

## REVIEW ARTICLE—FOCUS ISSUE: CARDIAC SARCOIDOSIS UPDATE

## Comparing and Contrasting Guidelines for the Management of Cardiac Sarcoidosis

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### Abstract

**Introduction:** The Japanese Circulation Society (JCS) recently published new guidelines for the diagnosis and treatment of Cardiac Sarcoidosis (CS). There are two other guideline documents, the World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ (WASOG) Assessment Instrument created in 1999 and updated in 2014. Also, in 2014, the Heart Rhythm Society (HRS) published their international guideline document. As co-chair of the HRS document I have been invited to compare and contrast the management aspects of the HRS guidelines with the new JCS document.

**Comments:** (i) The HRS document recommended a stepwise approach to VT management and the JCS document is somewhat similar; but with some key differences. (ii) The HRS statement suggested that an ICD for CS patients with an indication for a pacemaker “can be useful”. The JCS document take a similar position although with some additional criteria related to National Health Institute Coverage guidelines. (iii) Both HRS and the JCS documents agree that ICDs are recommended in patients with general guideline indications for primary prevention (i.e. LVEF less than 35%). However which additional patients should be considered for ICDs is controversial. The 2016 JCS document is broadly similar, with the major exception that it is recommended that all patients with LVEF 35–50% should have an EP study.

**Conclusion:** The Japanese have been leaders in many aspects of CS including in guideline development. It is clear that the future of CS management is bright, with increasing international collaborations and also multiple efforts underway to obtain higher quality data to inform future guidelines.

**Keywords:** Arrhythmias, Cardiac sarcoidosis, Management

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The Japanese Circulation Society (JCS) recently published new guidelines for the diagnosis and treatment of Cardiac Sarcoidosis (CS) (1). There are two other guideline documents. The World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ (WASOG) Assessment Instrument created in 1999 and updated in 2014 (2). Also, in 2014, the Heart Rhythm Society (HRS) in collaboration with the American College of Cardiology, American College of Chest Physicians, American Heart Association, Asia Pacific Heart Rhythm Society and the European Heart Rhythm Association published their international guideline document (3). The HRS document was closely aligned with the WASOG publication regarding the diagnosis of CS; but in addition included recommendations on the

management of CS, primarily related to CS related arrhythmias.

As co-chair of this HRS document I was previously invited to compare and contrast the diagnostic aspects our guidelines with the new JCS document (4). To briefly recap, there are many similarities, for example both have two diagnostic pathways, however there are a number of important differences. One major difference is the requirement for a positive extra-cardiac biopsy in the clinical diagnosis pathway. The HRS guidelines require this but the Japanese guidelines do not; specifically they state “granulomas are found in organs other than the heart, or the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis and at least 2 of the five characteristic laboratory findings of sarcoidosis.”

Another difference is in the need for multiple clinical criteria to make the diagnosis via the clinical pathway (two or more major criteria or one major and two or more minor criteria). This contrasts with the HRS document which only requires one ‘major’ criterion. Finally, the JCS guidelines tackle, for the first time, the definition of and criteria for the diagnosis for isolated cardiac sarcoidosis (ICS).

I have now been invited to compare and contrast the management aspects of the HRS guidelines with the new JCS document (4). It should be noted that the focus and organizational structure of the two documents are somewhat different. The HRS guidelines primarily focuses on arrhythmic issues whilst the JCS guidelines includes detailed sections on immunosuppression and heart failure management. Also, the following caveat to the JCS guideline should be highlighted “The present guidelines basically reflect treatments and procedures that are currently available and covered by the National Health Insurance (NHI) in Japan. Those not covered by the NHI are described as such.”

### Immunosuppression

The HRS document has only two recommendations regarding immunosuppression (both level IIa)

- Immunosuppression can be useful in CS patients with Mobitz II or 3<sup>rd</sup> degree heart block.
- Immunosuppression can be useful in CS patients with ventricular arrhythmias and evidence of myocardial inflammation.

The JC guideline suggests “Corticosteroid is recommended regardless of whether symptoms are present or not. (evidence Level 4b recommendation grade C1). The Japanese document also has detailed recommendations (Evidence Level 6, recommendation grade C1) on the initiating dose of prednisone (30mg per day), duration of initial dose (4 weeks), how to taper 5 mg reduction every 2–4 weeks and maintenance dose 5–10 mg per day.

Of course, immunosuppression recommendations are primarily based on expert opinions and small observational studies (5). Higher quality evidence is needed and should be forthcoming from ongoing studies including the Canadian/Japanese/US/European Cardiac Sarcoidosis multi-center randomized controlled trial (CHASM CS- RCT) (6).

### Management of ventricular tachycardia

*1. When to treat with immunosuppression for management of VT (see Table 1B)*

The HRS document suggested initial treatment with immunosuppression if there is evidence of active inflammation. This contrasts with the JCS document which states that treatment with immunosuppression is recommended, regardless of whether there is active inflammation. (class I if active

inflammation and class IIa if not).

*2. When to treat with antiarrhythmic medications for management of VT (see Table 1C)*

The HRS document states that antiarrhythmic drugs (AADs) can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy and implicitly as first line if there is no active inflammation. In contrast the JCS group states that AADs are indicated but do not state whether they should be given before, after or simultaneously with immunosuppression.

*3. When to consider catheter ablation for VT (see Table 1D)*

Macro re-entrant arrhythmias around areas of granulomatous scar are the most common mechanism of ventricular arrhythmia (7, 8). Reflecting extensive scarring and multiple inducible morphologies, ablation outcomes are modest. A recent systematic review of catheter ablation for CS reported on 83 patients from 5 studies. The median number of VTs was 3 (2.6–4.9) per patient; 18% required epicardial ablation. Over a follow-up of about 2 years, 38/83 (45.7%) patients had no recurrent VT and 61/83 (88.4%) patients improved following ablation (i. e., free from arrhythmia or had a reduction of burden). Reflecting these modest ablation outcomes the HRS document recommends ablation for patients with CS and ventricular arrhythmias refractory to immunosuppressive or antiarrhythmic therapy. In contrast the JCS group suggests ablation for patients’ refractory to immunosuppressive and antiarrhythmic therapy.

Yalagudri examined the HRS approach in 18 patients and found that in 4/18 patients with VT in the scar phase responded well to anti-arrhythmic drugs and ablation (9). The other fourteen had positive FDG-PET scans and were treated with immunosuppression and 4/14 patients in the inflammatory group had recurrence of VT during follow-up. Three were found to have disease reactivation. Intensified immunosuppression suppressed VT in all and in one patient, VT recurrence was found to be scar related and was successfully treated with ablation (9).

### Pacemaker and ICD implantation

*1. Should patients with AV block and normal or near normal ejection fraction receive a pacemaker or an ICD*

The HRS statement suggested that an ICD for CS patients with an indication for a pacemaker “can be useful” (3). The JCS document take a largely similar position although with some additional criteria related to National Health Coverage guidelines (see Table 1 for details).

The data to support the HRS recommendation is increasingly compelling. In a study of 22 Japanese CS patients with high-grade AV block, over a median follow-up of 45 months,

**Table 1** Key similarities and differences in recommendations between 2014 HRS and 2016 JCS documents

| HRS  | JCS   | Comparison |
|--|---|------------|
| Table 1A: When to consider immunosuppression?<br>For AV block and/or VT (if evidence of inflammation)  |   | different  |
|  | Corticosteroids are recommended regardless of whether symptoms are present or not   |            |
| Table 1B: When to treat with immunosuppression for management of VT?   |   | different  |
| 1. Immunosuppression can be useful in CS patients with frequent ventricular ectopy or non-sustained VT and evidence of myocardial inflammation.<br><b>(class IIa recommendation)</b><br>2. Immunosuppression can be useful in CS patients with sustained ventricular arrhythmias and evidence of myocardial inflammation.<br><b>(class IIa recommendation)</b> | <u>Indications for corticosteroid therapy</u><br>1. Patients with cardiac involvement demonstrated by positive 67Ga scintigraphy or 18F-FDG PET findings<br><b>(Class I, Evidence level 4a, Recommendation grade A)</b><br>2. Patients without cardiac involvement demonstrated by positive 67Ga scintigraphy or 18F-FDG PET findings<br><b>(Class IIa, Evidence level 4b, Recommendation grade C1)</b> |            |
| Table 1C: When to treat with antiarrhythmic medications for management of VT?  |   | different  |
| Antiarrhythmic drug therapy can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy<br><b>(Class IIa recommendation)</b>  | Amiodarone, sotalol, and class Ib antiarrhythmic drugs for the treatment of uncontrollable ventricular tachycardia <b>(Class IIa, Evidence level 6, Recommendation grade C1)</b>  |            |
| Table 1D: When to consider catheter ablation for VT?   |   | different  |
| 1. Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive and antiarrhythmic therapy.<br>2. Catheter ablation can be useful in patients with incessant ventricular arrhythmias.<br><b>(class IIa recommendations)</b>   | <u>Indications for Catheter Ablation</u><br>1. Patients with ventricular tachycardia uncontrollable with corticosteroids or antiarrhythmic drugs<br>2. Patients with paroxysmal ventricular tachycardia who cannot take antiarrhythmic drugs<br>3. Patients with or without ICD who experience storms of ventricular tachycardia<br><b>(Class I, Evidence level 5, Recommendation grade B)</b>          |            |
| Table 1E: When to implant a device for bradycardia?  |   | same       |
| Following standard device guidelines   | Following standard device guidelines  |            |
| Table 1F: When to implant an ICD in patients with an indication for a pacemaker?   |   | similar    |
| An ICD for CS patients with an indication for a pacemaker can be useful (i.e. regardless of LVEF)<br><b>(class IIa recommendation)</b>   | Patients who are indicated for pacemaker implantation AND with a LVEF of <50%, AND have either (a) non-sustained ventricular tachycardia** AND/OR (b) in whom sustained VT or VF was induced during electrophysiological Testing <b>(Evidence level 4a, Recommendation grade C1).</b>   |            |
| Table 1G: When to implant an ICD for secondary prevention of SCD?  |   | same       |
| After cardiac arrest or sustained VT   | After cardiac arrest or sustained VT  |            |
| Table 1H: When to implant an ICD for primary prevention of SCD (also see table 2)  |   | same       |
| LVEF <35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)   | LVEF <35%, despite optimal medical therapy and a period of immunosuppression**  |            |

\*\* ICD is not covered by the NHI in Japan

2/22 patients suffered aborted sudden cardiac death (SCD) and 9 had sustained ventricular tachycardia (VT) (10). Nordenswan et al (11) reported on the arrhythmic outcomes of 143 CS patients who presented with Mobitz II or 3rd degree AV block. Of these patients, 107 (75%) patients received pacemakers, 35 (24%) patients received ICD and 1 patient refused device implant. Over a median follow-up period of 4.1 years, 23/143 (16.1%) patients suffered either fatal (13) or aborted (n=10) SCD. An additional 21 patients had sustained VT and the combined endpoint of SCD/VT occurred in 44/143 (30.8%). The annual rate of the combined endpoint in the patients with

normal left ventricular ejection fraction (LVEF) was 5%. These two papers clearly support the HRS statement that an ICD for CS patients with indications for pacing “can be useful” (3).

## 2. Which patients with CS should receive an ICD for secondary prevention

The Guidelines agree that all patients with cardiac arrest or sustained VT should have an ICD implanted.

### 3. Which patients with CS should receive an ICD for primary prevention

Both HRS and the JCS documents agree that ICDs are recommended in patients with general guideline indications for primary prevention (i.e. LVEF less than 35%). However, it should be noted that the NHI in Japan do not cover ICD implantation in these patients unless they have a positive EP study.

Also, which additional patients should be considered for ICDs is controversial. What seems clear that is that CS, perhaps because of the patchy involvement of the LV and/or RV, and perhaps because of active inflammation, may not behave in the same fashion as other cardiomyopathies with regard to risk of ventricular arrhythmias (12–14). Although a lower LVEF was associated with occurrence of appropriate ICD therapy, CS patients with mildly impaired LV function had substantial risk of arrhythmia (12–14). Based on these observations the HRS consensus suggested that for patients with LVEF 36%–49% and/or an RV ejection fraction <40%, ICD implantation may be considered (class IIb recommendation) (3). For patients with preserved ventricular function, additional investigations (e.g. CMR assessment and an EP study (if LGE present) are suggested and prophylactic ICD is recommended if ventricular arrhythmia is inducible with an EP study (3). This latter recommendation was based on a study of 76 patients with evidence of CS on either a CMR or PET (15). Eight patients (10.5%) were inducible for sustained ventricular arrhythmia and underwent ICD implantation. Patients were followed for a mean period of 5.6 years and the primary endpoint of ventricular arrhythmia or death occurred 75% in the positive group and 1.5% in the Programmed electrical stimulation (PES) negative group (15). Importantly patients with positive PES had a mean baseline LVEF of  $36.4 \pm 4.2\%$ , which fell to  $21.0 \pm 12.0\%$  at 2 years. Only one patient with normal LVEF had a positive PES and this patient has been arrhythmia-free in follow-up. Whether a positive PES is more predictive of events than an estimation of LVEF is unclear and further research is needed. The 2016 JCS document is broadly similar, with the major exception that all patients with LVEF between 35 and 50% should have an EP study.

Recently the 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death produced largely similar guidelines for the use of ICDs in CS patients (16). The key difference between the 2 documents pertains to patients without significant LV systolic dysfunction (i.e. LVEF >35%). A summary of the relevant recommendations is shown in Table 2. The difference can in part be explained by new CMR data that have been published since 2014. In a meta-analysis of 7 studies involving 694 CS patients in whom 199

had LGE on CMR, Hultén et al. reported that cardiovascular mortality occurred in 10 LGE positive patients and two LGE negative subjects (17). In addition, ventricular arrhythmias occurred in 41 LGE-positive patients while no patient experienced VT/VF if the CMR was negative for LGE. These emerging CMR data are important but have some important limitations:

(i) Most of the studies were single center and/or were retrospective.

(ii) The confidence intervals around the odds ratios are very wide.

(iii) They were little data on how many of the cardiovascular deaths were SCD.

We think that our field of research can learn from similar research in other conditions. One specific example is hypertrophic cardiomyopathy (HCM) which has accrued a much larger data set. A recent meta-analysis of 2993 HCM patients showed that, after adjustment for baseline characteristics, there was a clear relationship between the extent of LGE and SCD risk (18). Some recent studies have started to show similar observations in CS with the great majority of events occurring in patients with greater extent of LGE (LGE expressed as % LV mass) e.g. LGE >21.4% (19), or >20% (20), or >8% (21). Location may also be important; in 51 patients with CS and LVEF >35%, the presence of RV delayed enhancement was associated with an increased risk of VT/VF or death (22). Cardiac PET is also emerging as a modality that may help with risk stratification (23).

#### Additional minor differences

(i) The HRS document has a section on the management of atrial arrhythmias (AAs). AAs in CS have in received relatively modest attention, but recent retrospective studies have suggested a substantial incidence (24, 25). Also there are a few case reports suggesting that immunosuppression and/or ablation may be useful (26–28). The HRS guidelines contain limited guidance; the only formal recommendations are to assess anticoagulation based on a standardized scoring, and to avoid Class I anti-arrhythmic drugs (3).

(ii) The JCS document includes some very detailed and helpful recommendations on the use of advanced heart failure therapies including the role of cardiac transplantation.

#### Conclusions and future directions

The Japanese have been leaders in many aspects of CS including in guideline development and there is much to like about the latest version, most importantly the first attempt at defining ICS. The future of CS management is bright, with increasing international collaborations and also multiple efforts underway to obtain higher quality data to inform future guidelines. An important limitation of our current knowledge

**Table 2** Comparison of recommendations for primary prevention ICDs in CS patients with near normal or normal ventricular function

| 2014 HRS expert consensus statement expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis (3) |   | 2016 Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis (1) |   | 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (16) |  |
|---|---|--|---|--|--|
| LVEF 36%-49% and/or an RV ejection fraction <40%  | ICD implantation ( <b>class IIb recommendation</b> )  | LVEF >35% and <50%   | Additional criteria for ICD implantation<br>One or more of a-b<br>(a) late enhancement in cardiac MRI<br>(b) positive findings of 18F-FDG PET or 67Ga-scintigraphy<br>AND<br>sustained ventricular tachycardia or ventricular fibrillation induced during electrophysiological testing**<br><b>(Evidence level 4a, Recommendation grade C1)</b> | LVEF >35%  | ICD Implantation in patients with evidence of extensive* myocardial scar by cardiac MRI or positron emission tomographic (PET) scan<br><b>(class IIa recommendation)</b> |
| LVEF normal   | Consider CMR and if LGE + then do EP Study<br><br>If EPS is positive then ICD implantation (class IIa recommendation)<br><br>ICD implantation is not recommended in patients with normal LVEF/RVEF and a negative EP Study (regardless if LGE on CMR) |  |   |  |  |

\*Extensive not defined

\*\*Sustained ventricular tachycardia is defined as having a duration of  $\geq 30$  seconds. Induction of VT/VF by 3 consecutive extrastimuli at a coupling interval of <220 msec is handled as a non-specific reaction.

is that most data is from Caucasian (largely Northern European) and Japanese populations; there is little information on CS from other ethnic groups.

Key unresolved questions include, but are not limited to:

(i) What is the best, most cost-effective method to screen for silent CS in patients with extra-cardiac disease? How frequently should patients be screened?

(ii) Can CS be diagnosed without a positive biopsy?

(iii) What is the effect of corticosteroid treatment on the clinical course of the various manifestations of CS? How long should patients be treated for? Do all patients need to be treated?

(iv) What is the role of other immunotherapy in the treatment of clinically manifest CS?

(v) Should we treat clinically silent CS? What is the prognosis of clinically silent CS?

(vi) How can we prevent SCD in CS? How should we stratify the risk for SCD? Who should receive ICDs?

(vii) What is the role of advanced imaging (PET and CMR) and novel biomarkers in diagnosis and guiding treatment of CS? How can we improve quantification of CMR and PET findings?

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#### Conflicts of interest

None.

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## Management of Cardiac Sarcoidosis

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