

FACTORS ASSOCIATED WITH IMPLANTABLE CARDIOVERTER DEFIBRILLATORS APPROPRIATE THERAPY IN CARDIAC SARCOIDOSIS: A META-ANALYSIS

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ABSTRACT. *Background:* Patients with cardiac sarcoidosis (CS) are at increased risk of atrioventricular blocks, ventricular arrhythmias, and sudden cardiac death. *Objectives* We aimed to investigate the characteristics associated with appropriate therapy in implantable cardiac defibrillator (ICD) -implanted CS patients. *Methods:* We performed a PubMed and Web of Science search for studies reporting patients with CS who underwent an ICD implantation. The primary criterion was an appropriate therapy. *Results:* We screened 705 studies, of which 5 were included in the final analysis. We conducted a meta-analysis including 464 patients (mean age 55 years, 282 males (60%)). The mean follow-up was 3.5 years. Among the 464 patients, 180 received an appropriate therapy (39%). Patients who received an appropriate therapy were younger (-3.33, 95% confidence interval (CI) -6.42 to -0.23, $p=0.004$), were more likely to be male (OR 2.06, 95% CI 1.37-3.09, $p=0.0005$), had a lower left ventricular ejection fraction (LVEF) (-10.5, 95% CI -18.23 to -2.78, $p=0.008$), had a higher rate of complete heart block (OR 2.19, 95% CI 1.20 to 3.99, $p=0.01$), and more frequently had ventricular pacing (OR 6.44 95% CI 2.57 to 16.16, $p<0.0001$). *Conclusions:* Appropriate ICD therapy during CS is associated with young age, male sex, low LVEF, history of complete heart block, and ventricular pacing. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (1): 17-23)

KEY WORDS: cardiac sarcoidosis, sudden death, implantable cardioverter defibrillator, complete heart block, meta-analysis

Sarcoidosis is a multisystemic granulomatous disease of unknown cause that occurs in young adults (1). Clinical cardiac involvement occurs in 5% of patients with sarcoidosis (2). However, autopsy studies suggest that cardiac involvement might concern more than 25% of patients with sarcoidosis (3-5). Patients

with cardiac sarcoidosis (CS) are at increased risk for atrioventricular blocks, ventricular arrhythmias, and sudden cardiac death (6-8). Implantable cardioverter defibrillator (ICD) implantation is a high cost procedure and may lead to severe complications, especially in young patients who have been exposed to immunosuppressive drugs (9). Recent guidelines suggest that ICD implantation is recommended for patients with spontaneous sustained ventricular arrhythmias or left ventricular ejection fraction (LVEF) <35% (class I); can be useful for patients with an indication for permanent pacemaker implantation, unexplained syncope or inducible sustained ventricular arrhythmias (class IIa recommendation); and may be con-

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sidered for patients with LVEF 36% to 40%, right ventricular ejection fraction <49%, or both (class IIb recommendation).

However, the efficacy and safety of ICDs in CS is debated. The subpopulation that benefits the most from an ICD implantation remains unknown. Appropriate ICD therapies refer to shock or anti-tachycardia pacing for ventricular tachycardia (VT) or ventricular fibrillation (VF). Appropriate therapy has been investigated in nonischemic cardiomyopathy and is a reliable surrogate criterion for sudden cardiac death (10).

We conducted a meta-analysis to identify the factors associated with appropriate ICD therapy in patients with CS.

METHODS

Literature search

Two main investigators (L.-D.A. and F.C.-A.) searched MEDLINE (1966-July 2018) and Web of Science (1900-2018) for original articles without language restrictions. The search strategy combined free text search, advanced research, exploded MESH/EMTREE terms, and all synonyms of the following Medical Subject Headings terms: *sarcoidosis*, *CS*, *ICD*, *cardiac sudden death*, *VT*, *VF*, and *cardiac arrhythmias*. (The search strategy is detailed in Supplemental Table S1.) We also searched for additional articles from the reference lists of relevant papers obtained from the electronic search.

Selection criteria were determined before data collection. Inclusion criteria were as follows: (1) studies reporting on ICD (2) in patients with definite or suspected CS as defined in the Heart Rhythm Society (HRS) consensus statement in 2014 or the Japanese Ministry of Health and Welfare criteria (11) (3), in which patients who received an appropriate therapy were compared with patients who did not. Studies reporting reviews, case reports, editorials and guidelines were excluded. Studies reporting on CS patients with insufficient available information or nonextractable data were excluded. Whenever disagreement occurred, it was resolved by discussion between the 2 investigators and the advice of a third one (Z.A.) until a consensus was reached. A flow chart of reasons for rejection of citations identi-

fied from the searches was performed and is shown in Figure 1.

Data extraction

The data were simultaneously and independently extracted by 2 investigators (L.-D.A. and F.C.-A.). For each study, the recorded information included the number of patients, inclusion criteria, CS diagnosis criteria, definition of appropriate therapy, number of patients in the appropriate therapy group, age, sex, LVEF, history of syncope or complete heart block (CHB), left or right bundle branch block (LBBB or RBBB), ventricular pacing, cardiac magnetic resonance imaging (MRI) results, and mean follow-up.

Risk of bias assessment

A subjective assessment of the methodological quality of the observational studies was evaluated by two investigators using the Newcastle-Ottawa Scale (NOS) (12), which is a quality assessment tool for nonrandomized studies. NOS uses a “star system” based on three major perspectives: the selection of the study groups (0 to 4 stars), the comparability of the groups by controlling for important and additional relevant factors (0 to 2 stars), and the ascertainment of outcome of interest or exposure (0 to 3 stars). A total score of 3 or less indicates poor quality, 4-6 indicates moderate quality, and 7-9 indicates high quality. We also used the thresholds for converting the NOS to the Agency for Healthcare Research and Quality (AHRQ) standards. Discrepant opinions between the investigators were resolved by consensus.

Data analysis

As previously indicated, appropriate therapy referred to shock or antitachycardia pacing for VT or VF. Percentages were assessed for dichotomous variables; means and standard deviations were assessed for continuous variables. We compared the characteristics of the patients in the “appropriate therapy” group versus the “no appropriate therapy” group. All included articles were analyzed using Cochrane Collaboration Review Manager statistical software (version 5.3; Cochrane Collaboration, Oxford, UK). The I^2 statistic was used to measure consistency. The

fixed-model effect was used, and a random-effects model was used whenever I^2 exceeded 0% (suggesting a mild, moderate or important heterogeneity). A $p < 0.05$ was considered significant. A Mantel-Haenszel test was used for dichotomous variables, and an inverse variance test was used for continuous variables. Odds ratio were estimated for dichotomous variables comparisons. The PRISMA checklist is detailed in Supplemental Figure S1.

RESULTS

We extracted 705 articles. According to the selection criteria, 68 articles were assessed for eligibility (Figure 1). The main reason that studies were excluded was the type of articles; many of them were case reports. Five retrospective cohorts, published between 2011 and 2018, were included in the final analysis (13-17). The main results of these studies are detailed in Table 1. These 5 studies were categorized as poor or fair quality studies, according to the NOS or AHRQ tools, respectively.

A total of 464 participants were included. Across the 5 studies, the mean age was 55 years (11.6). Among these 464 patients, 282 (60%) were male. The estimated mean follow-up was 3.5 years. One hundred and eighty patients (39%) received an appropriate therapy.

Five factors were significantly associated with receiving an appropriate therapy among the cardiac sarcoidosis patients who were implanted with an ICD: age, sex, LVEF, CHB, and ventricular pacing. These results are shown in Figure 2.

Patients who received an appropriate therapy were younger (- 3.33, 95% Confidence interval (CI) -6.42 to -0.23, $p=0.004$, $I^2=41\%$), more frequently male (OR 2.06, 95% CI 1.37 to 3.09, $p=0.0005$, $I^2=0\%$), and had a lower LVEF (-10.5, 95% CI -18.23 to -2.78, $p=0.008$, $I^2=85\%$). For LVEF, patients of the appropriate therapy group had a mean LVEF of 36.1% (14.8) versus 47.5% (14.4) in the no appropriate therapy group. Mean age in the appropriate therapy group was 53.9 years (11.8) versus 56 years (11.0) in the no appropriate therapy group.

For age: AT group 53.9 years (11.8); NAT group 56 years (11.0)

Three studies mentioned the presence of CHB, and the patients who received an appropriate therapy had a significant higher rate of CHB (OR 2.19, 95% CI 1.2 to 3.99, $p=0.01$, $I^2=0\%$) (13-15). Two studies mentioned the presence of ventricular pacing (14, 15). Patients who received an appropriate therapy were significantly more frequently paced (OR 6.44 95% CI 2.57 to 16.16, $p < 0.0001$, $I^2=0\%$).

Conversely, LBBB, RBBB, positive CMR, syncope were not associated with receiving an appropriate therapy. The data included in such analyses were

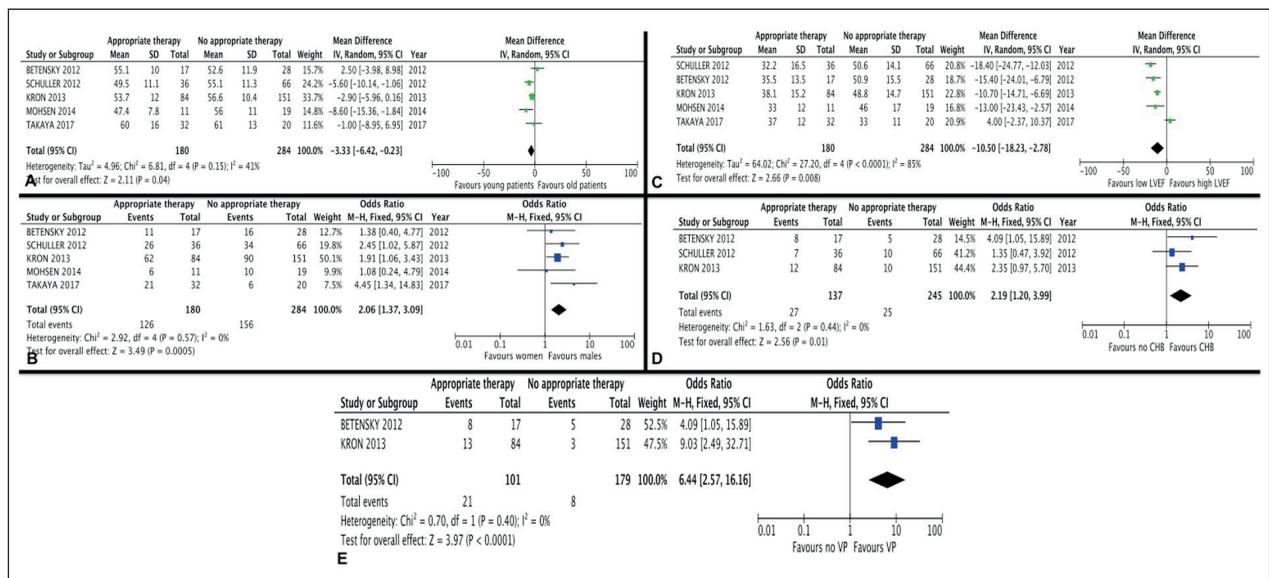


Fig. 1. Flow diagram of the assessment of studies identified in the meta-analysis

Table 1. Characteristics of the design and population in the 5 studies included in the meta-analysis

Ref	Schuller (2012)	Betensky (2012)	Kron (2013)	Mohsen (2014)	Takaya (2017)
n*	102	45	235	30	52 (27 definite CS, 25 suspected CS)
Design	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort
Inclusion criteria	CS receiving an ICD	CS receiving an ICD	CS receiving an ICD	CS receiving an ICD	CS receiving an ICD
Exclusion criteria	-	Coronary heart disease More plausible explanation for their heart disease	-	-	-
Cardiac sarcoidosis definition	Modification of the JMHW	JMHW or extra-cardiac sarcoidosis associated with a positive CMR, PET imaging, heart biopsy or explant pathology	Biopsy-proven CS or suggestive CMR or extracardiac sarcoidosis and a presumptive cardiac involvement	Biopsy proven CS or biopsy proven extra-cardiac sarcoidosis associated with 2 or more of the following criteria: clinical abnormality, low LVEF, suggestive CMR, suggestive ECG or EPS, suggestive PET scan	Definite CS or suspected CS according to the JMHW
Age (years) mean (SD)	53.1 (11.2)	53.5 (11.2)	55.6 (11.1)	53 (11)	60.1 (15.1) Definite CS 63 (13) Suspected CS 57 (17)
Male, n (%)	60 (59%)	27 (60%)	152 (65%)	16 (53%)	27 (52%)
LVEF (%) mean (SD)	44.1 (15)	45.4 (16.4)	45 (15.7)	41 (18)	36 (12) Definite CS 35 (14) Suspected CS 37 (10)
Syncope, n (%)	NA	NA	68 (29%)	16 (53%)	NA
RBBB, n (%)	30 (29%)	6 (13%)	63 (28%)	NA	NA
LBBB, n (%)	NA	3 (7%)	NA	NA	NA
Ventricular pacing	NA	13 (29%)	16 (7%)	NA	NA
Positive CMR definition	-	Focal or diffuse areas of delayed gadolinium enhancement occurrence in a distribution inconsistent with scar due to prior infarction	Delayed contrast enhancement, wall motion abnormalities, LV dysfunction, chamber dilation	Patchy late gadolinium enhancement of the mid- myocardium and/or epicardium	-
Positive CMR	NA	4 (9%)	99 (86%)	8 (27%)	NA
Primary prevention	NA	29 (64%)	147 (63%)	11 (37%)	27 (52%)
Follow-up from ICD implantation (years) mean (SD)	2.4	2.6 (2.7)	4.2 (4.0)	3.8 (4.0)	NA (Median: 2)

(continued on next page)

Table 1. Characteristics of the design and population in the 5 studies included in the meta-analysis

Appropriate therapy definition	ATP or shocks for VT or VF	1 or more ATP or shock for sustained monomorphic or polymorphic VT or VF; electrical storms were tabulated as a single "event"	ATP or shocks (for VT or VF)	ATP or shocks	ATP or shocks for ventricular tachyarrhythmias
Appropriate therapy					
Yes	36 (35%)	17 (38%)	84 (36%)	11 (37%)	32 (61%)
No	66 (65%)	28 (62%)	151 (64%)	19 (63%)	20 (39%)
NOS (stars)	Selection: 3 Comparability: 2 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2
Quality assessment	Fair quality	Fair quality	Fair quality	Fair quality	Fair quality
AHRQ standards	Poor quality	Poor quality	Poor quality	Poor quality	Poor quality

* number of patients included in the study

CS cardiac sarcoidosis; EPS electrophysiologic study; JMHW Japanese Ministry of Health and Welfare; ATP Antitachycardia pacing; VT Ventricular tachycardia; VF Ventricular fibrillation; AHRQ Agency for Healthcare Research and Quality; CMR Cardiac magnetic resonance; LVEF Left ventricular ejection fraction

NA Not available; ECG Electrocardiogram; RBBB Right bundle branch block; LBBB Left bundle branch block; ICD Implantable cardioverter-defibrillator; PET Positron emission tomography; NOS Newcastle-Ottawa Scale

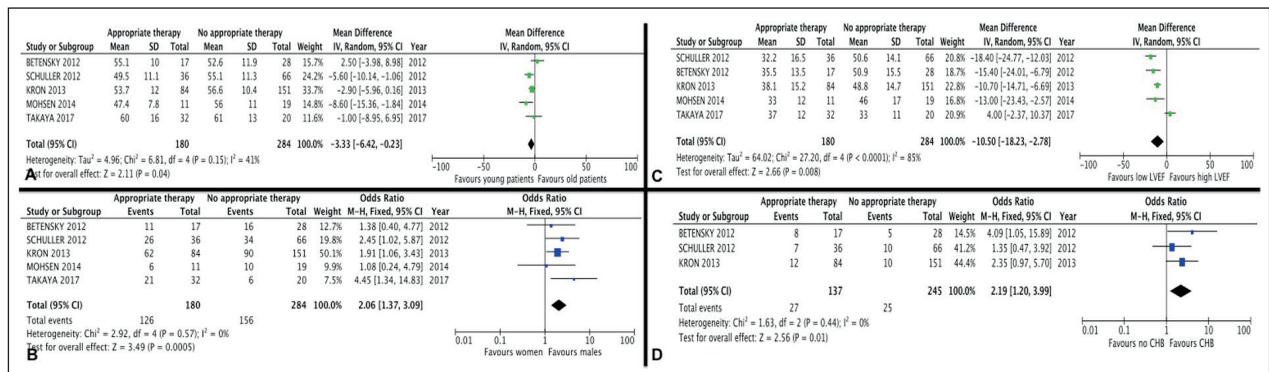


Fig. 2. Forest plot of trials that analyzed appropriate versus no appropriate therapy in patients with cardiac sarcoidosis and an implantable cardioverter defibrillator. Impact of age (A), sex (B), left ventricular ejection fraction (LVEF) (C), complete heart block (CHB) (D), and ventricular pacing (E)

obtained from 2 or 3 articles (Supplemental Figure 2).

Finally, receiving an appropriate therapy was not associated with being implanted with an ICD for secondary prevention. Four studies were included in this analysis (14–17). This result is probably explained by a marked heterogeneity ($I^2=80\%$).

DISCUSSION

Based on the results of 5 retrospective cohorts, this meta-analysis suggests that patients with cardiac sarcoidosis who were implanted with an ICD and received an appropriate therapy are more likely to be young males with a low LVEF, ventricular pacing, and a history of CHB.

In our meta-analysis, we found a higher rate (39%) of appropriate therapy than in previous studies reporting on other heart disease, such as ischemic heart disease or dilated cardiomyopathy, suggesting that patients with cardiac sarcoidosis are at high risk for arrhythmias. For example, 13.4% of patients received appropriate therapy after 1.9 years of follow up in a cohort of patients with ischemic heart disease and low LVEF (18). In a cohort of patients with low LVEF who had been implanted for primary prevention of cardiac sudden death, 18% had appropriate therapy during a 35-month follow up (19).

In this meta-analysis, we used appropriate therapy as the primary criterion. Appropriate shock has been investigated as a surrogate marker for sudden cardiac death in nonischemic cardiomyopathy in a randomized controlled trial including 458 patients. This study suggested that a 2:1 ratio was relevant for defining appropriate therapy as a surrogate for sudden cardiac death (10).

In addition to a LVEF <35% and spontaneous sustained ventricular arrhythmias, specific indications for ICD implantation in CS are not supported with a high level of evidence. HRS guidelines suggest an ICD implantation in patients with LVEF <35% (class I recommendation) or an LVEF between 36 and 49% or right ventricular ejection fraction (RVEF) <40% (class IIb recommendation). The impact of LVEF on the incidence of ventricular arrhythmias was recently investigated in CS (20). In this study, echocardiography recorded a LVEF <40% in 30 of 62 patients (48.4%); in the univariate analysis, these patients experienced worse survival compared with those patients with LVEF \geq 40% ($p=0.017$). No patient with an LVEF between 41 and 50% died or had a transplant. All the studies included in our meta-analysis reported a mean LVEF lower than 40% (32–38%) in the “appropriate therapy” group, whereas all of the LVEF means in the “no appropriate therapy” group were 46–51% (except the series by Takaya, which reports a mean LVEF of 33% in the “no appropriate therapy” group), supporting the finding that LVEF is a main determinant of arrhythmia occurrence.

Cardiac sarcoidosis is a class IIa (level of evidence C) recommendation for an ICD when a pacemaker implantation is required (high-degree atrioventricular block). We found that patients who received an appropriate therapy were more likely to have CHB. These results are consistent with recent

data: in a recent study, a high rate of ventricular arrhythmias and sudden cardiac death was found in patients with CS presenting with Mobitz II or CHB (21). The 5-year incidence of sudden cardiac death was 9% in the high atrioventricular block group (no VT and LVEF >50%), 14% if atrioventricular block was associated with an altered LVEF (between 35 and 50%), and up to 34% in the subgroup with VT or severe left ventricular dysfunction (<35%).

Our study has several limitations. First, the quality of all selected studies was poor to fair according to the NOS. All five were retrospective studies. Some patients were included in several studies: we could not determine which patients were included twice because it was not possible to obtain individual data. Thus, this could represent a substantial bias. However, cardiac sarcoidosis is rare and evidence level is low for its management. Thus, despite this bias, the results of this meta-analysis could help supporting low-grade recommendations (11). In this meta-analysis, we did not use data from randomized or controlled trials, because they were not available. Only retrospective studies were available. The primary endpoint was a surrogate marker of sudden cardiac death. Finally, 17 studies were excluded because the data could not be properly extracted.

Patients with CS are at high risk for sudden cardiac death, and ICD implantation should be considered in selected patients. In this meta-analysis, we identified 5 factors associated with appropriate ICD therapy in CS: age, male sex, LVEF, CHB, and ventricular pacing. These results suggest that in CS patients, low LVEF and a history of CHB should indicate ICD implantation, especially in young male patients. Ventricular pacing in a patient who was previously implanted with a pacemaker might be an indication for an ICD upgrade or subcutaneous ICD implantation.

Authors contributions

L.-D.A., X.W., and F.C.-A. designed the study; L.-D.A., X.W., and F.C.-A. collected the data; L.D.-A. and F.C.A. conducted the statistical analysis; L.-D.A., X.W., J.H., Z.A., and F.C.-A. analyzed and interpreted the data; L.-D.A. and F.C.-A. wrote the manuscript.

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