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Implantable Cardioverter Defibrillator Use in Patients with Different Types of Nonischemic Cardiomyopathy: Weighing the Evidence

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Abstract

Consensus guidelines recommend implantable cardioverter-defibrillator (ICD) placement in those with symptomatic heart failure and persistent, reduced left ventricular systolic function despite optimal medical therapy, independent of the etiology of underlying heart failure. While recent trials have suggested lack of mortality benefit for primary prevention ICD among all patients with nonischemic cardiomyopathy, it is important to recognize that certain subgroups of patients with nonischemic cardiomyopathy may be more likely to benefit from ICD therapy. This review will discuss the evidence within some of the causes of nonischemic cardiomyopathy for ICD implantation, particularly those with cardiac sarcoidosis, left-ventricular non-compaction, peripartum cardiomyopathy and arrythmogenic right ventricular cardiomyopathy.

Introduction

Consensus guidelines in general recommend implantable cardioverter-defibrillator (ICD) placement in those with symptomatic heart failure and persistent, reduced left ventricular systolic function despite optimal medical therapy, independent of the etiology of underlying heart failure [1,2]. In patients with ischemic cardiomyopathy, there is robust evidence to support reductions in sudden cardiac death and all-cause mortality including the Multicenter Automatic Defibrillator Implantation II (MADIT-II) trial [3-5]. In 2004, Desai et al. [3] performed a meta-analysis that demonstrated a 31% reduction in all-cause mortality thus supporting ICD implantation for patients with nonischemic cardiomyopathy as recommended by ACC/AHA guidelines.

However, there has only been one trial supporting ICD implantation amongst those with nonischemic cardiomyopathy, solely based on decreased mortality secondary to arrhythmia in those with preceding tachyarrythmia, without convincing evidence supporting all-cause mortality, thus mitigating its generalizability [6]. Additionally, the sudden cardiac death in heart failure trial (SCD-HeFT), in which half of enrolled patients had nonischemic systolic heart failure, remains the only evidence to support ICD implantation as a benefit to all-cause mortality. However, no patients received concomitant cardiac resynchronization therapy (CRT), and the benefit was confined to those with NYHA class II heart failure [7].

Since the advent of these landmark ICD trials, medical advances beyond the scope of the aforementioned trials have been developed, most notably cardiac resynchronization therapy (CRT). The comparison of medical therapy, pacing, and defibrillation in heart failure (COMPANION) trial, which comprised patients with NYHA III or IV heart failure, were randomly assigned to receive CRT pacemaker (CRT-P), CRT defibrillator (CRT-D), or medical therapy alone. While both CRT-Pand CRT-D showed significantly lower all-cause mortality compared to medical therapy alone, CRT-D was not shown to be superior to CRT-P [8]. While evidence existed for all-cause mortality benefit in non-ischemic cardiomyopathy from SCD-HeFT, and benefit from CRT from COMPANION, the recent Danish study to assess the efficacy of ICDs in patients with non-ischemic systolic heart failure on mortality (DANISH) trial did not show an association with improved overall mortality in nonischemic cardiomyopathy patients who received ICD implantation in addition to guideline based therapy that included CRT, although a possible benefit was seen in a sensitivity analysis of younger patients [9]. In a large observational, multicenter, European study, Barra et al. [10] also showed no significant difference in survival between those receiving CRT-D versus CRT-P in nonischemic cardiomyopathy, without variation upon subgroup analysis by age [11].

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Thus, while ICD implantation in nonischemic cardiomyopathy did not provide an overall survival benefit in the DANISH trial, two critical points have emerged. First, the risk of sudden cardiac death was halved with an ICD implantation, independent of CRT utilization. Second, age was inversely proportional to survival benefit from ICD implantation and implantation in younger patients was associated with improved mortality in some studies. This may be explained by summative risk secondary to ventricular arrhythmia in the nonischemic population. Multiple studies have demonstrated that nonischemic cardiomyopathy is a known predictor of improved response to CRT compared with ischemic cardiomyopathy, implying improved LV systolic function and reverse remodeling [8,12,13]. Additionally, those with clinical improvement with CRT are at lower risk for ventricular arrhythmia [14,15]. Thus, the impact of ICD therapy may not be appreciable amongst CRT responders with nonischemic cardiomyopathy.

Such discordant evidence has left referring cardiologists considering patient's indications for ICD implantation based on severity of underlying disease, concomitant arrhythmia risk with discussion of age and life expectancy with the risks of competing illnesses. A recently updated meta-analysis from Golwala et al. [8] reported a 23% reduction in all-cause mortality, while including those studies that did not show incremental benefit amongst those with CRT including COMPANION and DANISH [16].

Many of the trials evaluating primary prevention indications for ICD implantation over the past two decades implicate the heterogeneous nature of the population affected with nonischemic cardiomyopathy as a means for obfuscating the analysis within this subpopulation as to why it may not approach significance. No recent studies have been able to associate the underlying etiology of systolic dysfunction to alter our current guidelines. Thus, as electrophysiologists begin making personalized decisions given the plethora of diverging data, this review will discuss the evidence within some of the causes of nonischemic cardiomyopathy for ICD implantation.

Cardiac Sarcoidosis

Sarcoidosis in many ways represents the same therapeutic challenges as a disease that the class of non-ischemic cardiomyopathy represents to heart failure management, given its heterogeneous presentation, distribution of severity and clinical trajectory. While the minority of patients with sarcoidosis has cardiac involvement, almost three out of every four deaths in those with this disease are the result of progressive heart failure and malignant cardiac arrhythmias [17]. While immunosuppression, antiarrhythmic drug therapy and catheter ablation have shown benefit to mitigate ventricular arrhythmia, these therapies do not eliminate the risk of sudden cardiac death from arrhythmogenic granulomatous inflammation and scar. Despite the absence of prospective clinical trial data to support its utilization, cardiac sarcoidosis is a Class IIa indication for ICD implantation [18].

Currently, most data abstracted regarding cardiac sarcoidosis and ICD implantation relies on single center series data. In the studies by Schuller et al. [18] and Betensky et al. [19], about two-thirds of patients underwent ICD implantation for primary prevention with a mean LVEF of approximately 40% to 50%. While the appropriate ICD therapy rates were higher in these two studies (8% to 15%) compared to SCD-HeFT (5.1%), inappropriate shock therapy was seen in approximately one-quarter of patients, significantly higher the previously published literature [19,20]. Thus, research efforts turned to predictors of appropriate ICD therapy. Most studies show an association between reduced LVEF and appropriate ICD therapy. However, most appropriate ICD therapies occur in those with an LVEF >35%, implying that the conventional EF cutoff may not apply to those with cardiac sarcoidosis [21]. Secondly, appropriate ICD therapy has been associated with advanced conduction disease, including high-grade atrioventricular block or complete heart block. The presence of conduction disease may represent a surrogate marker for more extensive granulomatous infiltration of the myocardium and specifically the basal septum [22]. Similar findings have been found in catheter ablation for ventricular arrhythmia in this population, as presence of late gadolinium enhancement on MRI or lack of improvement at repeat PET post-ablation predicted worse arrhythmia-free survival [23]. Future research is needed on the role of specific findings on cardiac MRI or alternative predictive models that may guide appropriate ICD therapy. A recent meta-analysis showed that the presence of late gadolinium enhancement (LGE) on cMRI was a powerful predictor of ventricular arrhythmia risk irrespective of cardiomyopathy etiology, particularly in those with severely decreased EF [24]. Additionally, a recent risk model comparing identification of LVEF utilizing cMRI versus TTE, has shown improved prediction of VT or SCD amongst those with reduced ejection fraction thus providing novel methods for characterizing indication for ICD implantation [24].

Given the modicum of high-quality data, the Heart Rhythm Society generated a consensus statement that represented an international effort to address the challenges faced by clinicians caring for patients with cardiac sarcoidosis [25]. The following circumstances were those in which ICD implantation would be recommended:

- Class I indications: 1) LVEF <35% despite optimal medical therapy and a period of immunosuppression (in setting of active inflammation)
- Class IIa indications: 2) any indication for permanent pacemaker, 3) unexplained syncope or near-syncope, 4) inducible ventricular arrhythmias, 5) late gadolinium enhancement on cardiac MRI and positive electrophysiologic study
- Class IIb: LVEF 36% to 49% and/or RVEF <40% despite optimal medical therapy with period of immunosuppression

Left Ventricular Non-Compaction

Left ventricular noncompaction (LVNC) is a rare, genetic cardiomyopathy that is theorized to be the result of intrauterine failure of the myocardial compaction process. Characterized by echocardiographic evidence of deep intertrabecular recesses within the ventricular myocardium, patients have presented clinically with heart failure, embolic events, ventricular tachyarrhythmias and sudden cardiac death [26-28].

Ventricular tachyarrhythmias are reported in 38% to 47% and sudden cardiac death in 13% to 18% of patients with LVNC. Muser et al. [29] recently reported data in patients with LVNC presenting for catheter ablation of ventricular arrhythmias which demonstrated that patients presenting with VT had evidence of abnormal electroanatomic substrate involving the mid- to apical segments of the LV, matching segments of noncompacted myocardial substrate identified by preprocedural magnetic resonance imaging or

echocardiography [18]. The largest cohort to study this subpopulation in regards to ICD placement followed twelve patients in Switzerland. This study showed that in patients with LVNC, who were treated with an ICD for secondary prevention, appropriate ICD therapy occurred in 50% of the cases during follow-up. Among all, 25% of patients who received ICD for primary prevention had an appropriate ICD therapy during follow-up. All patients who were inducible for sustained ventricular tachycardia during EP study experienced appropriate ICD therapy during the follow-up time period of the study, indicating the possible benefit of pre-emptive EP study at the time of diagnosis of LVNC to risk stratify patients.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is an uncommon cause of systolic dysfunction which affects women during pregnancy or shortly after delivery. The incidence appears to be rising, likely due in part to increased awareness and diagnosis, rising maternal age, changing demographics, and rising multifetal pregnancies. Notably, PPCM is the leading cause of maternal cardiovascular death (23%) [30]. Retrospective analyses have attributed over one-third of deaths in those with PPCM to sudden cardiac death [31]. In a case-control series by Zunino et al. [31], patients with PPCM in whom ICDs were implanted were more likely to receive appropriate ICD therapy compared with matched controls with ICDs for primary prevention with alternative causes of non-ischemic cardiomyopathy, albeit not statistically significant (36.8% *vs.* 20%) [32].

Much of the hesitancy towards ICD implantation in those with PPCM is the high rate of resolution of left ventricular function. As a result, recent European studies have evaluated the utilization of wearable cardioverter-defibrillators (Life Vest; Zoll, Pittsburgh, PA, USA). In a study with seven patients with PPCM, 4 patients were appropriately shocked for ventricular fibrillation over a mean follow up of less than 3 months [33]. However, this data was not replicated in a larger retrospective study, as no therapies were applied over a 4-month period, with only 20% of the study population requiring ICD implantation after the follow-up period for persistent left ventricular dysfunction. Thus, while there is no clear evidence-based guideline for therapy in this population, this group may represent one that may benefit due to increased latency to events. Arany and Elkayam [33], posit that it may be reasonable to consider wearable cardioverter/defibrillators in patients with EF <30%, as a bridge to ICD implantation amongst those with perceived higher mortality risk [34]. Alternatively, early echocardiographic evaluation in women with recovered LV function revealed decreased contractile reserve in response to dobutamine challenge, raising concerns for the presence of subclinical dysfunction despite presumed resolution [35]. Additionally, many studies have elucidated genetic underpinnings to PPCM with high risk of recurrence with subsequent pregnancies, with recent evidence demonstrating stratification by degree of persistent left ventricular dysfunction, portending higher mortality rates in those with persistent LV dysfunction [36].

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by segmental or diffuse replacement of myocytes with fatty and fibrous tissue, typically resulting in ventricular arrhythmia. Patients typically present with symptoms related to ventricular arrhythmia and post-mortem analyses have demonstrated ARVC as an important cause of sudden cardiac death in younger patients. Thus, catheter ablation, anti-arhythmic medication and ICD placement have been utilized in this sub-population as a means of preventing sudden death.

Given the young average age of diagnosis, patients with ARVC have augmented ICD lead placement/replacement complication risk, further amplified by known right ventricular structural changes that may hinder ICD lead implantation, precluding ventricular sensing/pacing.

Current ACC/AHA guidelines recommend ICD implantation in those with ARVC and documented VT or VF, who are on optimal therapy and have a reasonable life expectancy (Class I), or for those with extensive disease, LV involvement, >1 family member with prior SCD, or ARVC and syncope without alternative diagnosis. A recent meta-analysis by Schinkel [36], evaluated 610 patients with ARVC who underwent ICD implantation. In pooled analysis, 61% had pre-syncope, 31% had syncope, 58% had documented VT, and the annualized rate of appropriate ICD therapy was 9.5%, representing significant sudden cardiac disease risk [37]. This value was also thought to under-represent therapy as a higher proportion of patients were on anti-arrhythmic drug therapy compared with prior large cohort data. However, there was considerable morbidity from ICD implantation. Annualized inappropriate ICD therapy rate was 3.7%, with a 4.4% annualized complication rate, presumed to be higher secondary to young age at implantation (mean age 40.4 years), high rates of supraventricular arrhythmia, and difficult lead placement, which was reported by electrophysiologists in 18.4% of patients [37]. One study demonstrated correlative data between extent of right ventricular involvement (based on angiography or endomyocardial biopsy) and the need for testing right ventricular lead placement in >2 placements [29]. While preliminary data may be skewed by limited experience, novel techniques in ICD placement such as subcutaneous ICD may mitigate morbidity in this high risk sub-population.

Conclusion

With the advent of the results from the DANISH trial, electrophysiologists have been left with discordance between prior accepted all-cause mortality benefit with ICD implantation in those with nonischemic cardiomyopathy and neutral data in the era of CRT therapy. While subgroup analysis from COMPANION and DANISH trials did not show incremental benefit from ICD therapy amongst those with concomitant CRT, collective data showed mortality benefit that approached significance. It is important that electrophysiologists recognize that the population of patients with noischemic cardiomyopathy is quite heterogeneous. As such, an individualized patient- and disease-specific approach should be taken to risk stratify patients to determine whether ICD would be beneficial.

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