HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis

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KEYWORDS Sarcoidosis; Heart block; Ventricular tachycardia; Catheter ablation; Immunosuppression; Implantable cardioverter-defibrillator; Atrial arrhythmias; Risk stratification

ABBREVIATIONS **AF** = atrial fibrillation; **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **AV**=atrioventricular; **CS**=cardiac sarcoidosis; **EMB** = endomyocardial biopsy; **ICD** = implantable cardioverter-defibrillator; **PES**=programmed electrical stimulation; **SVT** = supraventricular tachycardia; **VF** = ventricular fibrillation; **VT**=ventricular tachycardia (Heart Rhythm 2014;11:1304–1323)

Developed in collaboration with and endorsed by the World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG), the American College of Cardiology (ACC), the American College of Chest Physicians (ACCP), the American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the European Heart Rhythm Association (EHRA). **Address correspondence:** David H. Birnie and William H. Sauer. E-mail address: dbirnie@ottawaheart.ca; William.Sauer@ucdenver.edu.

1. Introduction

This international expert consensus statement was written by experts in the field who were chosen by the Heart Rhythm Society in collaboration with representatives from the American College of Cardiology, American College of Chest Physicians, American Heart Association, Asia Pacific Heart Rhythm Society, European Heart Rhythm Association, and World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG).

The goals of this document are as follows:

1. Establish working criteria for the diagnosis of cardiac sarcoidosis (CS) on the basis of expert opinion and the limited available data.
2. Provide guidance and recommendations to physicians treating extracardiac sarcoidosis on appropriate screening for possible cardiac involvement.
3. Provide guidance and recommendations to cardiologists and cardiac electrophysiologists on the management of specific arrhythmias associated with CS.

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4. Provide guidance and recommendations for risk stratification for sudden cardiac death.
5. Provide guidance and recommendations to cardiac electrophysiologists on appropriate indications for implantable cardioverter-defibrillator (ICD) implantation.
6. Identify key areas in which data are lacking to help guide future collaborative research efforts.

Developing consensus recommendations for rare diseases requires adapting the methodology for preparing traditional guidelines for clinical practice. The most obvious difference with rare diseases is that there are no randomized and/or blinded studies in the field. Therefore, the available data are derived from case series and registries that have followed patients and recorded outcome information. Thus, all consensus recommendations are level of evidence C (i.e., based on experts' opinions) based on the American College of Cardiology (ACC)/American Heart Association's (AHA) Classification of Recommendation and Level of Evidence grading scheme. The consensus recommendations in this document use ACC/AHA class I, IIa, IIb, and III classifications and the corresponding language: "is recommended" for a class I consensus recommendation; "can be useful" for a class IIa consensus recommendation; "may be considered" to signify a class IIb consensus recommendation; and "should not" or "is not recommended" for a class III consensus recommendation (failure to provide any additional benefit and may be harmful). Patients with CS can develop heart failure; however, the writing group felt that the management of this aspect of CS was beyond the scope of the current document.

It should be noted that although the ACC/AHA classification system was used, we did not otherwise follow their process for guideline development. The recommendations in this document are based on the consensus of the writing group following the Heart Rhythm Society's process for establishing consensus-based guidance for clinical care. Consensus does not mean unanimous agreement among all writing group members, nor does consensus imply sufficient evidenced-based data to confirm our opinions. We identified the aspects of patient care for which a true consensus could be found. To this end, we carried out surveys of the entire writing group. The authors predefined the threshold for agreement as a vote of more than 75% on all recommendations. When using or considering the guidance given in this document, it is important to remember that there are no absolutes with regard to many clinical situations. The ultimate judgment regarding care of a particular patient must be made by the health care provider and the patient in light of the individual circumstances presented by that patient.

A bibliography was created at the outset of the document with the following search terms of "sarcoidosis" "cardiac sarcoidosis" and "sarcoidosis related arrhythmias." Members of the writing group screened these relevant manuscripts for inclusion in discussions. All members of the writing group voted on all recommendations. Each section had writing groups (three to five members) who completed the initial drafts. The group assignments were based on individual interests and expertise. The co-chairs contributed equally to directing the writing group. All members of this writing group provided disclosure statements of all relationships that might present real or perceived conflicts of interest. Disclosures for all members of the writing group and peer reviewers are shown in Appendix 1.

2. Background

Sarcoidosis is a granulomatous disease of unknown etiology. Noncaseating granulomas are the pathological hallmark and are most often associated with pulmonary involvement but may also involve the heart, liver, peripheral lymph node, spleen, skin, eyes, phalangeal bones, parotid gland, or other organs and tissues. Recent studies suggest that the disease may be an immunological response to an unidentified antigenic trigger.[1,2] Sarcoidosis is a worldwide disease, with a prevalence of about 4.7–64 in 100,000; the highest rates are reported in northern European and African American individuals, particularly in women.[3,4] The annual incidence of sarcoidosis in the United States has been estimated at 10.9 per 100,000 in whites and 35.5 per 100,000 in African Americans.[2] Most disease (70%) occurs in patients aged 25–45 years; however, in Europe and Japan, there is a second peak in women older than 50 years.[3,4] Sarcoidosis is rare in people younger than 15 or older than 70 years.[5] It is challenging to diagnose, and there is no easy way to assess disease activity or severity.[6] Although CS is a known inflammatory disease and despite >50 years of the use of corticosteroids for treatment, there is no proof of survival benefit from this treatment.[7] There are also conflicting data on the efficacy of corticosteroids on long-term disease outcomes.[7–10]

Studies have suggested that symptomatic cardiac involvement occurs in perhaps 5% of the patients with pulmonary/systemic sarcoidosis. Clinical manifestations of CS are dependent on the location, extent, and activity of the disease.[11,12] The three principal sequelae of CS are (1) conduction abnormalities,[13–18] (2) ventricular arrhythmias,[19] and (3) heart failure.[12] Other data indicate that many patients with pulmonary/systemic sarcoidosis have asymptomatic cardiac involvement. For example, autopsy studies have estimated the prevalence of cardiac involvement to be at least 25% of the patients with sarcoidosis in North America.[20–22] Imaging studies have found asymptomatic cardiac involvement in 3.7%–54.9% of the patients with extracardiac sarcoidosis (see Table 1 for summary).[17,23–26]

Table 1 Prevalence of asymptomatic CS in patients with extracardiac sarcoidosis

Study	N	% of patients with asymptomatic CS	Test
2013[31]	155	25.5	LGE-CMR
2011[32]	152	19	LGE-CMR
2009[24]	81	25.9	LGE-CMR
2008[25]	62	38.7	PET/LGE-CMR
2005[17]	82	3.7	Mostly CMR, but only a few with LGE-CMR
2003[26]	50	14.0	Various
2002[23]	31	54.9	CMR

CS = cardiac sarcoidosis; LGE-CMR = late gadolinium–enhanced cardiovascular magnetic resonance; PET = positron emission tomography.

The wide range of prevalence data is likely related to a variety of factors, including patient selection as well as imaging techniques and protocols.

Patients with CS have a poorer prognosis than do patients without cardiac involvement.[27] In Japan, CS is reported to be responsible for as many as 85% of deaths from sarcoidosis.[28] Cardiac death is due to either heart failure or sudden cardiac death. A systematic review of mortality data in patients with clinically manifest CS was recently published.[29] The extent of left ventricular (LV) dysfunction seems to be the most important predictor of survival.[29] For example, Yazaki et al[18] reported that 89% of the patients with normal left ventricular ejection fraction (LVEF) were alive at 10 years; patients with reduced LVEF had a 10-year survival rate of 27%. Similarly, Chiu et al[30] found that all patients with normal LVEF were alive at 10 years; in patients with severe dysfunction (LVEF $<30\%$), the survival rate was 91% after 1 year, 57% after 5 years, and 19% after 10 years. However, it should be noted that these data were published in 2001[18] and 2005;[30] contemporary outcomes are likely to be better with modern heart failure therapies and broader use of ICDs for sudden cardiac death prevention. In contrast to patients with symptomatic CS and reduced LVEF, most data in the literature suggest that patients with asymptomatic CS and normal LV function have a relatively benign course.[17,23,25,26] However, more recent data have challenged this suggestion.[24,31]

Expert Consensus Recommendations on ***Criteria for the Diagnosis of CS***

There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. Histological Diagnosis from Myocardial Tissue
   CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).
2. Clinical Diagnosis from Invasive and Non-Invasive Studies:
   It is probable* that there is CS if:
   a) There is a histological diagnosis of extra-cardiac sarcoidosis
   and
   b) One or more of following is present
      - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
      - Unexplained reduced LVEF ($<40\%$)
      - Unexplained sustained (spontaneous or induced) VT
      - Mobitz type II 2nd degree heart block or 3rd degree heart block
      - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
      - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
      - Positive gallium uptake (in a pattern consistent with CS)
   and
   c) Other causes for the cardiac manifestation(s) have been reasonably excluded

*In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.[33]

3. Diagnosis of Cardiac Sarcoidosis

There are no currently accepted international guidelines for the diagnosis of CS. However, there are two proposed diagnostic guidelines. One is the Japanese Ministry of Health and Welfare's set of criteria. These were originally published in 1993[34] and then modified in 2007.[35] Imaging modalities suggested by the modified criteria include gallium-67 scintigraphy and late gadolinium-enhanced cardiovascular magnetic resonance (LGE-CMR).[35] It should be noted that the revised 2006 criteria did not mandate positive biopsies (either cardiac or extracardiac) for the diagnosis of CS. The second proposed diagnostic guideline is the National Institutes of Health's A Case Control Etiology of Sarcoidosis Study set of criteria published in 1999[36] and updated in 2014[33] by the WASOG.

The only absolute test for organ involvement in sarcoidosis is histological examination of tissue for the presence of granulomatous inflammation (and exclusion of other known causes of granuloma).[37] However, clinical features can suggest that an organ is involved even in the absence of an organ-specific biopsy if (1) sarcoidosis has already been demonstrated histologically in another organ and (2) other causes for the clinical manifestation have been reasonably excluded. The WASOG organ assessment instrument[33] used this premise to define three categories of the likelihood of organ involvement: highly probable, $>90\%$ likelihood of organ involvement; probable, 50%–90% likelihood of organ involvement; possible, $<50\%$ likelihood of organ involvement. For each organ, the WASOG assembled working groups of experts and these groups reached consensus on clinical criteria for the diagnosis of specific organ involvement. We wished to align this document closely with the WASOG publication. Indeed, the chair of the WASOG document was a member of this writing group (M.A.J.). We were able to agree with the WASOG document in terms of the likelihood of cardiac sarcoidosis being "probable" on all but one criterion. Their document included an eighth criteria, "defect on perfusion scintigraphy or SPECT scan."[33] The members of the writing group were presented with both options, that is, with and without the eighth criteria, and the majority voted in favor of excluding it.

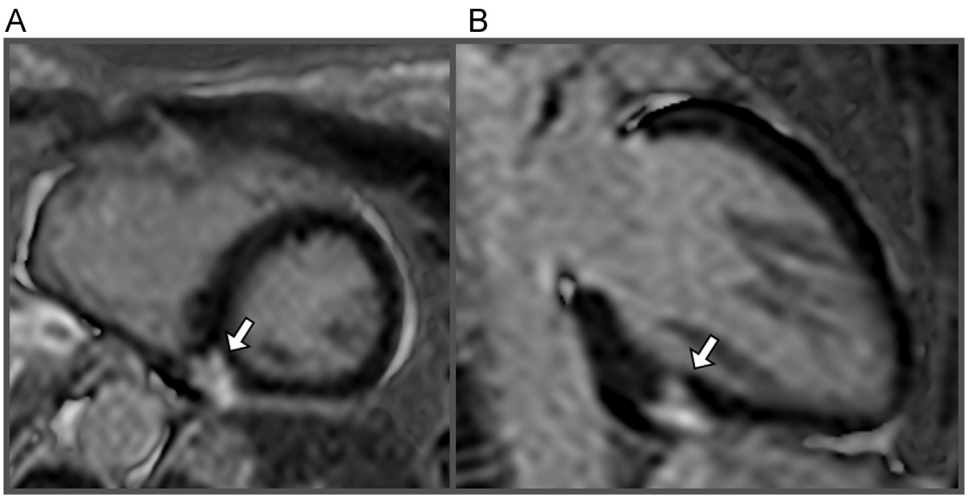


Figure 1 Late gadolinium-enhanced cardiovascular magnetic resonance images of a left ventricular short-axis slice (**A**) and a left ventricular two-chamber view (**B**). The arrows point to two different views of a small region of late gadolinium enhancement. Courtesy of Amit R. Patel, University of Chicago, reproduced with permission from Patel et al[32].

Role of CMR in the Diagnosis of CS

There is no specific pattern of LGE that is pathognomonic for CS; therefore, images must be interpreted in the context of the patient's history and by a cardiologist or radiologist with specific expertise. The most commonly described pattern is one or more patchy regions of LGE (see Figure 1) that would be atypical for myocardial infarction (i.e., sparing the endocardial border and not in the distribution of prior myocardial infarction)[38,39]; however, many other patterns of LGE and even a pattern that is typical for prior myocardial infarction can also represent CS.[24]

Role of ^{18}F-Fluorodeoxyglucose–Positron Emission Tomography Imaging in the Diagnosis of CS

^{18}F-Fluorodeoxyglucose (FDG) is a glucose analogue that is useful for differentiating between normal and active inflammatory lesions where the activated macrophages show a higher metabolic rate and glucose utilization.[40] While no individual clinical finding is pathognomonic for the diagnosis, FDG-PET has gained interest in functional imaging of inflammatory disease activity to assess fibrogranulomatous disease in the myocardium. There are three basic patterns of FDG-PET uptake that are typically described in patients with CS: diffuse, focal, and focal on diffuse. CS is most typically associated with focal FDG uptake either in isolation or on a background of mild diffuse uptake with or without resting perfusion defects and wall motion abnormalities.[41–43] Concomitant use of PET perfusion tracers can help exclude significant obstructive coronary artery disease. In addition, FDG-PET may be able to identify ongoing active inflammation and thus potentially detect reversible stages of CS (see Figure 2 for an example).[43] However, as with CMR, image interpretation can be challenging and must be made in the appropriate clinical context by a specialist with specific expertise.

Expert Consensus Recommendations on Screening for Cardiac Involvement in Patients With Biopsy-Proven Extracardiac Sarcoidosis

Class I	1. It **is recommended** that patients with biopsy-proven extracardiac sarcoidosis **should be** asked about unexplained syncope/presyncope/significant palpitations*
	2. It **is recommended** that patients with biopsy-proven extracardiac sarcoidosis **should be** screened for cardiac involvement with a 12-lead electrocardiogram (ECG).
Class IIa	1. Screening for cardiac involvement with an echocardiogram **can be useful** in patients with biopsy-proven extracardiac sarcoidosis.
	2. Advanced cardiac imaging, CMR or FDG-PET, at a center with experience in CS imaging protocols **can be useful** in patients with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.
Class III	1. Advanced cardiac imaging, CMR or FDG-PET, **is not recommended** for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.

*Palpitations were defined as "a prominent patient complaint lasting >2 weeks."[25]

Role of Endomyocardial Biopsy (EMB) in the Diagnosis of Cardiac Sarcoidosis

In patients with extra-cardiac sarcoidosis, lymph node or lung biopsy is typically targeted first due to the higher diagnostic yield and lower procedural risk. In cases of isolated CS or negative extra-cardiac biopsy, EMB may be required to confirm the diagnosis. However, EMB has low sensitivity due to the focal nature of the disease, revealing non-caseating granulomas in less than 25% of patients with CS.[44,45] To increase the sensitivity of the procedure, electrophysiological

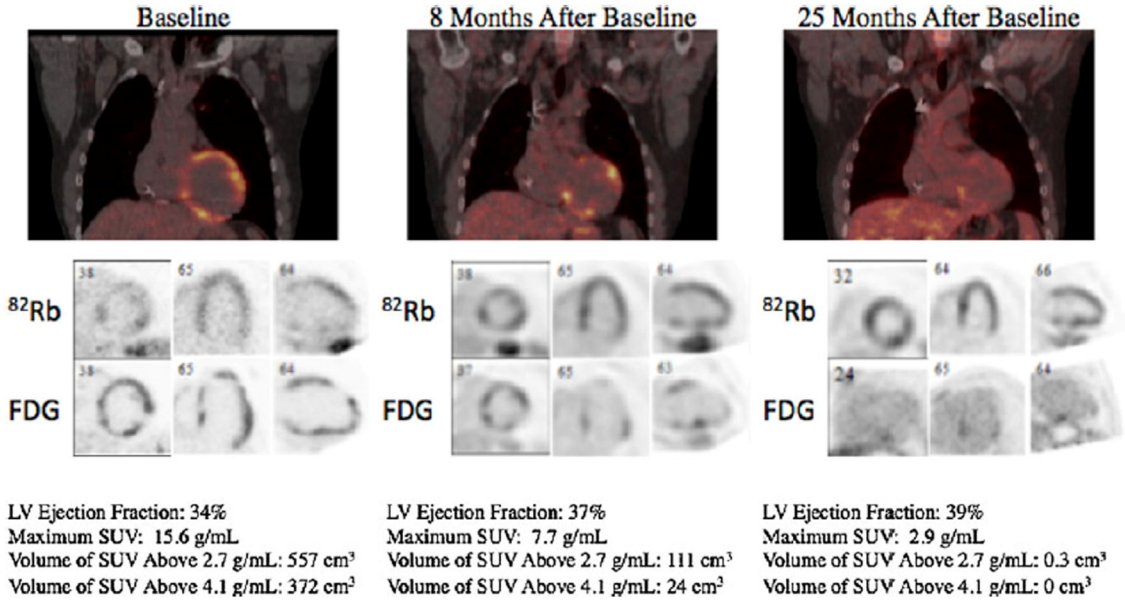


Figure 2 Serial FDG-PET examinations showing change in inflammation. The results of the three serial studies performed over a mean follow-up period of 25 months on a 46-year-old man treated with corticosteroids are shown. The color maps demonstrate the intensity of FDG uptake in a coronal view. FDG-PET = ^{18}F-fluorodeoxyglucose–positron emission tomography. Modified with permission from Osborne et al[99].

(electroanatomic mapping, see Figure 5)[46] or image-guided (PET or CMR)[47] biopsy procedures have been described. It is the opinion of the writing group that physicians should consider using electroanatomic map or image guidance for EMB and this is consistent with other guidelines.[48]

4. Screening for Cardiac Sarcoidosis

4.1. Screening for Cardiac Involvement in Patients With Biopsy-Proven Extracardiac Sarcoidosis

There are few data comparing the sensitivity and specificity of various screening tests for cardiac involvement in patients with sarcoidosis. Mehta et al[25] studied 62 patients with sarcoidosis. Those with symptoms (significant palpitations syncope, or presyncope) or abnormal results (ECG, Holter monitoring, and echocardiography, see Table 4 for definitions of abnormalities) were studied by CMR or FDG-PET scanning. The diagnosis of CS was based on abnormalities detected by PET or CMR. Patients with CS had more cardiac symptoms than those without CS (46% vs. 5%) and were more likely to have abnormal Holter monitor findings (50% vs. 3%) and transthoracic echocardiographic findings (25% vs. 5%).[25] The sensitivity and specificity of symptoms and individual tests and combinations of variables are listed in Table 2. It should be noted that the presence of one abnormal screening variable had a sensitivity of 100% and a specificity of 87% for the diagnosis of CS.[25] These data are limited by the small sample size, possible referral bias, and the use of a single imaging test (CMR or PET) to "diagnose" CS. However, this report is the most comprehensive one published to date. A second study had similar results using an assigned scoring system.[49]

On the basis of these data and the clinical experience of the writing group, we make specific recommendations and

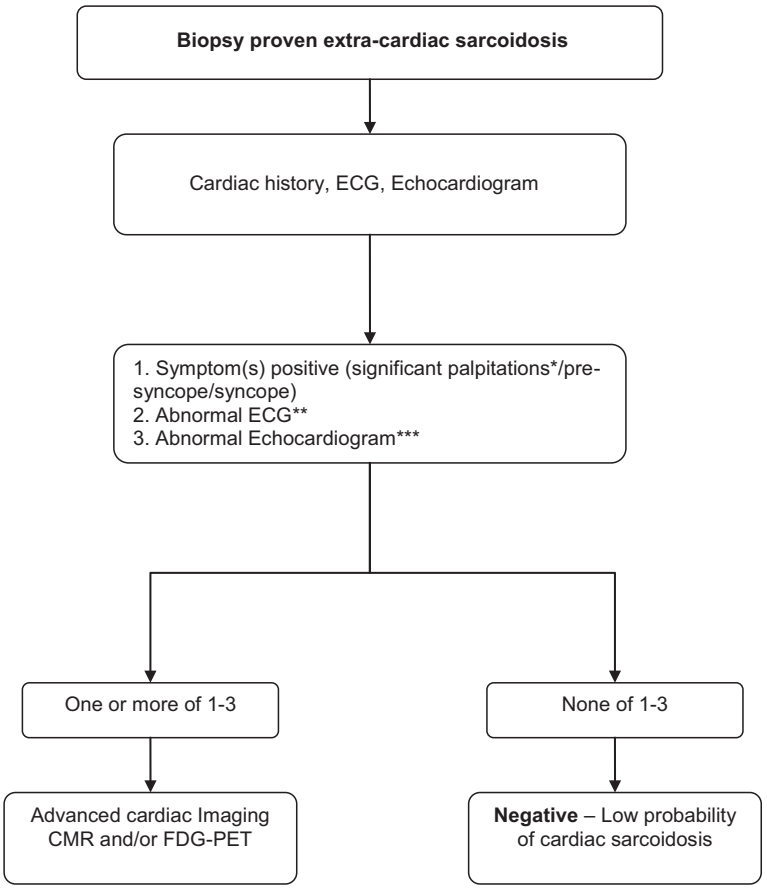
Table 2 Prevalence of abnormalities, sensitivity, and specificity of diagnostic criteria

Abnormality on baseline testing	Prevalence*	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
History of cardiac symptoms	12 (19)	46 (26–27)	95 (82–99)
Electrocradiogram	3 (50)	8 (1–27)	97 (86–100)
Holter	13 (21)	50 (29–71)	97 (86–100)
Echocardiogram	8 (13)	25 (10–47)	95 (82–99)
Any screening variable	29 (47)	100 (88–100)	87 (72–96)
Two or more screening variables	7 (11)	25 (10–47)	97 (86–99)
Three or more screening variables	1 (2)	4 (1–21)	100 (92–100)

CI = confidence interval.

Significant echocardiographic abnormality was defined as LV dysfunction (LVEF $\leq$45%), significant wall motion abnormalities (two or more segments), right ventricular (RV) systolic dysfunction in the absence of pulmonary hypertension, and/or significant diastolic dysfunction inappropriate for the patient's age. Significant abnormal Holter monitor finding was defined as premature ventricular contractions (>10 per hour) and/or nonsustained or sustained ventricular tachycardia (VT) and/or supraventricular tachycardia (SVT) (more than three beats).

*Values are presented as n (%). Adapted with permission from Mehta et al.[25]



* palpitations were defined as "prominent patient complaint lasting > 2 weeks[25]"
** abnormal ECG defined as complete left or right bundle branch block and/or presence of unexplained pathological Q waves in 2 or more leads and/or sustained 2nd or 3rd degree AV block and/or sustained or non-sustained VT[25]
*** abnormal echocardiogram defined as RWMA and/or wall aneurysm and/or basal septum thinning and/or LVEF < 40%*[25]

Figure 3 Suggested algorithm for the investigation of patients with biopsy-proven extracardiac sarcoidosis. AV = atrioventricular; CMR = cardiovascular magnetic resonance; ECG =electrocardiogram; FDG-PET = ^{18}F-fluorodeoxyglucose–positron emission tomography; LVEF = left ventricular; RWMA = regional wall motion abnormality; VT = ventricular tachycardia.

suggest the diagnostic algorithm shown in Figure 3. In addition, the writing group voted on a recommendation that screening for cardiac involvement with a Holter monitor can be useful. Although 10 of 14 (71%) members of the writing group voted to include this recommendation, the vote did not reach the predefined threshold to become a formal recommendation.

It is clear that larger studies are required to define the sensitivity and specificity (and cost-effectiveness) of various screening strategies/tests for cardiac involvement. These studies should critically appraise the screening strategy recommended in this document (see Figure 3). In addition, research is required to assess other proposed screening tests or potential risk markers, including signal-averaged ECG and fragmented QRS.[50,51] Finally, the writing group decided not to make a recommendation on rescreening of patients with an initial negative workup, as there are no data available to help with this important clinical question. However, clinicians should consider rescreening if the patient develops new significant cardiac signs or symptoms.

Expert Consensus Recommendations on Screening for CS in Patients With Specific Cardiac Presentations

Class IIa	1. Screening for CS in patients younger than 60 years with unexplained second-degree (Mobitz II) or third-degree AV block **can be useful.**
	2. If initial screening tests are suggestive of sarcoidosis, biopsies **can be useful.** Biopsies should be extracardiac if feasible, otherwise guided endomyocardial (see text for details).

4.2. Screening for CS in Patients With Specific Cardiac Presentations

There are a number of situations in which cardiac presentations can be the first and/or an unrecognized manifestation of sarcoidosis.

Unexplained Mobitz II or Third-Degree AV Block in Young Patients

A recent study from Finland reported on 72 patients younger than 55 years with unexplained, new onset, significant conduction system disease. Biopsy-proven CS was found in 14 of 72 (19%), "probable" CS in 4 of 72 (6%), and giant cell myocarditis in 4 of 72 (6%) patients. Patients with CS had a significantly poorer prognosis compared with patients with idiopathic heart block.[52] Nery et al presented with similar data from a tertiary Canadian center.[53] They prospectively evaluated patients aged 18 to 60 years who presented unexplained Mobitz II or 3rd degree AVB and no previous history of sarcoidosis. CS was diagnosed in 11/32 (34%). During an average follow-up of 21±9 months, major adverse cardiac events occurred in 3 patients with CS and none in subjects with idiopathic AVB.[53] Figure 4 provides a suggested algorithm for the investigation of patients with unexplained Mobitz II or third-degree AV block who are younger than 60 years. Initial testing should include a computed tomographic scan of the chest for pulmonary sarcoid and advanced cardiac imaging (CMR or FDG-PET). If one or more tests are positive, then biopsy confirmation is suggested.

Sustained Monomorphic VT of Unknown Etiology

In a recent prospective study, consecutive patients with VT of unknown etiology were screened for sarcoidosis.[54] Patients with classic outflow tract, fascicular VT, VT secondary to coronary artery disease, or prior diagnosis of sarcoidosis were excluded. Included patients underwent FDG-PET scans, and in those with scans that were suggestive of active myocardial inflammation, histological diagnosis was confirmed through extracardiac biopsy or endomyocardial biopsy(EMB). Of a total of 182 patients with VT, 14 met inclusion criteria. Of these 14 patients, 4 (29%) were subsequently diagnosed with CS.[54] Two other reports[19,55] also found that VT can be the first presentation of

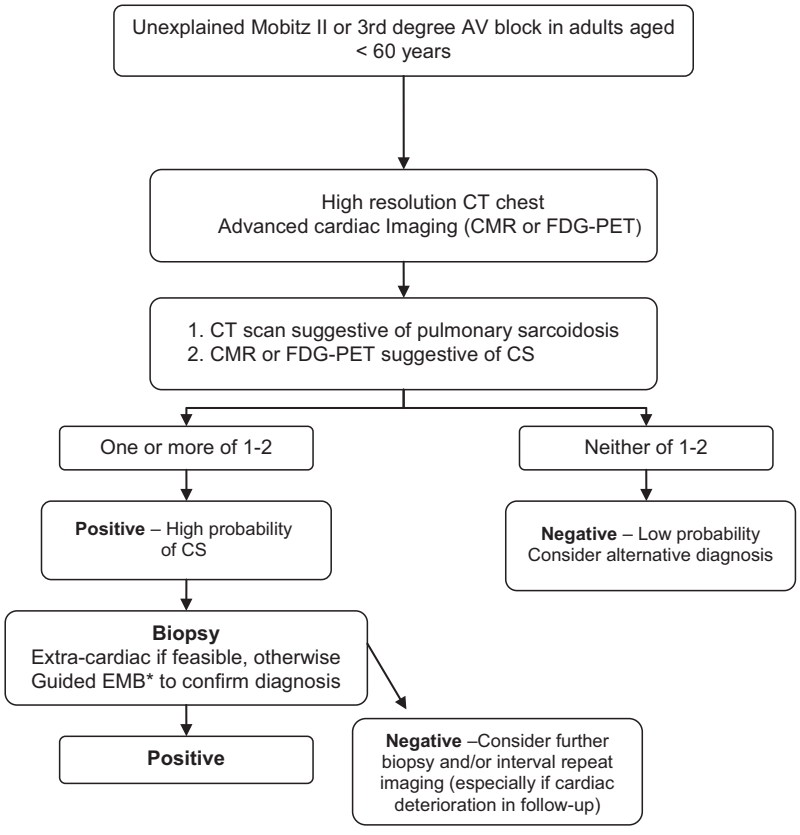


Figure 4 Suggested algorithm for the investigation of patients with unexplained Mobitz II or third-degree AV block who are younger than 60 years. AV = atrioventricular; CMR = cardiovascular magnetic resonance; CS = cardiac sarcoidosis; CT = computed tomographic; ECG =electrocardiogram; EMB = endomyocardial biopsy; FDG-PET = ^{18}F-fluorodeoxyglucose–positron emission tomography.

CS (although neither publication reported their denominator population). Koplan et al[55] found VT to be the initial manifestation of sarcoidosis in 5 of 8 patients with CS and recurrent VT requiring catheter ablation. Uusimaa et al[19] described 9 patients in whom VT was the initial manifestation of sarcoidosis.

The writing group voted on the recommendation that it can be useful to screen for CS in patients presenting with unexplained sustained monomorphic VT. A majority of the writing group, 10 of 14 (71.4%), felt that this was reasonable, but the vote did not reach the predefined threshold to become a formal recommendation.

Arrhythmogenic Right Ventricular Cardiomyopathy

CS can present with features similar to those of arrhythmogenic right ventricular cardiomyopathy (ARVC), including an epsilon wave,[46,56] and can fulfill task force diagnostic criteria for ARVC.[46,56,57] Establishing the differential diagnosis is essential because management of the two conditions is distinct (i.e., immunosuppression in CS and family screening in ARVC). Vasaiwala et al[57] investigated 15 patients who were diagnosed with ARVC on the basis of task force criteria and found that 3 of 15 (18%) patients had sarcoidosis on EMB. LV dysfunction was present in 3 of 3 patients with CS but only 2 of 17 patients with ARVC.[57] Dechering et al[58] prospectively compared patients with proven CS or ARVC who underwent radiofrequency catheter ablation of VT. Five of 8 (63%) patients with CS fulfilled diagnostic criteria for ARVC. Patients with CS had significantly lower LVEF and a greater number of induced morphologies of VT. Steckman et al[59] compared CMR patterns and found greater LGE in CS patients; furthermore, LV septal involvement was seen exclusively in patients with CS. The writing group noted this important emerging

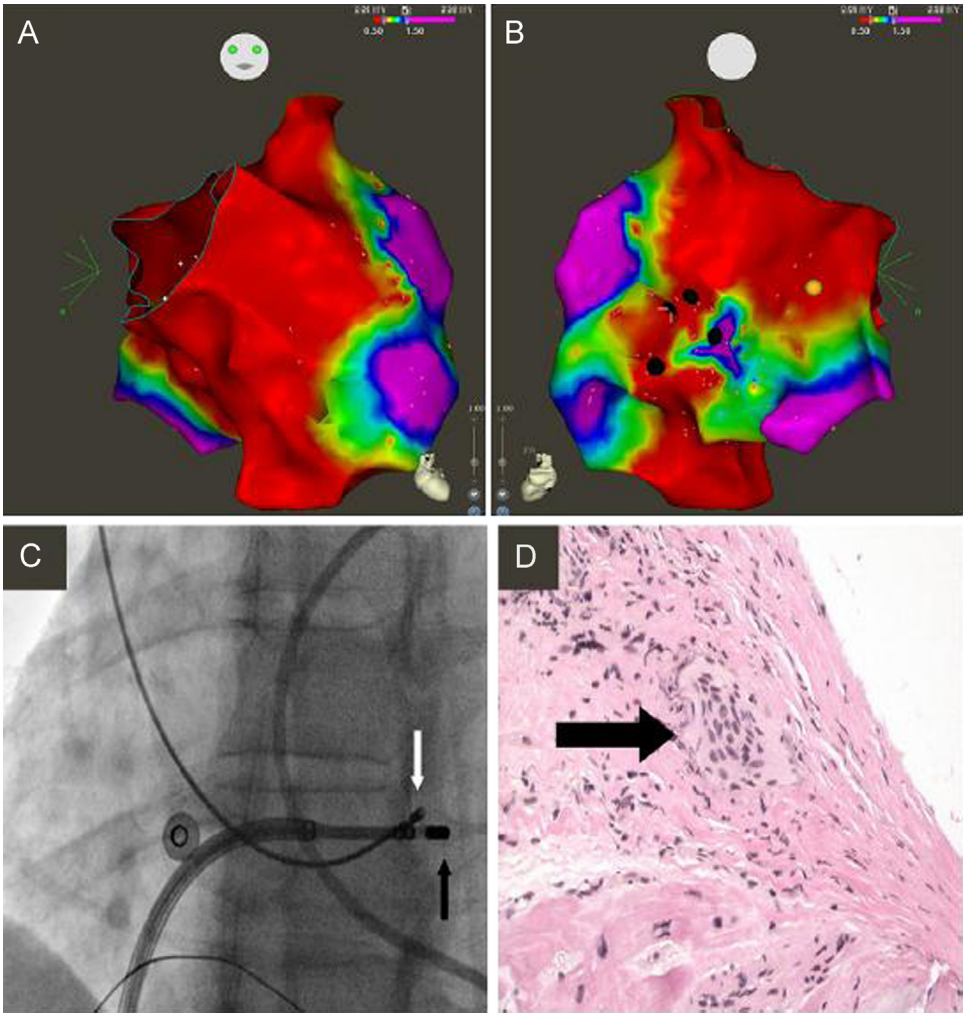


Figure 5 **A and B:** Electroanatomic bipolar voltage map of the right ventricle displaying anterior (panel A) and posterior (panel B) views. Green, yellow, and red indicate low-voltage regions; purple denotes regions of normal voltage, defined as >1.5 mV. Black circles illustrate areas targeted for biopsy. Yellow circle illustrates location of right bundle. **C:** Fluoroscopic image obtained in the left anterior oblique 25 projection, showing the bioptome (white arrow) targeting the low-voltage region in the right ventricular septum, adjacent to the mapping catheter (black arrow). **D:** Microscopic view of an endomyocardial biopsy specimen obtained from the right ventricular septum showing noncaseating granuloma (arrow) (hematoxylin-eosin, magnification 200×). Reproduced with permission from Nery et al.[46]

literature; however, it was felt that there were insufficient data to provide specific guidance on when to consider investigating for CS. However, physicians should be aware that the conditions may have overlapping clinical features and should consider investigating for CS in the presence of LV dysfunction and/or heart block.

Expert Consensus Recommendations for the Management of Conduction Abnormalities in CS	
Class I	1. It **is recommended** that physicians **should be** guided by the American College of Cardiology/American Heart Association/Heart Rhythm Society 2012 guidelines (see sections on Acquired Atrioventricular Block and Chronic Bifascicular Block)[60,61] for decisions regarding permanent pacing in CS patients.
Class IIa	1. Device implantation **can be useful** in CS patients with an indication for pacing even if the AV block reverses transiently. 2. Immunosuppression **can be useful** in CS patients with Mobitz II or third-degree heart block. 3. Implantable cardioverter-defibrillator implantation **can be useful** in patients with CS and an indication for permanent pacemaker implantation.

5. Management of Conduction Abnormalities

Heart block is a common presentation of clinically manifest CS because of the involvement of the basal septum by scar tissue, granulomas, or the involvement of the nodal artery.[16] Furthermore, it can be the first manifestation of sarcoidosis in any organ (see Section B).

Recent Heart Rhythm Society device guideline documents generally apply to patients who have CS and advanced heart block.[61,62] In addition, the writing group reached consensus on three CS-specific recommendations (all class IIa) as follows: pacemaker implantation can be useful in patients with CS with an indication for pacing even if the AV block reverses transiently. Immunosuppression can be useful in patients with CS presenting with Mobitz II or third-degree heart block. ICD implantation can be useful in patients with CS and an indication for permanent pacemaker implantation. Also, the writing group voted on a recommendation to consider an electrophysiology study in patients with first-degree AV block or fascicular block to define levels of conduction system disease. A majority of the writing group, 9 of 13 (64%), voted to include this recommendation, but the vote did not reach the predefined threshold to become a formal recommendation. Finally, there are no specific data related to the use of cardiac resynchronization therapy in CS patients. The writing group suggests that findings from the major clinical trials and relevant recommendations from the general device guidelines should apply to CS patients.[60,61]

The Role of Immunosuppression

Recovery of AV nodal conduction can occur, and treatment with corticosteroids seems to help. The reversibility of heart block with treatment has been summarized in a recent systematic review (see Table 3).[29] Twenty-seven of 57 (47.4%) patients treated with corticosteroids had improvements in AV conduction. In contrast, 16 patients were not treated with corticosteroids and none of them improved.[29] Despite the potential reversibility of heart block, device implantation is recommended because reversibility is unpredictable. The writing group suggests that physicians consider ICD implantation in patients with an indication for permanent pacing (see Section F). Immunosuppression likely increases the risk of device infection. Although there are no specific data related to infection in patients with CS, the writing group voted on a recommendation that, if possible, the device should be implanted first and immunosuppression started once the wound is healed. A majority of the writing group, 10 of 14 (71.4%), voted to include this recommendation, but the vote did not reach the predefined agreement to become a formal recommendation.

Table 3 Studies evaluating the effect of corticosteroids on atrioventricular conduction recovery in patients

	Steroids		No steroids	
Study	No. of patients	AV recovery, n (%)	No. of patients	AV recovery, n (%)
Okamoto et al[63]	3	3 (100)	0	–
Kato et al[64]	7	4 (57.1)	13	0 (0)
Chapelon-Abric et al[13]	9	7 (75)	0	–
Banba et al[65]	9	5 (56.6)	2	0 (0)
Yodogawa et al[66]	12	4 (33.3)	0	–
Kandolin et al[52]	17	4 (23.5)	1	0 (0)
Total	57	27 (47.4)	16	0 (0)

Modified with permission from Sadek et al.[29]

Expert Consensus Recommendations for the ***Management of Atrial Arrhythmias in CS***	
Class I	Anticoagulation **is recommended** in patients with CS and AF if there is sufficiently high risk, as determined by a $CHADS_2$ or CHA_2DS_2-VASc score.[67,68]
Class IIb	An invasive electrophysiological study **may be considered** in patients with atrial arrhythmias other than AF to direct therapy.
Class III	Antiarrhythmic medication therapy with class I agents **is not recommended** for the treatment of arrhythmias associated with CS.

6. Management of Atrial Arrhythmias

Incidence and Mechanism

The true frequency of atrial arrhythmias in CS is unknown. Atrial involvement is common in CS, but it tends to involve the atria less extensively than the ventricles.[16] It is likely that atrial arrhythmias associated with CS are due to inflammation and/or scarring. AF can be the presenting manifestation of CS.[68] Recent observational studies have reported a substantial prevalence of atrial arrhythmias in CS. Viles-Gonzalez et al[70] investigated 100 patients with biopsy-proven systemic sarcoidosis and evidence of cardiac involvement by performing CMR, PET, or EMB for a mean follow-up period of 5.8 years. On reviewing ECGs, device interrogation data, and ambulatory telemetry monitoring, they found a 32% prevalence of supraventricular arrhythmias. AF was the most common supraventricular arrhythmia in 18% of the patients, followed by atrial tachycardias in 7%, atrial flutter in 5%, and AV nodal reentry tachycardia in 2%.[70] In another series, 15 of 65 (23%) patients had 28 distinct symptomatic supraventricular arrhythmias (9 AF, 3 atrial flutter, and 16 atrial tachycardias). The arrhythmia mechanisms were found to be diverse: triggered activity in 2, abnormal automaticity in 9, and reentrant in 8 of the non-AF atrial arrhythmias. All non-AF arrhythmias were related to atrial scars identified by electroanatomic mapping.[71] In this cohort, catheter ablation proved effective for focal and reentrant atrial arrhythmias.[71] An important clinical problem associated with atrial arrhythmias in CS is the risk of inappropriate ICD therapy[72–74] (see Section G).

The Role of Immunosuppression

Evidence that immunosuppression is useful for the treatment of atrial arrhythmias in sarcoidosis patients is limited to case reports.[75,76] The writing group voted on a recommendation that a trial of immunosuppression can be useful in patients with AF. A majority of the writing group, 8 of 14 (57.1%), voted to include this recommendation, but the vote did not reach the predefined threshold to become a formal recommendation.

Thromboprophylaxis

Studies suggest that patients with sarcoidosis are at increased risk of pulmonary embolism, suggesting that sarcoidosis may be a prothrombotic state.[77] However, there are no data on the risk of thromboembolism in CS patients with AF or the effect of anticoagulation in this group. Hence, the writing group recommends applying guidelines for thromboprophylaxis in nonvalvular AF.

Drug Therapy and Ablation

There are no specific data to guide antiarrhythmic medication selection in patients with CS. β-Blocker, calcium-channel blockers, sotalol, dofetilide and amiodarone can be used. Class I agents are not recommended, because patients with CS often have myocardial scarring. Thus, the writing group felt that these agents should be avoided, based on adverse outcomes reported in other structural heart diseases (the Cardiac Arrhythmia Suppression Trial).[78] Data on catheter ablation of atrial arrhythmias in CS are scarce. In CS patients with non-AF atrial arrhythmias, an invasive electrophysiological study with the characterization of the arrhythmia substrate could be considered. It is not known whether pulmonary vein isolation is effective in CS patients with paroxysmal AF. In one case report of AF as the initial presentation of CS, the patient had recurrent AF after pulmonary vein isolation whereas AF burden decreased after immunosuppression.[76]

Expert Consensus Recommendations for the Management of Ventricular Arrhythmias	
Class IIa	1. Assessment of myocardial inflammation with FDG-PET **can be useful** in CS patients with ventricular arrhythmias. 2. Immunosuppression **can be useful** in CS patients with frequent ventricular ectopy or nonsustained VT and evidence of myocardial inflammation. 3. Immunosuppression **can be useful** in CS patients with sustained ventricular arrhythmias and evidence of myocardial inflammation. 4. Antiarrhythmic medication therapy **can be useful** in patients with ventricular arrhythmias refractory to immunosuppressive therapy. 5. Catheter ablation **can be useful** in patients with CS and ventricular arrhythmias refractory to immunosuppressive *and* antiarrhythmic therapy. 6. Catheter ablation **can be useful** in patients with incessant ventricular arrhythmias.

Most recommendations for the management of ventricular arrhythmias in patients with structural heart disease apply to patients with CS.[79] In addition to these global recommendations, this section focuses on the specific characteristics unique to patients with ventricular arrhythmias and CS. Section G addresses the role of ICD implantation in these patients.

A stepwise approach has been described in a registry of 42 patients with CS and VT.[80] The steps were initial treatment with immunosuppression followed by antiarrhythmic medication and finally catheter ablation if VT persisted. Medical therapy with corticosteroids alone or in combination with antiarrhythmic medication therapy effectively suppressed ventricular arrhythmias in 33 of 42 patients. In the remaining 9 patients, catheter ablation was performed and resulted in effective arrhythmia suppression in the majority.[80]

7. Management of Ventricular Arrhythmias

Mechanisms of Ventricular Arrhythmias

Triggered activity and abnormal automaticity have been described secondary to myocardial inflammation in myocarditis.[81,82] These non-reentrant ventricular arrhythmias are also observed clinically in patients with CS presenting with frequent ventricular ectopy, and some of these patients have a reduction in arrhythmia burden after taking corticosteroids.[66,83] However, the most common mechanism is likely to be macroreentrant arrhythmias around areas of granulomatous scar.[55,80,83] Active inflammation may play a role in promoting monomorphic VT due to reentry, either by triggering it with ventricular ectopy[83] or by slowing conduction in diseased tissue within granulomatous scar.[66,84]

The Role of Immunosuppression

Despite modest data, immunosuppression with corticosteroids is often used in patients with CS.[29] With respect to ventricular arrhythmias, several studies[66,80,85] have suggested a benefit of immunosuppression while others[86] failed to show benefit. Furthermore, a worsening of ventricular arrhythmias has been reported with corticosteroid therapy in a minority of patients.[87,88] The use of corticosteroids has also been linked to aneurysm formation.[16] Some data suggest that immunosuppression may be more beneficial for ventricular arrhythmias in the early disease phase in the presence of preserved LV function.[64,66]

Antiarrhythmic Therapy

Amiodarone and sotalol are widely used to treat VT in patients with CS.[80] Antiarrhythmic medication therapy guided by programmed ventricular stimulation has not been found to predict outcomes in patients with CS.[86]

Ablation for Ventricular Arrhythmias

Table 4 lists the studies evaluating the role of catheter ablation for the management of VT. Jefic et al[80] described the role of radiofrequency catheter ablation in 9 patients with CS after immunosuppression failed to control VT. The majority of the patients had either VT storm or incessant VT. Most of the VTs were due to a reentrant mechanism and were mapped using entrainment mapping and pace mapping. The most frequent location of the reentry circuit was the paratricuspid area. In patients with predominant RV involvement, critical sites in the RV apex have also been described.[58] In patients with epicardial scarring, an epicardial approach can be necessary to eliminate VT. Therefore, the approach of planning the ablation procedure based on the predominant location of scarring as detected by LGE-CMR was helpful in eliminating VTs in these patients.[89]

Mapping techniques that can be used to target VTs in patients with CS are similar to the criteria used for VT mapping in patients with structural heart disease, and the choice depends on inducibility and on the hemodynamic tolerance of VTs. These include pace mapping, entrainment mapping, and targeting sites with isolated and/or fragmented potentials.[80,90] Ablation outcomes in the study by Jefic et al[80] were favorable, with either elimination of VT recurrences or reductions in VT burden. In contrast, Koplan et al[55] reported recurrences of VT in most patients. A more extensive arrhythmogenic substrate with more advanced cardiac disease at the time of VT ablation may be the reason for this discrepancy since the mean reported LVEF was worse in the study of Koplan et al than that in the study of Jefic et al.[80]

Management of VT/Ventricular Fibrillation Storm

In patients with VT/ventricular fibrillation (VF) storm, it is suggested that initial treatment be a combination of antiarrhythmic medication (usually amiodarone) and immunosuppression

Table 4 Studies assessing the role of VT ablation in cardiac sarcoidosis

Study	N	EF (%)	Noninducible post, n/N (%)	Partial success, n/N	Recurrence, n/N (%)	Follow-up period (mo=months)
Koplan et al[55]	8	34	2/8 (25)	4/9	6/8 (75)	6–84
Jefic et al[80]	9	42	5/9 (56)	3/9	4/9 (44)	19.8
Dechering et al[58]	8	36	5/8 (63)			6

EF = ejection fraction; VT = ventricular tachycardia.

(if there is evidence of active inflammation). If the clinical situation or setting does not permit an urgent FDG-PET scan, then empiric immunosuppression should be given. If ventricular arrhythmias cannot be adequately controlled with these measures, then VT ablation should be considered even if there is active inflammation.

Expert Consensus Recommendations for Risk Stratification for Sudden Cardiac Death in CS*

Class IIb An electrophysiological study for the purpose of sudden death risk stratification **may be considered** in patients with LVEF >35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation).

CMR for the purpose of sudden death risk stratification **may be considered** in patients with CS.

*Recommendations are summarized in Figure 7

8. Risk Stratification for Sudden Cardiac Death

Patients with CS are at risk of suuden death, and there are few data to help with risk stratification. The writing group agreed, however, that data from the major primary and secondary prevention ICD trials were relevant. Hence, it follows that the recommendations from the general device guideline documents apply to this population.[60,61] Therefore, this section of the consensus document mainly focuses on patients who do not have a clear indication for ICD implantation, that is, those with chronic LVEF >35% and discusses risk stratification methods.

LV Function

CS, perhaps because of its element of active granulomatous inflammation and perhaps because of the variable involvement of the LV and/or RV, may not behave in the same fashion as other types of nonischemic cardiomyopathy with regard to ventricular arrhythmias, LVEF, and sudden death risk. For example, CS patient cohorts appear to have more frequent ICD therapies than do other populations. In the three large published series, annualized appropriate therapy rates were 8.6%, 13.2%, and 14.5%, respectively (see Table 5).[72–74] It should be noted that all three studies were from academic centers with an interest in CS; hence, there may be some important referral bias. In addition, there was some overlap between the cohorts.[72–74]

All three studies examined associations with appropriate ICD therapies (see Table 5). The only consistent finding was that a lower LVEF was associated with appropriate ICD therapy. However, it should be noted that patients with mildly impaired LV function also had a substantial risk of arrhythmia. For example in one study, most primary and secondary prevention patients who received appropriate ICD therapies had an LVEF of >35%, suggesting that patients with CS with mild or moderately reduced LVEF may still be at a substantial risk of ventricular arrhythmias.[74] In addition, in the study by Betensky et al,[73] 7 of 17 (41%) patients with appropriate ICD therapy had an LVEF of >35%. Importantly, Schuller et al[72] showed that in their primary prevention cohort, no patient with normal RV and LV function received an appropriate therapy.

In view of these data suggesting that patients with LVEF in the range of 36%–49% had a substantial risk of appropriate therapy, the writing group reached consensus on a recommendation that ICD implantation may be considered in patients with LVEF in the range of 36%–49% and/or RV ejection fraction <40%, despite optimal medical therapy and a period of immunosuppression (if indicated).

The Role of Programmed Electrical Stimulation

In a study by Mehta et al,[91] 76 patients with CS underwent programmed electrical stimulation (PES). Consecutive patients with an established diagnosis of CS referred to the electrophysiology service for risk stratification were included. All patients had extracardiac tissue biopsy-proven systemic sarcoidosis and evidence of CS as defined by typical imaging findings on either CMR or FDG-PET. Eight (10.5%) patients were inducible for sustained ventricular arrhythmia and underwent ICD implantation compared with none of the 68 patients with no inducible arrhythmia. Patients with positive PES had a mean baseline LVEF of 36.4% ± 4.2%, which decreased to 21.0% ± 12.0% at 2 years. Four of 6 patients in the PES-positive group who had arrhythmic events (ICD shocks or death) had an LVEF of <40% at the time of PES. Only one patient with normal LVEF had positive PES, and this patient had been arrhythmia-free during follow-up (D Mehta, personal communication, February 5, 2014). The mean LVEF in patients with negative PES was 55.8% ± 1.5% and remained

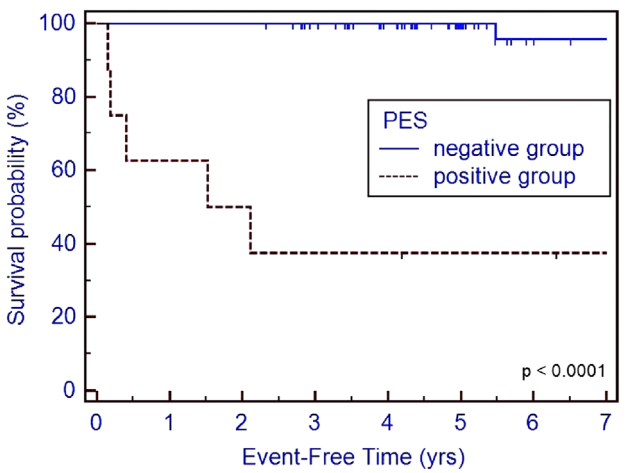


Figure 6 Kaplan-Meier estimation of event-free survival. Vertical markers indicate the time when follow-up was terminated in each patient. PES = programmed electrical stimulation. Reproduced with permission from Mehta et al.[91]

Table 5 Studies evaluating the role of the ICD in the prevention of sudden death in patients with CS

Study	Setting/design	N	Follow-up period (y)	Primary Prevention	Annualized appropriate therapy rate (shock + ATP)	Adverse events	Associations with appropriate ICD therapy	Comments
Kron et al[74]	United States, Canada, India/ multicenter academic retrospective	235	4.2 ± 4.0	62.6%	8.6%	17.4%	Male, syncope, lower LVEF, secondary prevention ICD, ventricular pacing on electrocardiogram	99 patients were included in the other two series[69,70]
Betensky et al[73]	United States/ single-center academic retrospective	45	2.6 ± 2.7	64.4%	14.5%	15.6%	Lower LVEF, complete heart block	23 (51.5%) patients were VT/VF-free, mean LVEF was 50.5% ± 16.6% in this group
Schuller et al[72]	United States/ three-center academic retrospective	112	2.8	74.1%	13.2%		LVEF <55%, right ventricular dysfunction, symptomatic heart failure	In the primary prevention cohort, no patient with normal right and left ventricular function received an appropriate therapy

ATP = Antitachycardic pacing; CS = cardiac sarcoidosis; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

normal during follow-up. Patients were followed for a mean period of 5.6 years. The event rate (ventricular arrhythmias per death) was 75% in the PES-positive group and 1.5% in the PES-negative group (Figure 6).[91] These data extend previous similar findings from the same institution in a mixed population with and without clinical VT.[92] Whether positive PES is more predictive of events than an estimation of LVEF is unclear. The writing group recognizes that these data need to be reproduced in larger cohorts. However, the majority voted that an electrophysiological study may be considered in patients with LVEF >35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation). It should be noted that given the potentially progressive nature of CS, the long-term predictive value of a negative electrophysiology study is not known and further research is needed.

The Role of CMR

Although in its more extensive stages CS can readily be identified using commonly available cardiac imaging tests such as echocardiography and single-photon emission computed tomography, more focal involvement can be challenging to detect. CMR is increasingly being utilized for the assessment of suspected CS in view of its ability to identify small regions of myocardial damage even in individuals with preserved LV systolic function (see Figure 1 for an example).[32] Patel et al[24] followed 81 patients (73% black) with biopsy-proven extracardiac sarcoidosis. Patients were followed for major adverse events (death, defibrillator shock, or pacemaker requirement). LGE-CMR identified cardiac involvement in 21 (26%) patients. Over a median follow-up of 5 years, 6 of 8 patients in the group with LGE had ventricular arrhythmia or died compared with 1 death in the group without LGE. LVEF was lower in LGE-CMR-positive patients than in LGE-CMR-negative patients (median 45% vs. 57%); however, 29% of the LGE-CMR-positive patients had an LVEF of >50%.[24] Recently, Greulich et al[31] reported on 155 consecutive patients with systemic sarcoidosis diagnosed by using biopsy and/or clinical criteria who underwent CMR. Primary end points were death, aborted sudden cardiac death, and appropriate ICD therapy, and the median follow-up time was 2.6 years. LGE was present in 39 (25.5%) patients, and 11 of 39 (28.2%) patients had a primary end point (all cardiac) during follow-up. In contrast, 1 of 114 (0.9%) LGE-negative patients had an end point and this was a noncardiac death. The presence of LGE had a Cox hazard ratio of 31.6 for death, aborted sudden cardiac death, or appropriate ICD discharge, which was superior to only LVEF.[31]

These data are in contrast to those reported in a number of other publications.[17,23,25,26] For example, Mehta et al[25] published a report on a cohort of 62 patients with biopsy-proven extracardiac sarcoidosis. Of these, 26 patients underwent CMR, and over a mean follow-up of 1.8 years, no patient died or had ventricular arrhythmias. The differences may be related to less-sensitive CMR techniques and different populations.

The writing group acknowledges the need for additional data from large multicenter studies or registries; however, despite the limitations of the current data, there was consensus that CMR for the purpose of sudden death risk stratification may be considered in patients with CS. In particular, CMR may be considered in patients with chronic LVEF >35%. The writing group suggests that CMR be performed and interpreted at centers with experience in CMR imaging and LGE interpretation in CS. The utilization of standardized CMR protocols published by the Society of Cardiovascular Magnetic Resonance[93] is advised to maximize the utility of CMR in patients with suspected CS.

The Role of Cardiac PET

A significant myocardial uptake of FDG (a glucose analogue), assumed to be indicative of active myocardial inflammation, may identify patients at higher risk of sudden death related to disease activity and increased risk of progression[94] (see Figure 2 for an example). The presence of both a perfusion defect and an abnormal FDG uptake was associated with death or sustained VT, even after adjusting for LVEF.[94] In another study, patients with CS and VT had significantly more FDG uptake as compared with CS patients with AV block and asymptomatic controls.[95] The writing group acknowledges the promising nature of these data, but there is a clear need for additional information. Thus, the writing group voted that there were insufficient data to include a recommendation on FDG-PET scanning for the purpose of sudden death risk stratification.

Expert Consensus Recommendations for ***ICD Implantation in Patients With CS***[†]	
Class I	ICD implantation **is recommended** in patients with CS and one or more of the following: 1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest;[61] 2. LVEF ≤35%, despite optimal medical therapy[61] and a period of immunosuppression (if there is active inflammation).
Class IIa	ICD implantation **can be useful** in patients with CS, independent of ventricular function, and one or more of the following: 1. An indication for permanent pacemaker implantation; 2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology; 3. Inducible sustained ventricular arrhythmias (>30 seconds of monomorphic VT or polymorphic VT) or clinically relevant VF.*
Class IIb	ICD implantation **may be considered** in patients with LVEF in the range of 36%–49% and/or an RV ejection fraction <40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).
Class III	ICD implantation **is not recommended** in patients with no history of syncope, normal LVEF/RV ejection fraction, no LGE on CMR, a negative EP study, and no indication for permanent pacing. However, these patients should be closely followed for deterioration in ventricular function. ICD implantation **is not recommended** in patients with one or more of the following: 1. Incessant ventricular arrhythmias; 2. Severe New York Heart Association class IV heart failure.
	*VF with triple premature beats of <220 ms is considered a nonspecific response.[91] †Recommendations are summarized in Figure 7

Expert Consensus Recommendations for ***Timing of ICD Implantation in Patients With CS***	
Class IIa	If VT ablation is planned, an indicated ICD **should be** implanted after ablation.

9. ICD Implantation and Follow-Up

Indications for ICD Implantation

There are few data specific to ICD use in the CS population. There is a class IIa recommendation in the general device guidelines with the following wording: "ICD implantation is reasonable for patients with CS, giant cell myocarditis, or Chagas disease."[60,61] The writing group felt that there were sufficient data to provide more detailed recommendations for ICD implantation in CS. The writing group agreed that data from the major primary and secondary prevention ICD trials were relevant. Hence, it follows that recommendations from the general device guideline documents apply to this population. Therefore, ICD implantation is recommended in patients with CS and spontaneous sustained ventricular arrhythmias, including prior cardiac arrest and/or if the LVEF is ≤35%, despite optimal medical therapy and a period of immunosuppression (if indicated). ICD implantation can be useful in patients with CS, independent of ventricular function, and one or more of the following: (1) unexplained syncope or near-syncope, felt to be arrhythmic in etiology; (2) inducible ventricular arrhythmias (>30 seconds of monomorphic VT or polymorphic VT) or clinically relevant VF.

The only additional CS-specific class IIa recommendation is that an ICD can be useful in patients with an indication for permanent pacemaker implantation. The writing group also reached consensus on a number of class IIb and III recommendations. The rationale for these latter recommendations is included in Section F. In addition, the writing group voted on a class IIb recommendation that ICD

implantation may be considered in patients with LGE on CMR imaging even if LVEF is normal. Although 4 of 12 (33.3%) members of the writing group (with 1 abstention) voted to include this recommendation, the vote did not reach the predefined threshold to become a formal recommendation. However, the writing group suggests that physicians may consider an electrophysiological study for further risk stratification in these patients (see Figure 7).

Finally it should be noted that in the primary prevention group the LVEF should be re-measured after a period of optimal medical therapy and immunosuppression if appropriate. Clearly there are no data to guide us regarding the duration of the waiting period. Some might argue that the waiting period for the non-ischemic patients in the Sudden Cardiac Death Heart Failure trial[96] (9 months) might apply. However it should be noted that this period was not adopted in the general device guidelines.[61] Therefore the writing group suggests that the waiting period should be individualized to the patient and probably should be at least 3 months.

ICD Implant Considerations

Because the presence of a newly implanted ICD has implications for both cardiac CMR and myocardial biopsy, it is important to keep the potential diagnosis of sarcoidosis in mind when contemplating the temporal sequence of diagnostic testing and device implantation. Implantation of a dual-chamber ICD in CS patients has several theoretical advantages, including maintenance of AV synchrony in patients who subsequently develop AV block, detection of AF, which may be more prevalent in patients with CS, and interpretation of tachyarrhythmia event electrograms. There are no data to guide relative timing of immunosuppression and device implantation, and clinician judgment is needed for individual cases. The writing group voted on a recommendation that ICD implantation should ideally be performed when immunosuppressive therapy is at the lowest possible maintenance dose or temporarily withheld, if clinically feasible. Although 10 of 14 (71%) members of the writing group voted to include this recommendation, the vote did not reach the predefined threshold to become a formal recommendation. In a patient felt to be at high risk of ventricular arrhythmia, ICD implantation followed by immunosuppression or even implantation while on high dose immunosuppression could be considered.

ICD Complications Specific to Patients With CS

No prospective study has evaluated the incidence of ICD complications in CS patients. In two retrospective studies, adverse events occurred in 15.6% and 17.4% of the patients, most commonly lead dislodgement or lead fracture.[73,74]

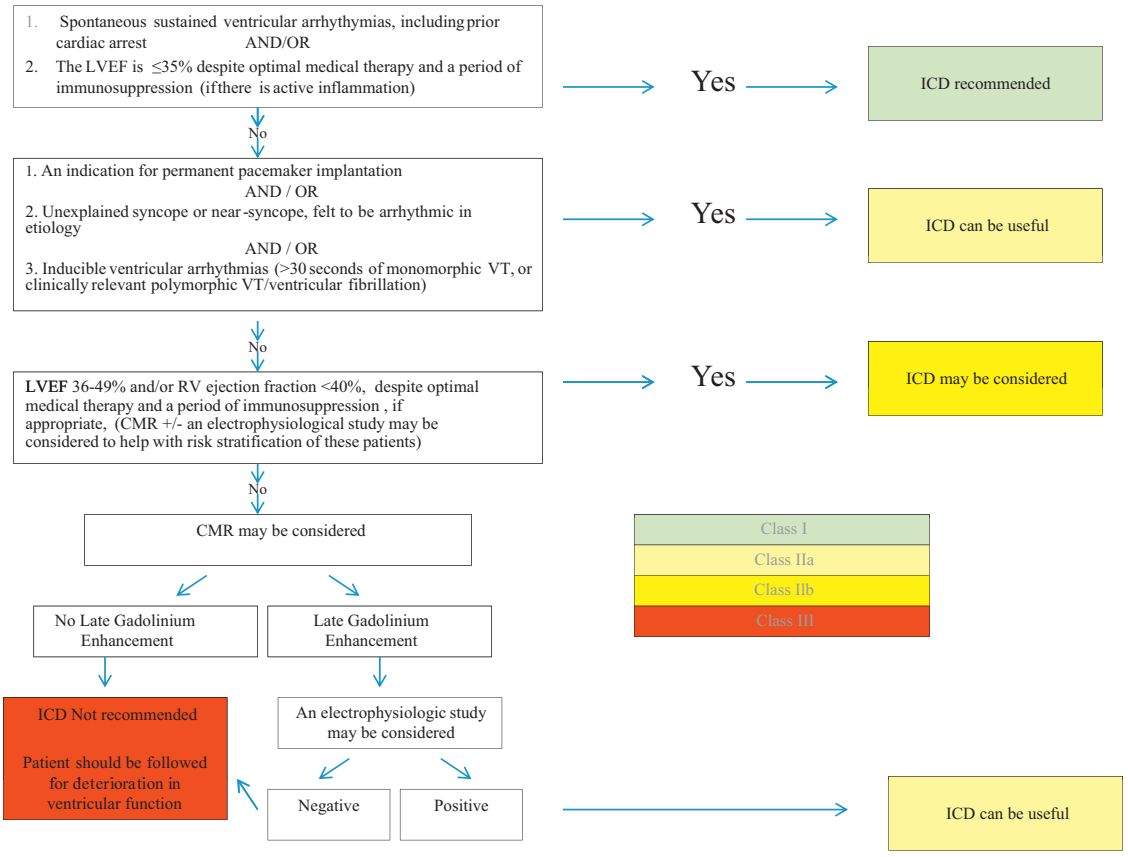


Figure 7 Consensus recommendations for ICD implantations in patients diagnosed with cardiac sarcoidosis. CMR = cardiovascular magnetic resonance; ICD = implantable cardioveter-defibrillator; LVEF = left ventricular ejection fraction; RV = right ventricle; VT = ventricular tachycardia

The reason for the high complication rate in this series is not known, but it may be due to young patient age, a high number of advisory ICD leads in the study groups, or referral bias. One case report describes a CS patient with fluctuations in ventricular sensing due to the loss of R-wave voltage resulting from inflammation related to CS,[97] but the stability of ICD lead sensing and capture threshold over time has not been prospectively studied.

ICD Programming Considerations Specific to Patients With CS

Inappropriate ICD shocks have been reported to occur at rates of 4.1%–5.7% per year, most commonly for atrial arrhythmias (see Table 5).[72–74] In one large cohort study, 56 of 235 (24%) CS patients experienced a total of 222 inappropriate ICD shocks over a mean follow-up period of 4.2 years.[74] AF was the most common reason for inappropriate therapy identified in 17 (30%) patients, and SVT caused inappropriate therapy in 7 (12%) patients.[74] In a study of 45 CS patients with ICD, 6 (13%) patients had inappropriate ICD therapy within 2.6 years because of SVT, most often AF, in 5 of 6 cases.[73] A third report found an incidence of inappropriate therapy in 13 of 112 (12%) CS patients (followed for a mean period of 29 months), but the reasons for inappropriate therapy were not reported.[72]

In view of these data, ICD ventricular arrhythmia detection and therapy settings should be programmed carefully and individualized to the patient. Heart block can resolve with immunosuppressive therapy,[29] allowing for the rapid conduction of atrial arrhythmias; this possibility should be considered when programming tachycardia detection and therapies in CS patients. In addition, because many CS patients have nonsustained/paroxysmal ventricular arrhythmias, programming longer tachycardia detection times may help avoid unnecessary delivery of ICD therapy for self-terminating arrhythmias.

10. Conclusions and Future Directions

Much remains to be learned about how to best diagnose and manage patients with CS. Key unresolved questions include, but are not limited to, the following:

1. What is the effect of corticosteroid treatment on the clinical course of the various manifestations of CS?
2. What is the effect of other immunotherapy on the clinical course of the various manifestations of CS?
3. What is the best, most cost-effective method to screen for CS? How frequently should patients be screened?
4. Should we treat clinically silent CS?
5. What is the prognosis of clinically silent CS?
6. How can we prevent sudden cardiac death in CS? How should we stratify the risk of sudden cardiac death? Who should receive ICDs?
7. What is the role of advanced imaging (PET and CMR) in diagnosis and guiding treatment of CS?
8. How can we best treat ventricular arrhythmias in CS? Should we treat ongoing inflammation before or after catheter ablation?
9. How can we best treat atrial arrhythmias in CS? Should we treat ongoing inflammation before or after catheter ablation?

The expert consensus opinions described in this document represent an international effort to address the challenges faced by clinicians caring for CS patients. Although we believe that this document will help in the management of patients with CS, it is only a starting point for understanding this complex disease. In this document, we attempt to summarize the few things we currently know and to make the best possible recommendations (given the limitations). Equally importantly, the document highlights the many knowledge gaps that still exist. It has been suggested that a multicenter collaborative approach to study CS is greatly needed.[98] The authors of this consensus document agree with this comment and strongly encourage such collaborations.

Appendix 1

See Tables A1 and A2.

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Table A1 Writing group disclosure table

Writing group	Consultant/advisory board	Speakers' bureau/ honoraria	Research grant	Fellowship support	Board Mbs/stock options/partner	Others
David Birnie, MD	None	None	0; Medtronic	0; Johnson & Johnson, Boston Scientific, Medtronic	None	None
Frank Bogun, MD	1: Boston Scientific, St. Jude Medical, Biotronik	None	1; Biosense Webster	None	None	None
Joshua M. Cooper, MD, FHRS	1:Medtronic, Boston Scientific, St. Jude Medical, Biotronik, Spectranetics, Biosense Webster	None	None	None	None	None
Daniel Culver, DO, FCCP	1: Celegene, Boehringer-Ingelheim, Mitsubishi Tanabe	None	3; GlaxoSmithKline	None	None	0: World Association for Sarcoidosis and Other Granulomatous Disorders
Claire S. Duvernoy, MD	None	None	1; University of California, San Francisco, VA Cooperative Studies Program, National Heart, Lung, and Blood Institute	None	None	0: American College of Cardiology
Marc Judson, MD	1: Celegne, Janssen	None	0: T2 Biosystems	None	None	Equity interest, 1: Up-to-date
Jordana Kron, MD	None	None	None	None	None	None
Davendra Mehta, MD, PhD, FHRS	None	None	None	None	None	None
Jens Cosedis Nielsen, MD	1: Biotronik, Biosense Webster, Medtronic, St. Jude Medical, Actelion	None	4; Biosense Webster	None	None	None
Tohru Ohe, MD, FHRS	1: Boston Scientific	None	None	None	None	None
Amit Patel, MD	None	None	2: Ventripoint; 3: Philips; 4: Astellas Pharma	None	None	Salary, 5: University of Chicago; equity interests, 1: Edwards Lifesciences
Pekka Raatikainen, MD	1: Bayer Finland, Boehringer Ingelheim, Pfizer, St. Jude Medical, Biosense Webster	Boehringer Ingelheim	None	None	None	None
Kyoko Soejima, MD	1: St Jude Medical, Medtronic, Boston Scientific	None	None	None	None	None
William H. Sauer, MD, FHRS, CCDS	1: Medtronic, Boston Scientific, St. Jude Medical	None	None	1; Medtronic	None	None

0 = $0; 1 = <$10,000; 2 = >$10,000 to <$25,000; 3 = >$25,000 to <$50,000; 4 = >$50,000 to <$100,000; 5 = >$100,000.

Table A2 Peer reviewer disclosure table

Peer reviewer	Consultant/ advisory board	Speakers' bureau/ honoraria	Research grant	Fellowship support	Board Mbs/stock options/partner	Others
Rachel Lampert, MD, FHRS	None	None	1: GE Healthcare; 5: Boston Scientific, Medtronic, St. Jude Medical	None	None	Salary, 1: American College of Cardiology Foundation
John F. Beshai, MD, FHRS	4: Lifewatch	None	None	None	1: American College of Cardiology	None
Alan Cheng, MD, FHRS	2: Biotronik, Boston Scientific, Medtronic, St. Jude Medical	None	3: National Institutes of Health	None	None	None
Timm-Michael Dickfeld, MD, PhD, FHRS	1: Biosense Webster	None	5: GE Healthcare, Biosense Webster	None	None	None

0 = $0; 1 = <$10,000; 2 = >$10,000 to <$25,000; 3 = >$25,000 to <$50,000; 4 = >$50,000 to <$100,000; 5 = >$100,000.