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Outcomes after transvenous defibrillator implantation in cardiac sarcoidosis: A systematic review

Ahmed Taha MBBCh[1,†] | Omar Assaf MBBCh[2,†] | Asgher Champsi MBChB[3] | Ramesh Nadarajah MA[1] | Peysh A. Patel PhD[4]

[1]Department of Cardiology, Leeds General Infirmary, Leeds, UK

[2]Department of Cardiology, Blackpool Victoria Hospital, Blackpool, UK

[3]Department of Cardiology, New Cross Hospital, Wolverhampton, UK

[4]Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK

Correspondence
Peysh A. Patel, Consultant Cardiologist, Queen Elizabeth Hospital, Mindelsohn Way, Birmingham, B15 2TH, UK.
Email: peysh.patel@uhb.nhs.uk

Abstract

Introduction: Sarcoidosis is a systemic inflammatory disorder associated with ventricular arrhythmias (VAs) and sudden death in the context of cardiac involvement. Guidelines advocate implantable cardioverter-defibrillator (ICD) implantation in specific subcohorts, but there is a paucity of data on outcomes.

Methods and Results: A systematic review was performed to assess outcomes in patients with definite or probable cardiac sarcoidosis (CS) treated with ICD. Observational studies were identified from multiple databases from inception to 21st May 2021. Outcomes of interest included appropriate and inappropriate ICD therapies in addition to all-cause mortality. Study quality was assessed individually using the Newcastle Ottawa Scale (NOS).

Eight studies were identified comprising 530 patients, with follow-up period of 24–66 months (weighted average 40 months). Mean age was 53.9 years with ejection fraction of 41.3%. Overall incidence of appropriate therapy was 38.1% during follow-up. Left ventricular systolic dysfunction (LVSD) with ejection fraction <40% was a predictor of appropriate therapy in the majority of studies, as were sustained VAs during electrophysiological testing (EP) in one study. There was no interaction with device indication (i.e. primary or secondary). Where documented, inappropriate therapy was primarily driven by atrial arrhythmias. All-cause mortality was 6.0% over a median follow-up period of 42 months. Only three studies achieved good quality in the comparability domain of NOS.

Conclusions: Appropriate ICD therapy in patients with CS is commonly associated with LVSD, which can act as a surrogate for scar burden. The utility of EP testing in this setting remains unclear.

KEYWORDS
cardiac sarcoidosis, implantable cardioverter-defibrillator, systematic review

[†]Denotes joint first authorship.

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1 | INTRODUCTION

Sarcoidosis is a systemic, multi-system inflammatory disease characterised by the formation of non-caseating granulomas.[1] Whilst underlying aetiology has not been fully defined, it is hypothesised that the disorder manifests as a result of environmental triggers combined with underlying genetic susceptibility.[2–4] Prevalence of sarcoidosis is rare with estimates in the region of 20 per 100 000, with highest rates reported within the northern European and African-American populations. Granuloma deposition can occur within multiple organs but primarily affect the lungs, lymph nodes, skin and eyes.[5,6] Occurrence of clinically detectable cardiac sarcoidosis (CS) is as low as 5%, although studies have demonstrated cardiac involvement in up to 25% of autopsy specimens and as high as 55% in imaging studies of patients with extra-cardiac sarcoidosis.[7–10]

CS is typified by the presence of myocardial inflammation, necrosis and granulomas, and is associated with significantly worse prognosis than sarcoidosis without cardiac involvement.[11] Early diagnosis is therefore paramount in order to initiate prompt therapy but is limited by the condition's typically insidious onset. Confirmation of cardiac involvement can be achieved via endomyocardial biopsy but is of low sensitivity due to patchy involvement.[12] As such, non-invasive imaging modalities such as cardiac magnetic resonance imaging (MRI) have enabled earlier detection. Computed tomography positron emission tomography (CT-PET) has also emerged as an effective imaging tool to assess myocardial perfusion and inflammation in CS, particularly if cardiac MRI is non-diagnostic or contraindicated.[13]

Primary cardiac manifestations include conduction abnormalities, ventricular arrhythmias (VA), congestive heart failure (CHF) and sudden cardiac death (SCD).[14] 2021 European Society of Cardiology (ESC) guidelines advocate primary prevention implantable cardioverter-defibrillator (ICD) implantation with concurrent cardiac resynchronisation therapy (CRT) as class IIa indication in patients with CS that have an indication for permanent pacing with left ventricular ejection fraction (LVEF) <50%.[15] 2017 American Heart Association (AHA) / American College of Cardiology (ACC) / Heart Rhythm Society (HRS) guidance recommends secondary prevention ICD implantation as class I indication in those with CS that have survived a cardiac arrest, have sustained ventricular tachycardia (VT) or have LVEF ≤35%.[16] It can equally be considered as class IIa indication for primary prevention in those with LVEF >35%, if there is concurrent syncope associated with scar on imaging and/or inducible sustained VAs on electrophysiological (EP) testing. Similarly, it is recommended in those where an indication for permanent pacemaker implantation exists (class IIa).

However, there is a paucity of data on these cohorts which is traditionally limited to small sample sizes and single centres. This systematic review sought to appraise the contemporary literature to evaluate outcomes in patients with CS that undergo ICD implantation, including those with or without concurrent CRT.

2 | METHODS

2.1 | Data sources and searches

MEDLINE (inception to 21st May 2021), EMBASE (inception to 21st May 2021), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, ClinicalTrials.gov and ISI Web of Science were searched using a priori database-appropriate MeSH terms relating to sarcoidosis, cardiomyopathy, ICD and CRT. Additional studies were sought using WorldCat database and Google Scholar, with derived references from these sources used to seek other potentially relevant citations.

2.2 | Study selection

Two authors (AT, OA) independently performed electronic searches of all databases. From this initial search, duplicate articles were removed and the remainder screened for suitability based on title and abstract. A third author (RN) aided with adjudication in instances where a consensus could not be reached. Studies were eligible if they included (a) participants with either definite or probable CS, (b) primary or secondary prevention ICD implantation, either transvenous or subcutaneous, and (c) reporting of one or more clinical outcomes.

The primary outcome for analysis was ICD therapies, with 'appropriate' defined as anti-tachycardia pacing (ATP) and/or shock for a confirmed VA. 'Inappropriate' was considered to be those contexts where ICD intervention resulted from supraventricular tachycardia (SVT), ventricular over-sensing, lead noise or phantom shocks. A secondary outcome of interest was all-cause mortality. Only original research articles were included, with consideration if published in English language and involving human participants.

2.3 | Data extraction and quality assessment

Data extraction was performed using a pre-specified template constructed on Microsoft Excel (Version 5.3.5, 2014). This was split and conducted independently by two authors (AT, OA), with subsequent verification by a separate author (AC) to ensure validity and accuracy. Relevant information pertaining to study designs, baseline characteristics, inclusion and exclusion criteria, follow-up period and outcomes was collated. The quality of each study was assessed independently by two authors (AT, OA) using the Newcastle Ottawa Scale (NOS).[17] A third author (RN) was consulted to resolve any discrepancies in interpretation.

2.4 | Data synthesis and analysis

Data extraction and synthesis was performed concurrently by two authors (AT, OA) using Microsoft Excel software (Version 5.3.5,

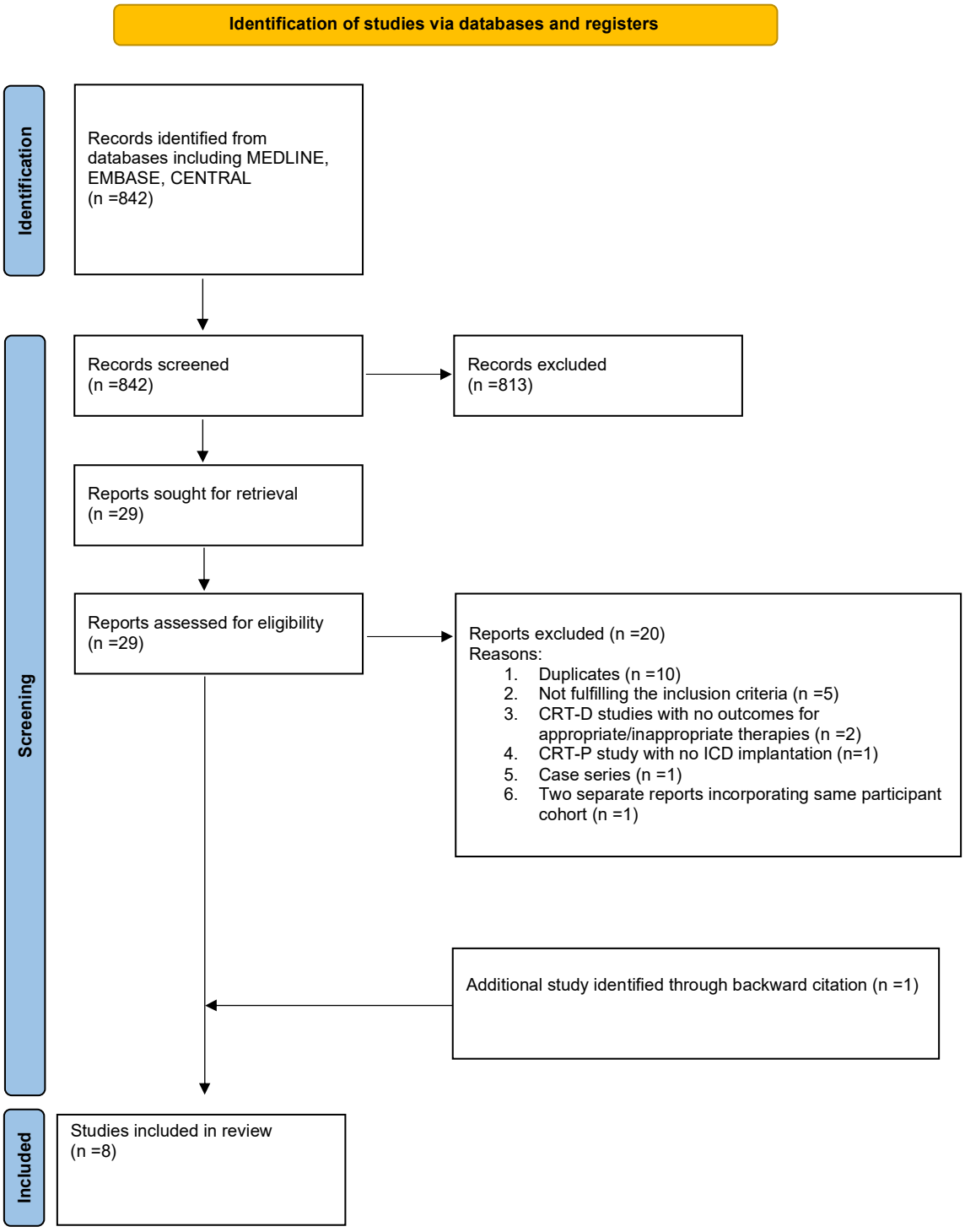

FIGURE 1 PRISMA study flow diagram

2014). All data were processed in accordance with the PRISMA statement.[18] Continuous data are presented as means (with associated standard deviations), unless otherwise stated, and categorical data as percentages. Where appropriate, subgroup analysis was performed to assess predictors of appropriate therapy. DerSimonian and Laird random effects models were fitted to accommodate for the expected inter-study variability in population characteristics.[19] Statistical significance was defined using two-sided p values and 95% confidence intervals (CIs) for all obtained pooled estimates. I^2 statistic was used to assess heterogeneity between studies and represents the proportion of variability amongst included studies that is not attributable to chance or random error, with threshold value >50% reflecting significance. All statistical analyses were conducted in R 4.1 using the meta package. AT and OA have full access to all the data in the study and take responsibility for its integrity and data analysis.

TABLE 1 Study criteria for diagnosis of cardiac sarcoidosis

Study ID	Criteria for diagnosis of CS	Number of participants with ICD (*n*)	CS + systemic involvement, *n* (%)	Cardiac biopsy, *n* (%)
Aizer et al.	1- Cardiac biopsy positive OR 2- Extra-cardiac biopsy or Kveim test positive + clinically suspected CS in absence of other diagnoses	15	15 (100)	5 (33)
Bandyopadhyay et al.	1- ACCESS criteria OR 2- No other ascertainable cause and FDG-PET or cardiac MRI positive.	33	NS	NS
Betensky et al.	1- Systemic sarcoidosis meeting JMHW criteria and/or A- Cardiac biopsy positive B- Explant pathology after cardiac transplantation C- Cardiac MRI positive D- FDG-PET positive	45	45 (100)	9 (20)
Kron et al.	One of the following: 1- Cardiac biopsy positive 2- FDG-PET positive 3- Cardiac MRI positive 4- Cardiac CT with late enhancement 5- Extra-cardiac biopsy positive + conduction disease or VA	235	222 (94)	5 (2)
Mehta et a.l	Extra cardiac biopsy positive and cardiac MRI or FDG-PET positive	8	8 (100)	0 (0)
Mohsen et al.	One of the following: 1- Cardiac biopsy positive 2- Extra-cardiac biopsy positive + at least two of: A- Suggestive clinical presentation B- Reduced LVEF with no other identifiable cause C- Cardiac MRI positive C- FDG-PET positive D- ECG findings of conduction abnormality or VA	30	30 (100)	5 (17)
Schuller et al.	Two of the following: 1- Cardiac biopsy positive 2- Cardiac MRI positive 3- EP study positive for inducible VA 4- FDG-PET positive 5- Perfusion defects with absence of obstructive CAD 6- Abnormal Echocardiographic findings 7- Abnormal ECG findings	112	112 (100)	NS
Takaya et al.	Definite or suspected CS according to JMHW criteria	52	NS	13 (25)

Abbreviations: ACCESS, a case control etiologic study of sarcoidosis; CAD, coronary artery disease; CS, cardiac sarcoidosis; CT, computed tomography; ECG, electrocardiogram; EP, electrophysiological; FDG-PET, fluorodeoxyglucose-positron emission tomography; JMHW, japanese ministry of health and welfare; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NS, not specified; VA, ventricular arrhythmia.

3 | RESULTS

3.1 | Study selection

Initial database searches and identification through other sources yielded 842 studies, of which 813 were excluded after screening based upon title and abstract. This resulted in 29 full-text articles which were individually assessed. Seven of these studies (0.83% of those initially screened) were deemed suitable for qualitative and quantitative analysis,[20–26] with one additional study[27] identified through backward citation. An overview of the study selection process is depicted using a PRISMA flow diagram (see Figure 1).

3.2 | Study designs

Eligible studies were conducted between 2005 and 2017, with all being retrospective and non-randomised in design. All were conducted primarily in the United States of America (USA), aside from the most contemporary report which was performed in Japan.[26] There was patient overlap between three studies,[22,23,25] and two others were performed at the same institution though cohorts were

TABLE 2 Study designs

Study ID	Study design and year	Country	Number of centres	Participants inclusion criteria	Total number of participants, *n*	Number of participants with ICD, *n* (%)	Type of device	Median follow up period (months)
Aizer et al.	Retrospective 2005	USA	1	1- Definite or Probable CS 2- Underwent PVS 3- +/− ICD implantation	32	15 (47)	ICD	32
Bandyopadhyay et al.	Retrospective 2015	USA	1	1- Definite or Probable CS 2- ARVD as comparator 4- CS patients underwent either ablation+/-ICD or ICD alone	61	33 (54)	ICD	50
Betensky et al.	Retrospective 2012	USA	1	1- Biopsy proven systemic sarcoidosis 2- Cardiac involvement 3- ICD implantation	45	45 (100)	ICD	31
Kron et al.	Retrospective 2015	USA, Canada, India	13	1- Definite or Probable CS 2- ICD implantation	235	235 (100)	ICD	48
Mehta et al.	Retrospective 2011	USA	1	1- Biopsy positive systemic sarcoidosis 2- Cardiac involvement 3- Underwent PVS 4- +/− ICD implantation	76	8 (11)	ICD	66
Mohsen et al.	Retrospective 2014	USA	1	1- Definite or Probable CS 2- ICD implantation	33	30 (91)	ICD (1 upgraded to CRT-D)	45
Schuller et al.	Retrospective 2012	USA	3	1- Definite or Probable CS 2- ICD implantation	112	112 (100)	ICD	29
Takaya et al.	Retrospective 2017	Japan	1	1- Definite CS 2- Probable CS 3- DCM as comparator 4- ICD implantation	102	52 (51)	ICD	24

Abbreviations: ARVD, arrhythmogenic right ventricular dysplasia; CS, cardiac sarcoidosis; DCM, dilated cardiomyopathy; EP, electrophysiological; ICD, implantable cardioverter-defibrillator; PVS, programmed ventricular stimulation.

TABLE 3 Participant characteristics

Study ID	Number of participants with ICD, *n*	Age, years	Male gender, *n* (%)	AMDs (anytime), *n* (%)	Steroid use (anytime), *n* (%)	EF, %	NYHA class II-IV, *n* (%)	AV conduction disease, *n* (%)	Primary prevention indication for ICD, *n* (%)
Aizer et al.	15 PVS positive: 10 PVS negative: 5	45 PVS positive: 40 ± 10 PVS negative: 51 ± 12	15 (100) PVS positive: 8 (53) PVS negative: 7 (47)	NS	NS	33 PVS positive: 33 ± 17 PVS negative: 34 ± 22	NS	4 (27)	8 (53)
Bandyopadhyay et al.	33	46 ± 10	13 (39)	28 (85)	15 (45)	38 ± 15	NS	6 (18)	11 (33)
Betensky et al.	45	54 ± 11	27 (60)	NS	NS	45 ± 16	NS	19 (42)	29 (64)
Kron et al.	235	Isolated CS (54 ± 8) CS + systemic involvement (56 ± 11)	152 (65)	102 (43)	142 (60)	Isolated CS (38 ± 17) CS + systemic involvement (45 ± 16)	114 (49)	3[a] (1.3)	147 (63)
Mehta et al.	8	49 ± 5	5 (63)	0 (0)	6 (75)	NS	NS	1 (13)	8 (100)
Mohsen et al.	30	53 ± 11	16 (53)	21 (70)	21 (70)	41 ± 18	NS	8 (27)	11 (37)
Schuller et al.	112	53 +/ - 11	63 (56)	NS	NS	45 +/ - 17	48 (43)	17 (15)	83 (74)
Takaya et al.	52	Definite CS (63 ± 13) Probable CS (57 ± 17)	27 (52)	47 (90)	NS	Definite CS (35 ± 17) Probable CS (37 ± 10)	30 (58)[b]	23 (44)	27 (52)

Abbreviations: AMD, arrhythmia-modifying drugs; AV, atrioventricular; CS, cardiac sarcoidosis; EF, ejection fraction; NYHA, new york heart association; ICD, implantable cardioverter-defibrillator; NS, not specified; PVS, programmed ventricular stimulation; VT, ventricular tachycardia.

a3 out of 13 patients with isolated CS.

bNYHA class III or IV only.

TABLE 4 Newcastle Ottawa scale quality assessment

NOS assessment points	Aizer et al.	Bandyopadhyay et al.	Betensky et al.
Selection: 1-Representativeness of the exposed cohort	☆(Truly representative)	☆(Truly representative)	☆(Truly representative)
2- Selection of the non- exposed cohort	☆ (drawn from the same community of the exposed cohort)	☆ (drawn from the same community of the exposed cohort)	☆ (drawn from the same community of the exposed cohort)
3- Ascertainment of exposure	☆ (Secure record)	☆(Secure record)	☆ (Secure record)
4- Demonstration that outcome of interest was not present at start of study	☆ (Yes)	☆ (Yes)	☆ (Yes)
Comparability of cohorts on the basis of the design or analysis controlled for confounders		☆ (The study controls for age, sex and comorbidities)	
Outcome: 1-Assessment of outcome	☆ (Record Linkage)	☆(Record Linkage)	☆ (Record Linkage)
2-Was follow-up long enough for outcomes to occur	☆ (Yes)	☆(Yes)	☆ (Yes)
3-Adequacy of follow-up of cohorts	☆(Complete follow up of all subjects accounted for)	☆(Complete follow up of all subjects accounted for)	☆(Complete follow up of all subjects accounted for)
Converting NOS to AHRQ standards	Poor quality	Good quality	Poor quality

Abbreviations: AF, atrial fibrillation; AHRQ, agency for healthcare research and quality; LVEF, left ventricular ejection fraction; NOS, newcastle ottawa scale; NSVT, non-sustained ventricular tachycardia; NYHA, new york heart association.

specified to be unique.[20,27] One study subcategorised participants based on use of radiofrequency ablation (RFA) with or without concurrent ICD versus ICD alone.[20] As it was not possible to delineate those in the RFA arm that had undergone device implant, only the latter cohort were included for the purposes of this analysis.

The criteria used to diagnosis CS for each included study is detailed in Table 1. All studies incorporated positive histological diagnosis from myocardial biopsy specimens for eligibility, with one mandating a confirmatory result from extra-cardiac tissue only.[27] In all studies, inclusion was also accepted without the need for biopsy positivity if there were imaging features, typically from cardiac MRI or CT-PET, consistent with the diagnosis. Two studies included application of the Japanese Ministry of Health and Welfare (JMHW) criteria,[22,26] whilst one applied A Case Control Etiologic Study of Sarcoidosis (ACCESS) criteria.[21]

Presence of systemic involvement in addition to CS was specified in all but two studies,[21,26] with the largest study demonstrating positivity in 94.5% (222/235) of ICD recipients.[23] Cardiac biopsy was not performed in the smallest study,[27] and details not specified in two others.[21,25] In the remainder, two studies had 100% positive predictive value (PPV) post-biopsy.[22,23] One of these included the largest study of 235 participants, of which five underwent cardiac biopsy with one diagnosis from autopsy and the other after orthotopic cardiac transplantation.[23] One study performed cardiac biopsy in 16.7% (5/30) with a positive result only in a single isolated case.[24]

696 participants were included in total across the eight studies, of which 530 underwent ICD implantation. All were transvenous systems via traditional access routes and one was subsequently upgraded to CRT. The largest study was from 2015 and collected data on 235 individuals post-ICD implant from 13 different institutions within the United States, Canada and India. Median follow-up period for the included studies ranged from 24 to 66 months (weighted average 40 months). An overview of study designs, inclusion parameters and diagnostic criteria is provided in Table 2.

3.3 | Participant characteristics

Mean age ranged from 40 to 63 years (weighted mean 53.9 years), with 39–100% being of male gender. The proportion of patients on arrhythmia-modifying drugs (AMDs) as defined by the Vaughan Williams classification ranged from 0 to 85% (weighted average 46.2%), though it was not consistently reported whether commencement was before or subsequent to ICD device. Class II AMDs (i.e. beta-blockers) were documented to be administered in four studies,[20,23,24,26] with proportions ranging from 25% (3/12) to 90% (47/52). Class III AMDs were utilised in four studies,[20,23,24,26] with sotalol most commonly utilised in all.

Steroid use at time of implant was reported in four studies,[21,22,25,26] with variability from 42 to 71%. Four studies highlighted concurrent steroid therapy at any timepoint pre-implant or during the follow-up period after device implantation,[21,23,24,27] with a range of 45–75%. Three studies detailed other immunosuppressive

Kron et al.	Mehta et al.	Mohsen et al.	Schuller et al.	Takaya et al.
☆(Truly representative)	☆(Truly representative)	☆(Truly representative)	☆(Truly representative)	☆(Truly representative)
☆ (drawn from the same community of the exposed cohort)	☆ (drawn from the same community of the exposed cohort)	☆ (drawn from the same community of the exposed cohort)	☆ (drawn from the same community of the exposed cohort)	☆ (drawn from the same community of the exposed cohort)
☆(Secure record)	☆ (Secure record)	☆ (Secure record)	☆ (Secure record)	☆ (Secure record)
☆ (Yes)	☆ (Yes)	☆ (Yes)	☆ (Yes)	☆ (Yes)
☆ (The study controls for age, sex and comorbidities)				☆ (The study controls for age, sex) ☆ (NYHA class, LVEF, Presence of NSVT, AF and QRS duration)
☆(Record Linkage)	☆ (Record Linkage)	☆ (Record Linkage)	☆ (Record Linkage)	☆ (Record Linkage)
☆(Yes)	☆ (Yes)	☆ (Yes)	☆ (Yes)	☆ (Yes)
☆(Complete follow up of all subjects accounted for)	☆(Complete follow up of all subjects accounted for)	☆(Complete follow up of all subjects accounted for)	☆(Complete follow up of all subjects accounted for)	☆(Complete follow up of all subjects accounted for)
Good quality	Poor quality	Poor quality	Poor quality	Good quality

therapies, with one specifying adjunct methotrexate[21] and the other utilisation of methotrexate, azathioprine and hydroxychloroquine.[23] Mean ejection fraction ranged from 33 to 45% (weighted mean 41.3%). 1–44% (weighted average 15.2%) had evidence of atrioventricular (AV) conduction disease at time of implant, with one study reporting five patients with complete heart block (CHB).[24] Primary prevention indication for ICD ranged from 33–100% (weighted average 61.3%). An overview of participant characteristics is provided in Table 3.

Two studies detailed results of EP testing. In one ($n = 15$), 6 had spontaneous, sustained VA on presentation with 6 demonstrating inducible VA during programmed ventricular stimulation (PVS).[20] In the remaining three instances, ICD implantation was offered due to sustained VT after EP testing, syncope with non-sustained VT during PVS and bradyarrhythmia warranting device with preference for ICD after EP consultation. The other study mandated induction of VAs during PVS for device implantation.[27]

3.4 | Quality assessment

Assessment of the quality of included studies as per the NOS is summarised in Table 4. All included studies had participants that were adequately selected and representative, with secure recording. Only three studies achieved good quality in the comparability domain.[21,23,26] All studies assessed outcomes appropriately via record linkage, with complete follow-up of all subjects and of sufficient duration to enable outcomes to occur. When converting to Agency for Healthcare Research and Quality (AHRQ) standards, five studies were considered of poor quality due to lack of comparability.[20,22,24,25,27]

3.5 | Adverse clinical outcomes

3.5.1 | Appropriate therapies

Table 5 provides a summary of adverse clinical outcomes. Out of 530 patients with CS that underwent transvenous ICD implantation, appropriate therapy was reported in all eight studies with overall incidence of 38.1% (207/530) during the follow-up period (weighted average 39.2 months). All studies aside from one provided full details of therapy classified by device indication,[27] with weighted average of 42.2% when implanted as primary prevention (range 22–63%) and 52.7% for secondary prevention (range 26–60%). In one study, patients who received primary prevention ICD had similar occurrence of ATP and/or shocks as those with implantation for secondary prevention.[22] However, a non-significant divergence in appropriate therapy was observed at 2 year follow-up with a trend towards increased burden in the secondary prevention cohort.

Left ventricular systolic dysfunction (LVSD) was observed to be a predictor of appropriate therapy in five studies, defined as EF

TABLE 5 Adverse clinical outcomes

Study ID	Number of participants with ICD (*n*)	Appropriate therapy (ATP or shock), *n*, (%)	Appropriate therapy - primary prevention, *n* (%)	Appropriate therapy - secondary prevention, *n* (%)	Inappropriate therapy, *n* (%)	All-cause mortality, *n* (%)
Aizer et al.	15	9 (60)	NS	NS	NS	1 (7)
Bandyopadhyay et al.	33	14 (42)	4/11 (36)	10/22 (45)	NS	3 (9)
Betensky et al.	45	17 (38)	8/29 (28)	9/16 (56)	7 (16)	1 (2)
Kron et al.	235	84 (40)	33/147 (22)	51/88 (58)	57 (24)	NS
Mehta et al.	8	4 (50)	4/8 (50)	NA	1 (13)	2 (25)
Mohsen et al.	30	11 (37)	6/11 (55)	5/19 (26)	9 (30)	3 (10)
Schuller et al.	112	36 (32)	23/83 (28)	13/29 (45)	13 (12)	6 (5)
Takaya et al.	52	32 (62)	17/27 (63)	15/25 (60)	4 (7)	NS

Abbreviations: ATP, anti-tachycardia pacing; ICD, implantable cardioverter-defibrillator; NA, not applicable; NS, not specified.

<40%[21,25,27] or <35%.[22,24] A separate study found no difference when stratified according to severity comparing LVEF <35% vs ≥35% (46% [6/13] vs 79% [11/14]; $p = 0.08$ on log-rank testing).[26] An isolated study found CHB as a predictor of appropriate therapy, with events in 47% (8/17) of those with CHB compared to 18% (5/28) without ($p = 0.048$).[22] This trend persisted in a subgroup analysis of patients with primary prevention devices ($p = 0.009$). Of note, VT detection cut-off rates did not differ between patients with and without CHB (183 vs 190 bpm; $p = 0.46$). Sustained VAs on PVS during EP testing were shown to be associated with appropriate therapy in one study ($n = 15$), with a hazard ratio of 4.47 (95% CI: 1.30–15.39).[20] In the subgroup of those without spontaneous, sustained VAs, PVS positivity remained a significant predictor ($p = 0.01$).

Two studies specifically explored non-predictors of appropriate therapy. In one study of 33 participants, this included extent of cardiac involvement on CT-PET and pre-procedure VA burden.[21] The other study found non-predictors to be age >60 years, New York Heart Association (NYHA) class III/IV, LVEF <35%, non-sustained VT, paroxysmal atrial fibrillation (AF), QRS interval >150 ms, QTc interval >470 ms and concurrent amiodarone therapy.[26]

3.5.2 | Inappropriate therapies

Occurrence of inappropriate therapy during the follow-up period was reported in all studies apart from two,[20,21] with a weighted average of 19.4% (range 0–63%). Two studies highlighted incidence due to either SVT, T wave over-sensing or lead noise but did not provide details of the split.[25,26] In one study of 45 patients, there were six discrete events of which five were due to SVT (mostly AF) and one due to lead fracture.[22] In another, incidence was 30% (9/30) and driven by atrial arrhythmia, with 3 cases due to SVT, 3 due to AF and 3 due to atrial tachycardia (AT) or sinus tachycardia.[24] In the largest study, occurrence was 24.3% (57/235) with the majority (30%, 17/57) deemed secondary to AF.[23]

3.5.3 | All-cause mortality

All-cause mortality was reported in six studies,[20–22,24,25,27] with weighted average of 6.0% over a median follow-up period of 42 months. The highest reported incidence was 25% (2/8), in the study with the lowest number of ICD participants but longest follow-up period at 66 months.[27] One occurred 18 months post-implant secondary to VT storm, with the other 2 months after implantation and of unknown aetiology. All patients in this study had an ICD implant for primary prevention indications. Two other studies provided further details regarding mode of death when reported.[20,24] Two events were deemed to be secondary to refractory CHF, with one case of secondary VT storm and multiple appropriate therapies despite AMD, steroids and cyclophosphamide. The other occurrence was resultant from septic shock and multi-organ failure precipitated by a complicated urinary tract infection.

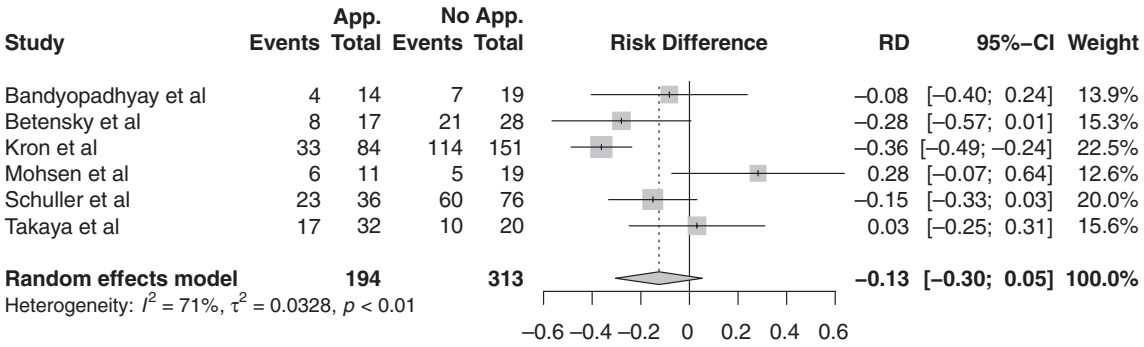

FIGURE 2 Appropriate therapies based on primary prevention indication

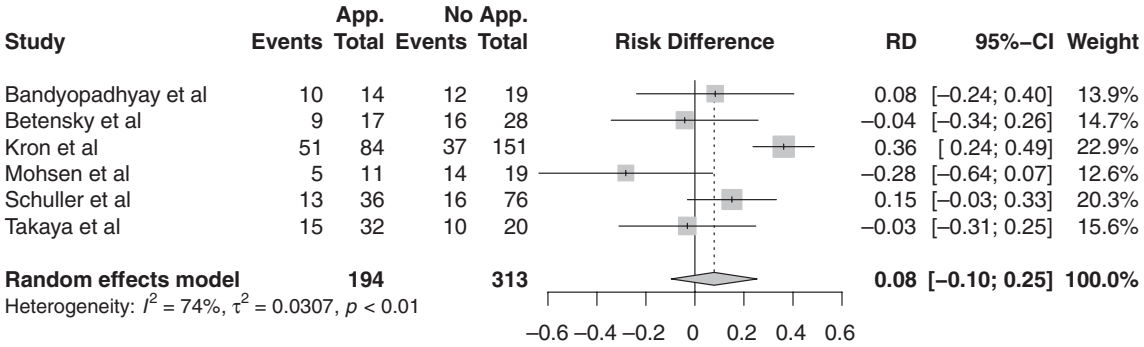

FIGURE 3 Appropriate therapies based on secondary prevention indication

3.5.4 | Subgroup analysis

Based on availability and reporting of data, a subgroup analysis was conducted in six out of eight studies that provided information on burden of appropriate therapies based upon device indication (see Figures 2 and 3).[21–26] There was no observed interaction, with risk difference of −0.13 (95% CI: −0.30 to 0.05;I^2 = 71%) if primary prevention indication and 0.08 (95% CI: −0.10 to 0.25; I^2 = 74%) if secondary prevention indication for ICD implant.

4 | DISCUSSION

This review examined 8 available studies comprising 688 patients with cardiac sarcoidosis, 530 of which had ICDs. All implants were transvenous as opposed to subcutaneous devices, although evidence of concurrent AV block at time of implant was variable (ranging from 1–44%). This is unsurprising given the inherent risk of progressive conduction disease in the context of CS due to propensity for involvement of the basal septum.[28] Weighted mean LVEF was 41%, providing a plausible explanation for de novo implants being ICD as opposed to CRT-D.

Two studies were performed at the same institution,[23,25] but of note, patient cohorts were unique and without overlap. There was some variability between studies in the criteria used to diagnose CS, though nearly all incorporated positive histological diagnosis from myocardial biopsy as part of the eligibility criteria. Due to predictable inter-study heterogeneity limiting external generalisability, meta-analysis was not performed. Nonetheless, quality assessment was conducted with use of the NOS deemed most appropriate in view of non-randomised study designs. The weighted follow-up period in this systematic review was 40 months, hence providing data on relatively long-term outcome measures.

Appropriate therapy occurred with an overall incidence of 39% during the follow-up period. This is comparatively higher than other non-ischaemic aetiologies such as dilated cardiomyopathy (DCM). For instance, one study found that incidence was 56% in patients with definite CS, 68% if suspected CS but only 32% in those with DCM.[26] The original indication for device therapy did not appear to be a significant risk modifier (42% if primary, 53% if secondary), and this finding is consistent with that derived from a recent meta-analysis.[29]

Notably, LVSD was observed to predict likelihood of appropriate therapy in five studies with three identifying this association when EF <40%. However, a retrospective study of registry data found significant risk of SCD with or without LVSD over a follow-up period of 2.8 years, albeit all had concomitant AV block at time of presentation.[30] Assessment for scar burden via late gadolinium enhancement (LGE) on cardiac MRI may be a more prudent strategy. In a multivariate analysis of 155 patients, LGE was shown to be the best independent predictor of potentially lethal events and superior to functional parameters including LVEF.[31] Those with CS without LGE did not experience VT or SCD during a follow-up period of 2.6 years, even when LVEF was significantly impaired. A separate meta-analysis of 7 studies incorporating 694 patients has shown 20-fold higher risk

of VAs and 11-fold higher risk of cardiovascular mortality in LGE-positive versus negative cohorts.[32] Indeed, LGE has also been shown to reliably predict adverse events in other types of cardiomyopathies including myocarditis and hypertrophic cardiomyopathy (HCM).[33]

The dominant substrate for dysrhythmia in CS arises from myocardial scarring secondary to granulomatous inflammation, with re-entry circuits implicated in genesis and localised to either ventricle in addition to any myocardial depth.[34] It may therefore be considered a reasonable strategy to explore de novo ICD implantation (with or without CRT) in all patients with traditional pacemaker indications irrespective of LVEF. Indeed, in a study of 22 patients with CS and high-grade AV block, 41% had sustained VT and 9% had aborted SCD over a median follow-up period of 45 months.[35] With regards to dysrhythmic risk, CS appears to behave differently from other cardiomyopathies due to its patchy ventricular involvement and fluctuant levels of active inflammation. Contemporary AHA/ACC/HRS guidelines reflect emerging cardiac MRI data and highlight the role of ICD implantation in patients with extensive myocardial scar even when LVEF is not significantly impaired (>35%). Unfortunately, individual studies within our review did not provide data on scar burden to enable meaningful conclusions to be reached.

Another implicated mechanism for VAs aside from scarring may relate to active myocardial inflammation as observed via FDG uptake on CT-PET. In such clinical contexts, immunosuppressive therapy is broadly recommended but its impact on propensity for dysrhythmias is not established. In a small study of 31 patients with non-sustained ventricular tachycardia (NSVT) and/or premature ventricular contractions (PVCs) with burden ≥300 per day, no differences were observed after a 6 month tapering regimen of prednisolone although late potentials on signal-averaged electrocardiography (ECG) were abolished in three cases.[36]

Data on immunosuppression in the context of CS-related cardiomyopathy is equally unclear. In a study of 47 patients, 66% (31/47) had initial objective improvement in LVEF by ≥10% but 49% (23/47) had a subsequent decline during median follow-up period of 44 months.[37] No differences were observed based on adjunct use of immunosuppressive agents. There are, however, case reports where therapy in patients with high-grade AV block and dual chamber pacemaker implantation has resulted in reverse remodelling and obviated the need for device upgrade to CRT.[38] Early therapy has also been shown to retard progression of LVSD and potentially prolong survival.[39] In a cohort of 32 patients with CS undergoing serial CT-PET and steroid treatment, cardiac inflammation and extent of LV involvement was significantly reduced irrespective of prednisolone dosing regimen (<40 vs ≥40 mg).[40] A prior systematic review has suggested potential benefit of steroid use in those with mild–moderate LVSD, though included studies were deemed of poor to fair quality.[41] In later stages with advanced ventricular dysfunction, steroids appear to be less effective in suppressing VAs and this is primarily attributable to irreversible myocardial fibrosis and adverse LV remodelling.[42] Unfortunately, steroid use at time of implant was only reported in four studies and with significant variability in administration regime that limits further interpretation.

In view of long-term sequelae relating to chronic steroid use, there is current interest in exploration of steroid-sparing agents including methotrexate, azathioprine and tumour necrosis factor (TNF)-α inhibitors. The Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM CS-RCT) is the first ever clinical trial in CS and designed to compare low-dose prednisolone/methotrexate combination with standard-dose prednisolone in CS who are treatment-naive, with results eagerly anticipated.[43]

One study within this review identified occurrence of sustained VAs during EP testing to be a predictor of appropriate therapies, even in the absence of spontaneous dysrhythmia.[20] This is consistent with other analyses in the literature. In a group of 25 patients, positive predictive value (PPV) of PVS for VAs was 100% over a follow-up period of 4.8 years.[44] A larger study included in our systematic review separately observed that 6 of 8 patients with inducible VAs had clinical arrhythmic events over a follow-up period of 5 years, in comparison with 1 of 69 patients without inducible VAs.[27] ACC/AHA/HRS guidelines stipulate ICD implantation as a Class IIa indication in CS patients with LVEF >35% but inducible VAs, whilst it is not specifically referenced in ESC guidance. Whether positive EP testing truly predicts risk of dysrhythmic events or is a surrogate for severity of decline in LVEF remains unclear with requirement for further research in this area.

All-cause mortality rate was observed to be 6.0% over our follow-up period, despite a relatively young cohort with mean age of 54 years. Results are consistent with the longest longitudinal study in patients with CS over 25 years ($n = 110$), although only half received an ICD.[45] During a median follow-up of 6.6 years, 9.1% succumbed to a cardiac cause, 10% underwent transplantation and another 10% suffered an aborted SCD. Kaplan–Meier estimates for transplantation-free survival at 10 years was 83%, which is broadly lower than occurrence in cohorts with ischaemic and non-ischaemic cardiomyopathies.[46,47] Unfortunately, no extensive details on mode of death were available in our review to inform our understanding of pathogenesis, though most events appeared to arise from refractory CHF or VT.

There are two other systematic reviews in the literature that have assessed outcomes in patients with CS after ICD implantation. One differs in only including five studies that exclusively reviewed factors associated with appropriate ICD therapies rather than generalised outcomes. As per our study, LVSD was found to be an independent predictor.[48] The other was a meta-analysis of 10 studies, but with less stringent inclusion criteria; notably, one was a conference paper and another solely reported modulators of inappropriate therapy.[29] Appropriate therapy was reported to be 39% with all-cause mortality of 8% over a mean follow-up period of 25 months, results that are broadly consistent with our analysis.

4.1 | Limitations

This systematic review has notable limitations. All included studies were retrospective and observational which carries the risk of

selection bias, though each reported clear inclusion criterion for CS diagnosis to mitigate this risk. There was study heterogeneity pertaining to participant characteristics, particularly with regards to timing, nature and specification of AMD regimen, although age, steroid use and baseline EF were broadly similar. No consistent details were available on baseline scar burden and concurrent biologic therapy which could both conceivably modulate occurrence of device therapies. Data was absent on device programming settings which are likely to be dependent upon manufacturer used and local provisions. Moreover, details on ICD lead position (i.e. apical or septal) were lacking which may theoretically have pro-arrhythmic tendency if placed at site of scar.

5 | CONCLUSION

LVSD with ejection fraction <40% appears to be a predictor of appropriate therapy in patients with CS after ICD implantation, which may act as a surrogate for scar burden. The utility of EP testing in this setting remains undefined. Large-scale, prospective trials are warranted to accurately define factors that modify occurrence of adverse outcomes in the context of CS.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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ORCID

Ahmed Taha https://orcid.org/0000-0001-7327-7260

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