ICD in Cardiac Sarcoidosis: Variables associated with appropriate therapy, inappropriate therapy, and device complications

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Abstract

Introduction: Those with cardiac sarcoidosis (CS) are at risk of sudden cardiac death (SCD), which may be prevented using an implantable cardioverter defibrillator (ICD). There is limited data available that follows the post-procedural outcomes of patients with cardiac sarcoidosis (CS) who have had an ICD implanted. **Areas Covered:** This review will highlight studies that focus on both appropriate and inappropriate therapies in those with an ICD, as well as device complications in this group. There were several variables inclusive of age, gender, ventricular characteristics and findings on cardiac imaging that were investigated and discussed as influencing factors in predicting appropriate and inappropriate therapies. **Conclusions:** Adverse events in those with an ICD and CS were minimally reported in the literature. Individuals diagnosed with CS are at high risk of ventricular arrhythmia, with comparable rates of appropriate therapy but higher incidence of side effects and inappropriate therapy. The younger average age of CS patients in comparison to other ICD cohorts warrants the need for further, large-scale, prospective trials with periodic interim follow-ups focused on those with this condition.

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Keywords: appropriate therapy; cardiac sarcoidosis; implantable cardioverter defibrillator; inappropriate therapy; sudden cardiac death;

Introduction

The potentially fatal arrhythmias secondary to cardiac sarcoidosis (CS) have spurred research into the use of the implantable cardioverter defibrillator (ICD) in this condition. Appropriate ICD therapy refers to either an appropriate shock, or correct device-based rhythm analysis and recognition of anti-tachycardia pacing, for ventricular tachyarrhythmias such as ventricular tachycardiac (VT) or ventricular fibrillation (VF). An Ellenbogen et al. article helped frame the utility of "appropriate therapy" as an important surrogate marker of sudden cardiac death (SCD) in non-ischaemic cardiomyopathies, albeit one that will over-estimate the benefits of ICD shocks(1). Inappropriate therapy, however, is a shock that is delivered in the absence of VT or VF, the consequence of which has been previously shown to lead to myocardial dysfunction, advancement of heart failure and increased mortality(2–4). Understanding the patient groups that receive appropriate therapies, as well as identifying those in whom device complications are more prevalent, will help guide future guidelines and recommendations to improve patient care.

Figure 1: Central illustration of appropriate & inappropriate therapies, as well as device complications in CS

Abbreviations List

Abbreviation	**Meaning**
AVB	Atrioventricular Block
CHB	Complete Heart Block
CI	Confidence Interval
CMR	Cardiovascular Magnetic Resonance
CS	Cardiac Sarcoidosis
CT-PET	Computed Tomography - Positron Emission Tomography
ICD	Implantable Cardioverter-Defibrillator
LBBB	Left Bundle Branch Block
LGE	Late Gadolinium Enhancement
LVEF	Left Ventricular Ejection Fraction
OR	Odds Ratio
RBBB	Right Bundle Branch Block
SCD	Sudden Cardiac Death
SCD-HeFT	Sudden Cardiac Death In Heart Failure Trial
VA	Ventricular Arrhythmia
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

Factors associated with appropriate therapy

Table 1: Overview of the reviewed sources relating to appropriate therapy in CS

Authors	**Publication Year**	**Location**	**Study design**	**Cohort Size**	**Findings relevant to this section**

Ellenbogen et al.(1)	2006	North America	Prospective	458	"Appropriate therapy" is an effective proxy of SCD in non-ischaemic cardiomyopathies.
Azoulay et al.(5)	2020	Global	Retrospective	464	Statistically significant factors in predicting appropriate therapy are: Young age, male sex, low LVEF, ventricular pacing, complete heart block. Statistically non-significant factors in predicting appropriate therapy are: LBBB/RBBB, positive CMR & syncope
Taha et al.(6)	2022	Global	Retrospective	530	(Includes several non-predictors of appropriate therapy, please see main text)
Schuller et al.(7)	2012	North America	Retrospective	112	Higher rates of appropriate therapy in those with RV dysfunction.
Halawa et al.(8)	2020	Global	Mixed prospective & retrospective	585	Rates of appropriate therapy higher in those with AVB.
Franke et al.(9)	2020	Global	Mixed prospective & retrospective	1247	Higher rates of appropriate therapy in those whom ICD was implanted for secondary prevention.

Mathijssen et al.(10)	2022	Netherlands	Retrospective	105	Higher rates of appropriate ICD therapy in male sex, 2nd/3rd degree AVB, prior VA, and presence of LGE on CMR – most strongly with LGE in the area of RV.
Kron et al.(11)	2013	North America	Retrospective	33	Young age and reduced LVEF predict appropriate ICD therapy.

Several retrospective studies from across North America, India and Japan sought to investigate an association between appropriate therapy and patient characteristics in those with CS(12,7,13,14,11,15,16). Many of these single-centre studies were pulled together in a meta-analysis by Azoulay et al(5), showing that of the 464 participants, 39% of CS patients received appropriate therapy – a value significantly higher when compared to other studies focusing on non-sarcoid related heart disease, and a similar value to that of a recent UK-based single-centre study where they showed rates of appropriate therapy were 32.7%.(17)

Variables that were identified in this study, alongside other presently discussed studies, fit into three broad categories which will be discussed in greater detail below:

- Patient characteristics
- Ventricular characteristics
- Imaging findings

Patient characteristics

Epidemiological differences between individuals with CS were found to be significant determinants of appropriate therapy in some studies, most notably age and sex. Male sex was shown to be a predictor of appropriate therapy in research from Schuller et al. (72.2% vs. 51.5%, P = 0.025)(7), Kron et al. (73.8% vs. 59.6%, P = 0.0330)(14), and more recently from Mathijssen et al. (HR 2.33, P = 0.046)(10). Azoulay et al.'s meta-analysis also showed that male sex predicted appropriate therapy (OR 2.06, 95% Confidence Interval (CI) 1.37-3.09, P = 0.0005), also finding young age to be a significant factor (-3.33, 95% CI -6.42 to -0.23, P = 0.004)(5). This finding was also significant in the Mohsen et al. study (47.4 vs. 56, P = 0.031), however only approached statistical significance in the aforementioned Schuller et al. and Kron et al. studies (P = 0.052 for both).

It is worth noting that the burden of CS differs between ethnic groups, with previous studies showing varied rates of cardiac sarcoid-related death between them(18–20). Many of the above studies do not include this dataset, and as such are unable to draw conclusions around the impact of appropriate therapies in differing populations.

Ventricular Characteristics

A large meta-analysis found that having a low left ventricular ejection fraction (LVEF) (-10.5, 95% CI -18.23 to -2.78, P = 0.008), receiving ventricular pacing (OR 6.44 95% CI 2.57 to 16.16, P < 0.0001)

and having a history of complete heart block (CHB) (OR 2.19, 95% CI 1.20 to 3.99, P = 0.01) predict appropriate therapy. Regarding ejection fraction, mean LVEF was generally shown to be lower in those who experienced appropriate therapy when compared to those who did not receive appropriate therapy, and furthermore, no patients within the group with a higher ejection fraction required transplant or died. These findings emphasise the highly arrhythmogenic nature of those with CS and a reduced LVEF, supporting the recommendations in the 2014 HRS Consensus, 2017 AHA/ACC/HRS and 2022 ESC Guidelines of implanting an ICD in order to prevent sudden cardiac death (SCD).(21–23)

A recent 2022 study found that $2^{nd}/3^{rd}$ degree atrioventricular block (AVB) and prior ventricular arrhythmias were indicative of patients receiving appropriate therapy(10). Interestingly, in contrast with the aforementioned meta-analysis, there was no significant difference in LVEF between those who received appropriate therapy and those who did not. As discussed by the authors, this may be as a contribution from the greater prevalence of high degree AVB in their population, and it's previously shown association with VA, even in patients with a preserved LVEF(24). Prior to this study, AVB had been shown to be predictive of appropriate ICD therapy, a finding which likely corresponds to the greater severity and extent of disease in order for AVB to manifest which, as such, will predispose individuals to increased risk of arrhythmias(8).

This increased risk of arrythmia, and as such appropriate therapy, in those with CS was further explored in a different meta-analysis from Franke et al. In those studies which analysed individuals who received multiple shocks, nearly 1 in 5 patients received [?]5 therapies. They found that combined overall rates of appropriate ICD therapy or SCD were 29.0%, and that across the entire cohort, 39.0% of patients received an ICD. As expected, the results showed higher rates of appropriate therapy in those who met secondary prevention indications when compared with primary prevention (22.7% vs 58.4%)(9).

Imaging Findings

Advances in cardiac imaging, in particular using Cardiovascular Magnetic Resonance (CMR) scanning, has given clinicians the ability to improve the quality of care for patients with CS. A recent 2022 study concluded that it was patients with late gadolinium enhancement (LGE) on CMR who most frequently received appropriate therapy, and moreover that all 10 patients without LGE did not receive appropriate ICD therapy. This association between appropriate therapy and LGE distribution was seen most strongly in those with uptake in the area of the right ventricle (RV), but also in the anterior and inferior walls. Involvement of the RV in CS predicts both poor outcome, but also high rates of arrhythmia(25–27). It is this scarring pattern that likely accounts for the high levels of appropriate therapy seen in this cohort – a theory evidenced in a study from Schuller et al. (OR 6.73, 95% CI 2.69–16.8, P < 0.01)(7).

Although there is an association between^{18}F-flourodeoxyglucose positron emission tomography (FDG-PET) and Major Adverse Cardiovascular Events (MACE) (Citation needed here), to our knowledge there was no research available that connected a positive finding on this imaging modality and appropriate therapy. This is perhaps a gap in the literature that future research should address.

Non-predictors of appropriate therapy

Whilst there were many positive predictive variables associated with appropriate therapy in the above works, Azoulay et al. also identified other factors that were not associated with receiving appropriate therapy in their meta-analysis. These were LBBB, RBBB, a positive cardiovascular magnetic resonance (CMR) and syncope. Two of the studies included from this meta-analysis had separately analysed factors that were non-predictors of appropriate therapy. The conclusions of these agreed with those from the above meta-analysis, with the exception of having a lower mean LVEF. This was discussed in Taha et al.'s review(6): "One found that extent of cardiac involvement on CT-PET and pre-procedure ventricular arrhythmia (VA) burden were non-predictors(15). The other described being >60 years old, New York Heart Association (NYHA) class III/IV, LVEF <35%, non-sustained VT, paroxysmal atrial fibrillation (AF), QRS interval >150ms, QTc interval >470ms and concurrent amiodarone therapy as non-predictors of appropriate therapy(16)".

Inappropriate therapy & Device Complications

Table 2: Overview of the reviewed sources relating to inappropriate therapy and device complications in CS

Authors	**Publication Year**	**Location**	**Study design**	**Coho**
Franke et al.(9)	2020	Global	Mixed prospective & retrospective	1247
Mathijssen et al.(10)	2022	Netherlands	Retrospective	105
Betensky et al.(14)	2013	North America, Canada & Japan	Retrospective	235
Kron et al.(14)	2012	Global	Retrospective	235

Franke et al.'s meta-analysis drew conclusions from 19 studies and showed rates of inappropriate therapy to be 17.9%(9). Other studies show rates of inappropriate therapy varied widely, from anywhere between 2.9% to as high as 30%(7,14,8–10). The lowest of these was from a retrospective cohort analysis of 105 patients where 3 subjects (2.9%) received inappropriate shocks (having previously received appropriate therapy). All 3 were implanted for secondary prevention, and were all triggered by atrial fibrillation(10). Kron et al.'s study demonstrated one of the highest rates of inappropriate therapy in 24.3% of their patients, again most commonly caused by supraventricular arrhythmias – a theme reflected across multiple of the abovementioned papers(14). Mohsen et al was another study in the literature which showed that, although 36.7% patients received appropriate therapy, 63.3% received no appropriate therapy, and 30% of individuals received inappropriate therapy(11).

Although a well-recognised drawback of ICD implantation, there are few studies that have thoroughly investigated inappropriate therapy. The most expansive study in the collection described above has a relatively short follow-up period and, as previously highlighted, the small sample size limits and underpowers the ability for statistical analysis. We were unable to find significant data that identifies patients who are at higher risk of inappropriate therapy based on their demographics.

The association of ICD device complications and risk factors in patients with cardiac sarcoidosis

With sudden cardiac death accounting for up to 80% of all fatalities in cardiac sarcoidosis, ICD implantation should always be considered in those selected groups in whom it is appropriate(28), however implantation of an ICD is a high-cost procedure with its own risk profile. A Danish study in 2014 of nearly 6000 patients with cardiac implantable electronic devices (CIED) for a variety of indications (not necessarily CS) estimated approximately 10% of their patients experienced device complications(29).

The first publication to analyse the association between ICD complications in CS patients was Kron et al. in 2012, showing adverse events in 17.4% of their 235 patients at a median follow-up of 4.2 ± 4.0 years. Over half of these complications were related to lead dislodgement or fracture(14). A later retrospective study of 105 patients showed device-related complications at a comparable rate of ˜18% at a shorter median follow-up time of 2.8 years(10). Again, complications were most commonly caused by lead malfunction in nearly 1/3 of patients. Both of these papers link this specific complication to the young age and increased level of activity of CS patients when compared to the average ICD patient – a difference of 10 years at point of implantation(30,5). As commented on by the authors, combining this variable with the high failure rates of the 'Medtronic Sprint Fidelis' leads (particularly in the younger population), which were prominent at the time of the study, may account for these particularly high rates of adverse effects(31).

Many patients are also treated with immunosuppressive drugs such as prednisolone and methotrexate. We expected this to have an impact on infection rates in the CS cohort. In both the Kron et al. and Mathijssen et al. papers, infection was the second commonest adverse event after lead-related complications at rates of 2.6% and 4.8% respectively. CIED analysis from the previously referenced Danish study showed infection rates of 0.83% in a their population(29).

Strengths & Limitations

The researchers in many of the above studies have recognised the need for a global approach to the management of CS, with results being amalgamated from studies across multiple continents. It is worth noting,

however, that the lack of multivariable analysis in some of these studies from the meta-analysis prevented independent predictors of ICD appropriate/inappropriate therapy to be elicited. As discussed earlier, there was little data available to reflect the wide-ranging consortium of patients that can be affected by CS, and as such further determine which ethnic groups may be at lesser or greater chance of appropriate or inappropriate therapies. Future studies should collect data that spans across a broad array of ethnic backgrounds to capture a true reflection of the disease. Another limitation common to several CS meta-analyses is the risk of data overlap. Patient identifying features had been removed due to lack of consent, and as such there will certainly be inaccuracies in results, particularly given the relatively small sample size. As well as this, the retrospective study design lends itself to objectively poor result quality. Finally, although previously discussed as an effective proxy in light of no better alternative, the use of "appropriate therapy" as a surrogate endpoint is not a true representation of SCD and is generally accepted to be an imperfect tool that likely over-estimates risk.

Discussion

At this relatively early point in our knowledge of CS, most implementable changes found from studies this paper analysed will be targeted at the "ground-level". That is, aiding clinicians in their practice to filter patients deemed best to benefit from ICD implantation for CS. Review of the literature made it clear that balancing the higher rates of appropriate therapy with the largely unknown, but likely increased, likelihood of device complication in this younger patient cohort is challenging but important. The crux of ICD usage in CS hinges around scarring patterns and the consequential increased risk of arrhythmia. Although made more challenging by the high heterogeneity of the disease, identifying these high-risk patients and discussing treatment options to achieve a shared but informed decision is essential.

We have seen the influence that some of the discussed papers have had on the management of ventricular arrhythmias in those with CS in several iterations of guidance and recommendations, most recently in the ESC Guidelines from 2022(23). More widely speaking this paper aims to provide a stepping stone for further research to support revision of these guidelines if necessary – especially relating to the information we have amalgamated about the drawbacks of ICD implantation.

Although a consequence of the innate rarity of the condition, the low cohort sizes seen in several of the previous studies lends itself to statistically underpowered analyses and therefore limits the ability to draw stronger conclusions. This highlights the need for larger-scale trials that are prospective in nature to truly characterise the utility of ICDs in CS. In particular, there is a need for more data surrounding both device complication and inappropriate therapy. This should compare a variety of different variables, examples of which may include analysing ICD therapies in those treated with and without immunosuppression, or perhaps looking at outcomes in patients with sarcoid isolated to the heart versus those with systemic manifestations of the disease.

Inappropriate therapy will likely remain an unavoidable complication of ICD therapy. However, through improvement of VA therapy detection systems and supraventricular tachycardia (SVT) discrimination algorithms, rates of inappropriate therapy will be reduced, and will make ICD implantation a more viable option for a greater proportion of patients. We envisage machine learning to play a pivotal role in this by using AI-based pattern recognition on an ever-growing collection of patient datasets from devices and constantly refining the 'correct rhythm' to deliver a shock to. We have already seen some advancements made in this field recently(33), and expect this to grow further and impact positively on those with CS as well.

Increasing clinician awareness alongside more accurate and improved cardiovascular imaging & diagnostic testing has led to higher numbers of cases being diagnosed each year. In the coming years, we would expect this trend to continue to increase. We also picture formulation of a more definitive diagnostic criteria that can be more specifically applied to a variety of ethnic groups.

Conclusion

We showed that those with an ICD implanted for CS receive comparable rates of appropriate therapy

but are at higher risk of complication than the average ICD patient. Young age, male sex and ventricular characteristics such as low LVEF were frequently found to be significant factors in predicting appropriate therapy. There was little significant information available globally relating to device complications in those with CS.

It was evident that in many of the previously reviewed studies, those with CS experience more frequent ICD therapies than other cohorts. In comparison to the "Sudden Cardiac Death In Heart Failure Trial" (SCD-HeFT), rates of ICD therapy were more than double that of the ˜5% appropriate shocks delivered per annum(32). However, as discussed, the benefits of ICD therapy are double-edged in nature, with extensive side effect profiles and high rates of inappropriate therapy.

Although the conclusions drawn by the authors from the aforementioned studies are based largely off small data sets, the research groups should be commended on their contributions in such a rare condition which has helped to improve the quality of care delivered. Although a niche field, cardiac sarcoidosis proves to be an interesting research area with a broad array of research opportunities for those in whom it piques interest.

Conflict of Interest

There are no conflicts of interests that the authors wish to declare.

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