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# Cardiac sarcoidosis – when should you insert a defibrillator?

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## Take Home Messages

- Cardiac sarcoidosis is underdiagnosed and is associated with high rates of life-threatening ventricular arrhythmia.
- There are three main international guidelines that advise, with varying degrees of evidence, on when an ICD should be implanted in cardiac sarcoidosis (CS).
- Over 50% of those with CS who do not initially meet Class I or IIa indications (HRS criteria) for an ICD later went on (5 year follow-up) to develop one of these, or experienced sudden cardiac death (SCD) or sustained ventricular arrhythmia.
- Patients with a definite histological diagnosis of cardiac sarcoidosis were shown to be at significantly higher risk of SCD than those without.
- This study signifies the importance of regular outpatient follow-up in those with cardiac sarcoidosis, particularly in those who may not initially meet ICD indications.

### Introduction

Sarcoidosis is a multisystem inflammatory disorder of unknown aetiology characterised by the presence of non-necrotizing granulomas. Myocardial involvement, termed cardiac sarcoidosis (CS), occurs in up to 30% of cases and can manifest with an initial presentation of high degree atrioventricular block, ventricular arrhythmias, heart failure and sudden cardiac death (SCD) (1). Investigations to aid diagnosis include echocardiogram, cardiac MRI, FDG-PET scan and endomyocardial biopsy (EMB) (2,3). Implantable cardiac defibrillator (ICD) use in CS has been widely shown to reduce risk of SCD from life-threatening arrhythmias, but factors that identify the most appropriate recipients remains unclear and is the focus of research across the world. One area of excellence spearheading new research around this topic is in Finland (4), with ongoing analysis of the MIDFIN registry – a 5-centre cardiology network first established in the 1980's.

Research has helped to make inroads in predicting patients who would benefit most from ICD implantation; however, the single-most 'best' guideline is yet to be formulated, and there is variation between recommendations. The presently discussed paper from Nordenswan et al.

analysed the cumulative rates of SCD, sustained ventricular tachycardia (sVT) and emerging ICD indications in those with and without Class I and IIa ICD recommendations as per the first two leading American guidelines (2014 HRS Consensus Statement and 2017 AHA/ACC/HRS guideline) highlighted in Table 1:

**Table 1:** ICD Recommendations in cardiac sarcoidosis based on three guideline

| Level of Evidence | 2014 HRS Consensus(2) | 2017 AHA/ACC/HRS Guideline(5) | 2022 ESC Guidelines(7) |
|---|---|---|---|
| I | Sustained VT | | |
| | Survivors of SCA | | |
| | LVEF <35%(a)(b) | | |
| IIa | Those with an indication for permanent pacing & LVEF >35% | | |
| | LVEF >35% with syncope(a)(b) | | |
| | Inducible sustained VA on EP study | | Inducible sustained monomorphic VA on EP study in those with LVEF 35-50% and minor LGE on CMR |
| | | LVEF > 35% with evidence of myocardial scar on CMR or PET | LVEF >35% with significant myocardial LGE on CMR after resolution of acute inflammation |
| IIb | LVEF between 35-50% or RVEF <40% | | |

Abbreviations - ICD, implantable cardioverter-defibrillator; HRS, Heart Rhythm Society; AHA/ACC/HRS, American Heart Association/American College of Cardiology/Heart Rhythm Society; ESC, European Society of Cardiology; VT, ventricular tachycardia; SCA, sudden cardiac arrest; LVEF, Left Ventricular Ejection Fraction; VA, ventricular arrhythmia; EP, electrophysiology; LGE, Late Gadolinium Enhancement; CMR, Cardiac Magnetic Resonance; PET, positron emission tomography; RVEF, Right Ventricular Ejection Fraction.
(a)HRS consensus: Despite optimal medical and immunosuppressive therapy (in presence of active inflammation)
(b)AHA/ACC/HRS guidelines: Providing expected meaningful survival of more than 1 year

**Study Analysis**

This Finnish study analysed 398 patients across a 30-year period, with mean age of 51 and 72% of the cohort being female. They found that when using the 2014 HRS Consensus

criteria, 85% of patients with clinically manifest CS had either Class I/IIa recommendations for ICD. However, in the remaining 15% of patients – the cohort thought not to benefit from ICD insertion – combined rates of fatal and non-fatal ventricular arrhythmia were comparable to those within the group with Class I/IIa indications. Furthermore, at the 5-year follow-up point, over half (53%) of this group without initial Class I/IIa indications, either went on to develop these indications, or experienced SCD or sVT.

Despite this, those in the group with class I/IIa indications received an ICD nearly 2 times as often as those who did not have an indication for early ICD implantation. In comparison, applying the 2017 AHA/ACC/HRS criteria to the same cohort demonstrated that 100% of patients had Class I or IIa indications for ICD implantation.

They also found the risk of SCD was 2 times higher in those with definite histological diagnosis of myocardial involvement. Across the entire cohort, the 5-year risk of SCD was nearly 10%, with a cumulative risk (SCD, sVT or appropriate ICD therapy) of 24% when including sVT in their composite secondary endpoint. Even in those with absent ICD indications in accordance with the 2014 HRS Consensus, the 5-year risk of SCD was approaching 5%, with a risk of 12% when analysing the outcome of SCD or sVT at follow-up.

**Strengths and Limitations**

The strengths of this paper undoubtedly lie in the long study period and nationwide representation of the data reducing tertiary referral bias. The diagnoses were standardised against internationally recognised criteria, and post-mortem cases that would have induced reverse survivorship bias to the results were excluded. Moreover, 193/398 (48.5%) patients had a definite CS diagnosis from EMB which makes the data robust. Indeed, many other CS studies have suspected or presumed cases only.

Limitations of this study include firstly the objectively small cohort size that is restricted due to the innate rarity of CS, and secondly the unrecordable episodes of ventricular

tachycardia that might have occurred more frequently in the group without an ICD because of the reduced number of intracardiac devices present in this cohort. As such, the true value of the secondary endpoint in this group is likely to have been underestimated. Moreover, subclinical cases of CS, screened during extra-cardiac sarcoidosis diagnosis, were excluded in this study. This exclusion could have over-estimated the event rate in those CS patients not meeting Class I-IIa criteria included in this study. In addition, details of advanced imaging such as signs of inflammation and oedema on cardiac MRI and FDG-PET scan were not always available on follow-up. Similarly, the study is silent on whether any patients received VT ablation procedures which may mask future events. Details on inappropriate ICD therapies and device complications are also not given which are very relevant factors in planning an ICD, especially in a patient on immunosuppressants and likely increased risk of infections. Lastly, the study was published before the 2022 ESC guidelines (7) came and as such no comparison of results are drawn to it (Table 1).

## Future Directions

Nonetheless, the authors and those involved in the ongoing growth of the MIDFIN registry should be commended on their transformative contributions to this field and allowing several conclusions to be drawn.

One of these is the link between SCD and 'definite' histological diagnosis of CS, which makes sense as those with more extensive disease and myocardial scarring would likely be more readily identified on testing and would be at greatest risk of SCD.

The study also highlights that, due to the highly arrhythmogenic nature of CS alongside high rates of emerging ICD indications in this cohort, regularly assessing risk and maintaining routine follow-up is a necessity. Additionally, it emphasises the importance of clinicians engaging in comprehensive discussions with their patients regarding the advantages and disadvantages of inserting an ICD. The cut-off values for ICD insertion in other cardiomyopathies, such as hypertrophic cardiomyopathy, have been recommended in SCD at rates exceeding 4%[(6)], and as such, truly identifying those at 'low risk' in CS remains an important pocket of knowledge to be explored.

Does this study answer the question on when ICD should be inserted in a CS patient? It brings novel conclusions yes. However, prognosis of CS varies across different geographical locations and it is the need of the hour that an international CS registry with global collaboration is developed to answer this question.

## Disclosures

None

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