantation, no. (%) | 1 (16%) | 5 (83%) |
| Time from ICD implantation to last follow-up, mean ± *SD*, months | 14 ± 10 | 28 ± 30 |
| Survival after first appropriate ICD therapy | 1 Patient received appropriate ICD therapy and was deceased 7 months after the ICD therapy | Patient 1 received appropriate ICD therapy and is still alive 12 years after the first ICD therapy<br>Patient 2 received appropriate ICD therapy and was deceased on the same day of the ICD therapy<br>Patient 3 received appropriate ICD therapy and was deceased 1 month after the first ICD therapy<br>Patient 4 received appropriate ICD therapy and was deceased 8 years after the first ICD therapy |
| Primary prevention | 2 (33%) | 2 (33%) |
| Secondary prevention | 4 (66%) | 4 (66%) |
| Indication for pacing | 0 | 1 (16%) |
| Appropriate ICD therapy | 1 (16%) | 4 (66%) |
| Inappropriate ICD therapy | 2 (33%) | 1 (16%) |

Abbreviations: CAV, cardiac allograft vasculopathy; CI, confidence interval; ICD, implantable cardioverter defibrillator; OHT, orthotopic heart transplantation; *SD*, standard deviation.

[a]Patients who have an LVEF ≤ 35% have an odds ratio (95% CI) of 0.1 (0.006–1.544), $p = .079$ to survive at 1 year post-ICD implantation.

### 3.4 | Cardiac resynchronization therapy

There were 3 patients who had a biventricular ICD implanted and 1 patient had a His-bundle pacing lead placed after an unsuccessful BiV device implantation. At the time of this writing, 3 of these patients were still alive and 1 had a peri-procedural pulseless electrical activity cardiac arrest. The latter had end-stage heart failure at the time of implantation. The mean follow-up for the surviving patients was 45 ± 14 months.

The patient who received a His-bundle pacing had LBBB, and the ejection fraction improved from 25% to 62% and was published as a case report abstract.[6]

The LVEF recovered to baseline (from 20% to 45%) in the second patient who had a LBBB, and the LVEF remained unchanged at 30%

**TABLE 3** Characteristics of patients according to indication of ICD implantation

| | Primary prevention Total *n* = 8 | Secondary prevention Total *n* = 8 |
|---|---|---|
| Age, mean ± *SD*, years | 40 ± 22 | 45 ± 15 |
| Duration from OHT to ICD, years | 8 ± 4 | 9 ± 6 |
| Age at ICD Implantation, mean ± *SD*, years | 48 ± 21 | 54 ± 19 |
| Hypertension | 7 (88%) | 8 (100%) |
| Diabetes mellitus | 2 (25%) | 1 (13%) |
| Significant CAV | 4 (50%) | 5 (63%) |
| Severe CAV | 4 (50%) | 4 (50%) |
| Coronary artery disease | 6 (75%) | 5 (63%) |
| Atrial fibrillation | 2 (25%) | 0 (0%) |
| Cerebrovascular disease | 0 (0%) | 0 (0%) |
| Obstructive sleep apnea | 1 (13%) | 3 (38%) |
| Chronic kidney disease | 5 (63%) | 3 (38%) |
| Survival at 1 year post-ICD implantation, no. (%) | 5 (63%) | 5 (63%) |
| Survival at 2 years post-ICD implantation, no. (%) | 5 (63%) | 4 (50%) |
| Appropriate ICD therapy | 0 (0%) | 5 (63%) |
| Inappropriate ICD therapy | 1 (13%) | 2 (25%) |

Abbreviations: CAV, cardiac allograft vasculopathy; ICD, implantable cardioverter defibrillator; OHT, orthotopic heart transplantation; *SD*, standard deviation.

in the second patient with a RBBB (QRS duration of 168 ms) at 3.5 years of follow-up. All 4 patients had their ICDs implanted as part of primary prevention management. None of these patients received any appropriate or inappropriate ICD therapies.

### 3.5 | Literature review

We identified three case series of transvenous ICD implantation post-OHT.[7–9] The study by Ptaszek et al.[10] was excluded as these subjects were included in the case series by Tsai et al.[8] We excluded the study by McDowell et al.[4] as well due to our concern that some of their subjects might be included in the case series by Tsai et al.[8] Additionally, that report did not include procedure/device-related complications, nor did it state the outcome after appropriate device therapies. The results of the case series are summarized and combined in Table 4.

## 4 | DISCUSSION

Our retrospective multicenter study suggests that using ICDs in heart transplant recipients who are at high risk for SCD may be safe and effective if implanted for secondary prevention in patients without severe cardiomyopathy. In this small series, patients who received appropriate and life-saving device therapies all had ICDs implanted for secondary prevention purposes. We also observed benefits from CRT-D, however, none of these patients received appropriate ICD therapy, and the observed benefit was from CRT-P therapy.

Cardiac transplantation is the gold standard in the treatment of chronic stage D heart failure refractory to heart failure guideline-directed medical therapy.[11] SCD is a common cause of death in patients after OHT, reported at 0.7%,[12] 2.3%,[12] and 10%[1] over a follow-up of 1 year,[12] 4.7 years,[12] and 6.5 years,[1] respectively. While the incidence of overall and non-SCD posttransplantation mortality has decreased, SCD mortality has not.[1] The major risk factors for SCD are LVEF < 40%,[1,13] allograft rejection,[12,14] including CAV,[12–14] and higher donor age.[1] Vaseghi et al.[2] reported that the findings at the time of SCD in OHT patients were asystole in 34%, pulseless electrical activity in 20%, and ventricular fibrillation in 10%. This suggests that ICD might be beneficial in reducing SCD and improving survival in some OHT patients.

Scant literature exists on the use of ICD in patients with OHT.[7–9,15–18] The 2017, AHA/ACC/HRS guidelines stated that ICD use after OHT for patients with severe allograft vasculopathy with LV dysfunction may be reasonable if meaningful survival of greater than 1 year is expected. This is a class IIb indication (level of evidence is B-NR).[3] There are no further specific guidelines for ICD implantation in OHT recipients. However, whether the standard guideline criteria for ICD implantation are appropriate for patients with OHT remains unclear. There have been 4 published cases of heart transplant patients who had SCD despite having functioning ICDs.[15,16] Furthermore, while ICDs have been shown to decrease mortality in patients waiting for their first heart transplantation,[19] a similar decrease has not been seen for patients who have had OHT and are waiting for a second transplant.[17] However,

**TABLE 4** Summary of case series for ICD placement in patients with OHT

| Study findings | Study | | | | |
|---|---|---|---|---|---|
| | Tsai et al.[8] | Neylon et al.[7] | Rubin et al.[9] | Our study | Combined |
| Years/location | ICD implantation between 1995 and 2005, Five Centers, USA | ICD for OHT done between 1983 and 2012, Single Center, Ireland | ICD after OHT 2005–2020. Single center, Columbia university, USA | ICD implantation between 2000 and 2020, Four Centers, USA | Multicenter, Ireland and USA |
| Number of patients | 36 | 10 | 18 | 16 | 80 |
| Male/female | 29/7 | 8/2 | 15/3 | 12/4 | 49/13 |
| Average age at OHT | 44 ± 14 years | 39 ± 14 years | 54 | 43 ± 18 years | 45 ± 5 years[a] |
| Indications for OHT | N/A | Dilated CM (5), Myocarditis (1) | N/A | Nonischemic CM (10/16) | Nonischemic CM (16/26) |
| | | Ischemic CM 40% (4) | | Ischemic CM (6/16) | Ischemic CM (10/26) |
| Mean Duration from OHT to ICD implantation | 8 ± 6 years | 16 ± 6 years | 5.4 years | 9 ± 5 years | 8.5 ± 3 years[a] |
| Indications for placement | Severe CAV ($n$ = 12, 33%)<br>Unexplained syncope ($n$ = 9, 25%)<br>Secondary prevention for ventricular arrhythmia ($n$ = 8, 22%)<br>Severe LV dysfunction (LVEF ≤ 35%) ($n$ = 7, 19%) | Severe CAV ($n$ = 8, 80%)<br>Secondary prevention for unexplained syncope ($n$ = 2, 20%) | Secondary prevention ($n$ = 4, 22%)<br>Low LVEF ($n$ = 5, 28%)<br>CAV ($n$ = 1, 6%)<br>Syncope + CAV ($n$ = 1, 6%)<br>Low LVEF + CAV ($n$ = 7, 39%) | Severe CAV ($n$ = 1)<br>Syncope with positive EP study ($n$ = 1)<br>Primary prevention for severe LV dysfunction ($n$ = 7)<br>Secondary prevention for ventricular arrhythmia ($n$ = 7) | Severe CAV ($n$ = 23)<br>Syncope ($n$ = 11)<br>Primary prevention ($n$ = 28)<br>Secondary prevention ($n$ = 21) |
| Allograft CAV | 26/36 | 8/10 | 9/18 | 9/16 | 52/80 |
| | Single chamber ICD 10 | | Single chamber ICD 10 | Single chamber ICD 6 | Single chamber ICD 26 |
| ICD device type | Dual chamber ICD 20 | Not mentioned | Dual chamber ICD 5 | Dual chamber ICD 6 | Dual chamber ICD 31 |
| | BiV ICD 6 | | Subcutaneous ICD 1<br>BIV ICD 2 | BiV ICD 3 + 1 His-Pacing | BiV ICD 11 + 1 His-Pacing |
| LVEF at ICD placement | 45 ± 12% | 49 ± 12% | 40 ± 22% | 35 ± 17% | 42 ± 5%[a] |
| Mean QRS duration | 123 ± 36 ms | 111 ± 23 ms | Not mention | 137 ± 34 ms | 125 ± 8 ms[a] |
| Mean follow-up | 51 ± 26 months | 29 ± 12 months | Not available | 24 ± 23 months | 40 ± 13 months[a] |
| DFT testing at ICD implantation | All patients: 21 ± 9 J | NA | Not available | 9/16 | |
| Complication rate | 17% ($n$ = 6) | 0% ($n$ = 0) | 17% ($n$ = 3) | 12.5% ($n$ = 2) + Late Complication 6% ($n$ = 1) | 12/80 (15%) |

**TABLE 4** (Continued)

| Study findings | Study | | | | |
|---|---|---|---|---|---|
| | Tsai et al.[8] | Neylon et al.[7] | Rubin et al.[9] | Our study | Combined |
| Complications details | Pocket site infection ($n = 2$)<br>Displaced lead ($n = 2$)<br>Pocket hematoma ($n = 1$)<br>Lead fracture ($n = 1$) | None | Venous obstruction ($n = 1$)<br>Lead fracture ($n = 1$)<br>Infection requiring system extraction ($n = 1$) | Pocket infection ($n = 1$)<br>Hematoma ($n = 1$)<br>Deep vein thrombosis ($n = 1$)<br>PEA arrest ($n = 1$) | *See case series specifics* |
| ICD therapy | 22 Shocks for 10 patients:<br>12 Appropriate shocks for 8 patients (all effective)<br>10 Inappropriate shock for 3 patients | 1 × Appropriate and effective ATP<br>1 × Appropriate and effective shock<br>No Inappropriate shocks | 1 Appropriate therapy<br>2 Inappropriate therapies<br>15 No therapies | 5 Patients with appropriate shocks<br>3 Patients with inappropriate shocks | 16 Patients received appropriate therapy<br>15 Patients received inappropriate therapy |
| Outcome | 32 Survived (including 3 patients who received 2nd transplant)<br>7/8 Patients with appropriate shocks were still alive | 9 Survived | Survival 1-year post-ICD was 56% | Post-ICD survival:<br>1 year: 63% (10/16)<br>2 years: 56% (9/16)<br>6/16 still alive (follow-up was 24 ± 23 months) | *See case series for other specifics* |
| | 4 Deaths (3 deaths from stage D heart failure and 1 death from sepsis) | 1 Death despite effective shocks for VF with subsequent electromechanical dissociation | Causes of death 1-year post-ICD included: progressive CAV/allograft failure (terminal PEA), infection (asystole), and subdural hemorrhage | 5 Patients received appropriate ICD therapy, of which 4 are still alive 30 days post-ICD therapy | |
| Outcome Subgroup by LVE ≤ 35%<br>All studies | Total $n = 80$<br>LV ≤ 35% $n = 33$ | Appropriate therapy<br>LVdysfx ($n = 5$, 15%) vs. no LVdysfx ($n = 11$, 23%), $p = .364$ | | Inappropriate therapy<br>LVdysfx ($n = 2$, 6%) vs. no LVdysfx ($n = 6$, 13%), $p = .325$ | |
| Outcome Subgroup by Severe CAV | Total $n = 80$<br>sCAV $n = 51$ | Appropriate therapy<br>sCAV ($n = 11$, 22%) vs. no sCAV ($n = 5$, 17%), $p = .642$ | | Inappropriate therapy<br>sCAV ($n = 7$, 14%) vs. no sCAV ($n = 1$, 3%), $p = .141$ | |
| Outcomes by indication for ICD implantation | Total 34 (HF and Rubin et al.) | Appropriate therapy<br>Secondary prevention (6/12) vs. Primary prevention (0/22), $p < .001$ | | Inappropriate therapy<br>Secondary prevention (2/12) vs. Primary prevention (3/22), $p = .812$ | |

Abbreviations: BiV, biventricular; CAV, cardiac allograft vasculopathy; CM, cardiomyopathy; DFT, defibrillation thresholds; ICD, implantable cardioverter defibrillator; LV, left ventricle; LVdysfx, severe left ventricular dysfunction LVEF, <35%; LVEF, left ventricular ejection fraction; OHT, orthotopic heart transplant, PEA, pulseless electrical activity; sCAV, severe cardiac allograft vasculopathy; US, United States; VF, ventricular fibrillation.

[a]Weighted average and standard deviations.

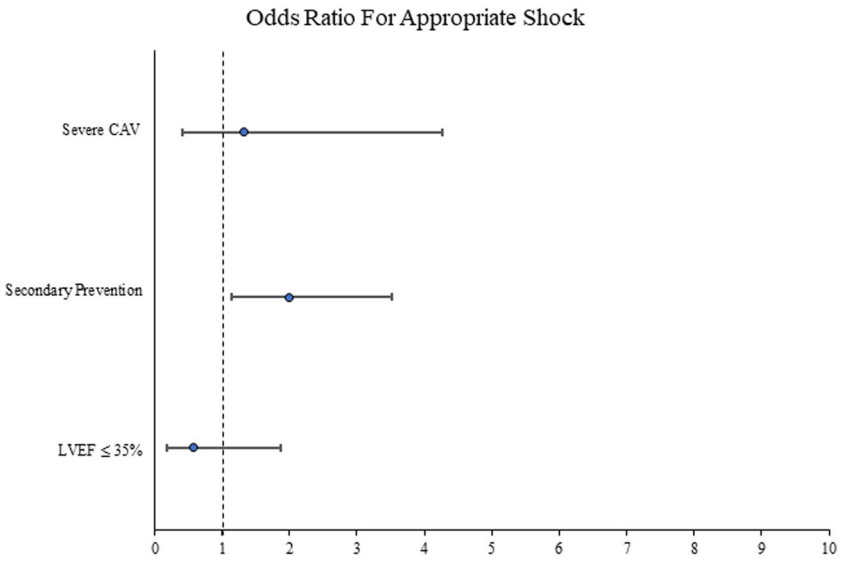


**FIGURE 1** Forrest plot with variables associated appropriate shocks

**TABLE 5** Implantable cardioverter defibrillator characteristics

| Characteristic | Number (%) |
|---|---|
| Side of ICD implantation | |
| Left | 14 (87) |
| Right | 2 (13) |
| Type of ICD | |
| Single chamber | 6 (38) |
| Dual chamber | 6 (38) |
| Biventricular | 4 (24) |
| Single coil | 7 (44) |
| Dual coil | 9 (56) |
| Defibrillation threshold testing | 9 (56) |
| Complications at implantation | 2 (12.5) |
| Hematoma | 1 |
| Cardiac arrest | 1 |
| Late complications | |
| Pocket infection (4 years from ICD implantation) | 1 (6) |
| Appropriate ICD therapy | 5 (31) |
| Inappropriate ICD therapy | 3 (19) |

Abbreviation: ICD, implantable cardioverter defibrillator.

patients who have had OHT and are awaiting a second heart transplant are at an overall higher risk of complications, and compared to patients who are waiting for a first OHT, they experience twice the mortality both during the wait list period and after the second transplant.[20]

There are only 2 published case series that have described ICD outcomes in patients with OHT.[7,8] The findings of the 2 series are summarized in Table 4 and Figure 1 alongside our case series, totaling 80 patients. In the combined series, most of the patients were men (79%). In the series by Tsai et al.,[8] the causes of ICD implantation followed a temporal distribution: SCD was the most common reason <1-year post-OHT; graft failure and sudden death occurred 2–4 years post-OHT; and severe graft vasculopathy was seen >5 years post-OHT. In our series, only 1 patient had the ICD implanted within 1 year of OHT, and the indication was for secondary prevention.

In the series by Tsai et al.,[8] all the patients with appropriate therapy had allograft vasculopathy compared to only 64% of patients with inappropriate shocks. This was not the case in our case series, where we observed no correlation between CAV and appropriate therapy. This is also true when all cases from studies with available data (our study, Tsai, and Neylon) are combined (Table 4) with no difference in appropriate or inappropriate therapies in patients with severe CAV. No statistically significant difference in appropriate/inappropriate therapies was observed in patients with or without severe LV dysfunction (LVEF ≤ 35%) within the pooled data analysis (Table 4 and Figure 1). In our series, all the patients with appropriate therapies had their ICD implanted for secondary prevention and secondary prevention was significantly associated with appropriate shocks (Table 4 and Figure 1). The guidelines advocate for ICD implantation for SCD prevention if a meaningful survival of greater than 1 year is expected.[3] In our series, patients who were deemed to be candidates for ICD therapy did not have optimal survival if their LVEF ≤ 35%. This may be because cardiomyopathy advances more rapidly among patients with OHT. Therefore, an earlier intervention is warranted for ICD implantation at higher than traditional indications for ejection fraction (mild to moderately decreased LVEF) which may indicate severe graft malfunction with potential irreversible and accelerated graft failure in this unique cohort of patients.

In the study by Neylon et al.,[7] no procedure-related or follow-up complications, including late infection, were seen, and no inappropriate shocks occurred. The complication rate observed by Tsai et al.[8] was around 17% (Table 4), which is similar to our complication rate (12.5%) (Tables 5 and 3), in addition to 1 late pocket infection 4 years from ICD implantation. The higher than expected complication rate for ICD

implantation[21] may be due to the patients' overall poor clinical status, comorbidities, and immunosuppression. There is 1 case report that describes a first subcutaneous ICD that was placed in the immediate post-transplantation period after acute cellular rejection and cardiac arrest.[22] This approach may theoretically lower the rate of infection.[22] Two of our patients had their ICDs implanted on the right side, and both of these patients had prior left-sided explanted devices following the OHT. We therefore recommend a venous patency assessment before planned ICD implantation in OHT patients with history of an explanted device following their OHT surgery.

In the Tsai et al.[8] series, 6 out of 36 patients received a BiV ICD, but none of these patients had a LBBB. In a national survey of 59 medical directors of heart transplant programs (response rate 56%), 47.5% felt that cardiac resynchronization therapy was not indicated for heart transplant recipients, even in the presence of heart failure symptoms and a wide QRS on the electrocardiogram.[4] In our case series, 3 patients had a BiV ICD, and 1 of these patients died during the implant procedure. As noted, this patient had severe end stage heart failure. An additional patient had a His-bundle pacing instead of LV lead for an attempted BiV ICD. The 2 patients who had a wide QRS (>150 ms) with LBBB had improvement in their LVEF back to baseline, and the patient who had a RBBB had no change in LVEF over a follow-up period of 3.5 years. In a recently published study, His-CRT provided comparable clinical and physical improvement to BiV-CRT for heart failure patients with LBBB.[23] Therefore, for patients who meet class I or IIa indication for BiV-CRT or His-CRT pacing after OHT, we anticipate a good CRT outcome as those without OHT.

Several landmark trials have shown benefits from ICD therapy[24–26] with a relatively low number needed to treat. Further studies will be required to validate the benefit of ICD implantation in patients post-OHT, as this patient population may have a shorter median survival in general in addition to a higher complication rate.

## 5 | LIMITATIONS

Our study is retrospective and, therefore, is subject to limitations. The study cohort was small and included a select group of patients who were candidates for ICD implantation. Furthermore, patients in our study had the OHT and ICDs placed at varying times during a wide timeframe and may have had different post-OHT management and outcomes. While our systematic review was comprehensive, scant literature exists, with only two case series identified per our inclusion criteria. This subjects our conclusions to reporting bias. Furthermore, most of the patients in our published case series were male. Considering these limitations, generalizability to other OHT patients is limited, and further multicenter and prospective studies are required to verify our results.

## 6 | CONCLUSIONS

SCD is a common cause of death post-OHT. ICD placement was safe among OHT recipients. However, in our case series, patients with primary prevention indications did not benefit from ICD therapy, likely due to poor survival postgraft dysfunction. Patients with secondary prevention indication were more likely to benefit from ICD therapy. Whether routine primary or secondary prevention with ICDs is indicated in high-risk post-OHT patients requires further validation. The observed benefits in patients with CRT-Ds is likely due to resynchronization pace therapy as none of these patients received appropriate shock therapy. We suggest a "lower" risk of SCD criteria (e.g., higher LVEF cutoff than non-OHT patients, and/or less significant CAV) to guide ICD utilization in patients post-OHT. ICD implantation in these patients, especially for primary prevention, warrants careful evaluation of risks and benefits and shared decision-making.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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