Cardiac Sarcoidosis

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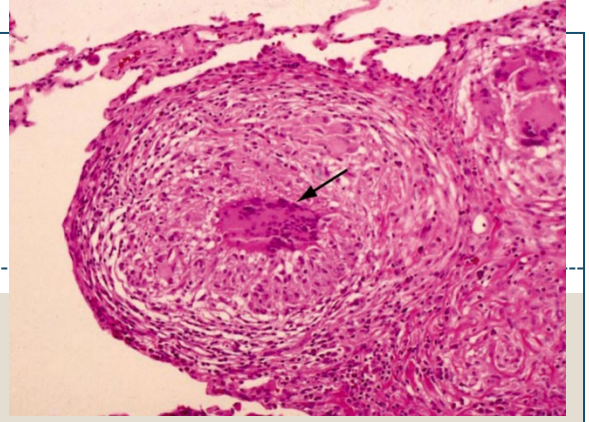
Cardiac Sarcoidosis :Which is the true statement?

- 1. Up to 50% involvement in Patients with Sarcoidosis
- 2. CHB with normal EF should get an ICD
- 3. ICD may be indicated if EF<49%
- 4. CMR important in diagnosis and risk stratification
- 5. Hard to do a CS talk in 20 min

Sarcoidosis Background



- Granulomatous disease of unknown etiology. 60/100,000 in US
- Studies suggest may be an immunological response to a yet unidentified antigenic trigger, in genetically susceptible individuals.
- Hallmark :Non- caseating granulomas

Most often pulmonary and intrathoracic LN but may involve heart, CNS, liver, lymph nodes, spleen, skin, eyes, phalangeal bones, parotid gland, or other organs or tissues.

- 60-70% may have spontaneous resolution
- Higher Prevalence in Northern Europeans and African Americans. Average age of disease presentation is 30-50 years

Sarcoidosis Background

- **Cardiac Sarcoidosis** classically described to be present <5%. Recent studies with Imaging suggest >30% involvement in asymptomatic patient
- A rare disease, therefore no randomized controlled trials or blinded studies have been performed to date.
- Therefore all recommendations in the consensus statement are level of evidence C (based on experts' opinions). Required a vote of >/=75% for all recommendations.
- Lack of Reference Standard. EMBx low yield 20-30%.
- 3 clinical Criteria. HRS. JMHW. WASOG

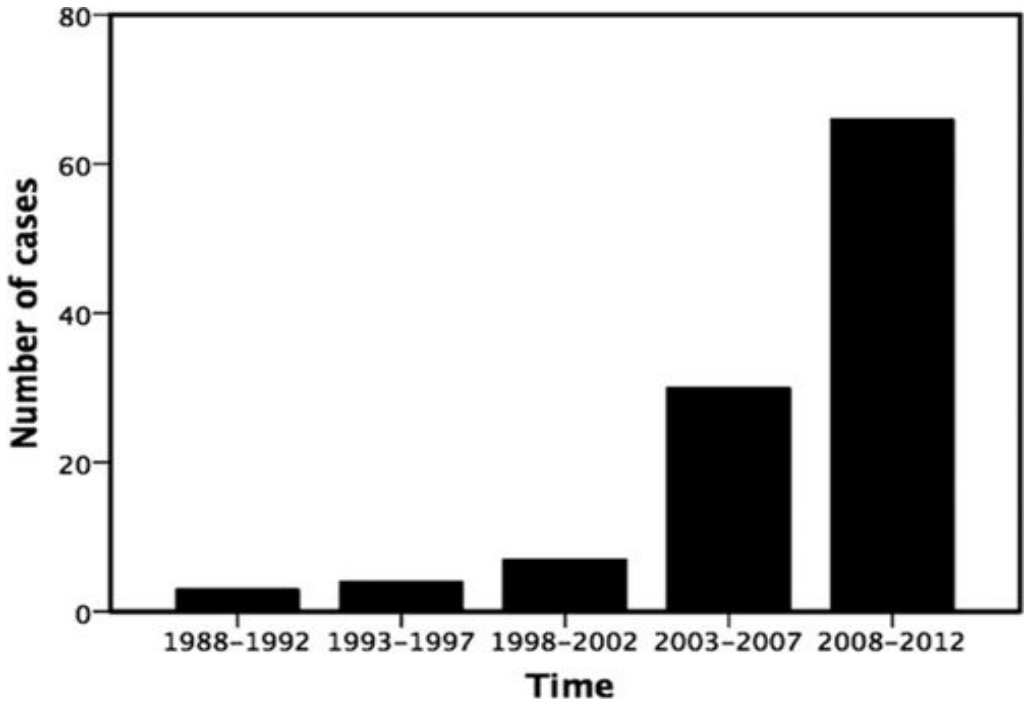
Outline

Cardiac Sarcoidosis (CS) Recommendations (HRS2014)

1. Diagnosis
   A. Diagnostic Criteria
   B. Screening asymptomatic
   C. When to ECG, echo, cMRI or FDG-PET, biopsy

2. Management : Specific Therapies
   1. Pacing /Heart block
   2. Arrhythmia Mgmt (atrial and ventricular)
   3. SCD Risk Stratification /ICD Implantation
   4. Immunosuppressant therapy
   5. Multidisciplinary approach

The number of new cases of cardiac sarcoidosis diagnosed in the 5-year periods between 1988 and 2012.



Increased awareness
Wider use of advanced imaging modalities

Riina Kandolin. Circulation. Cardiac Sarcoidosis, Volume: 131, Issue: 7, Pages: 624-632, DOI: (10.1161/CIRCULATIONAHA.114.011522)

CS Prevalence Based on Imaging

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.

Diagnosis of Cardiac Sarcoid

Chest. 2008 Jun;133(6):1426-35. doi: 10.1378/chest.07-2784. Epub 2008 Mar 13.

Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing.

Mehta D[1], Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M, Machac J, Teirstein A.

Small study by Mehta et al (Chest 2008) of 62 pts with sarcoidosis
Those with symptoms (sig palps, syncope, or presyncope) or abnormal ECG, Holter, or echo underwent CMR or FDG-PET.
Found the presence of any abnormal screening variable has a sensitivity of 100% and a specificity of 87% for the Dx of CS.
Remains the most comprehensive study to date, and a second subsequent study found similar results.

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

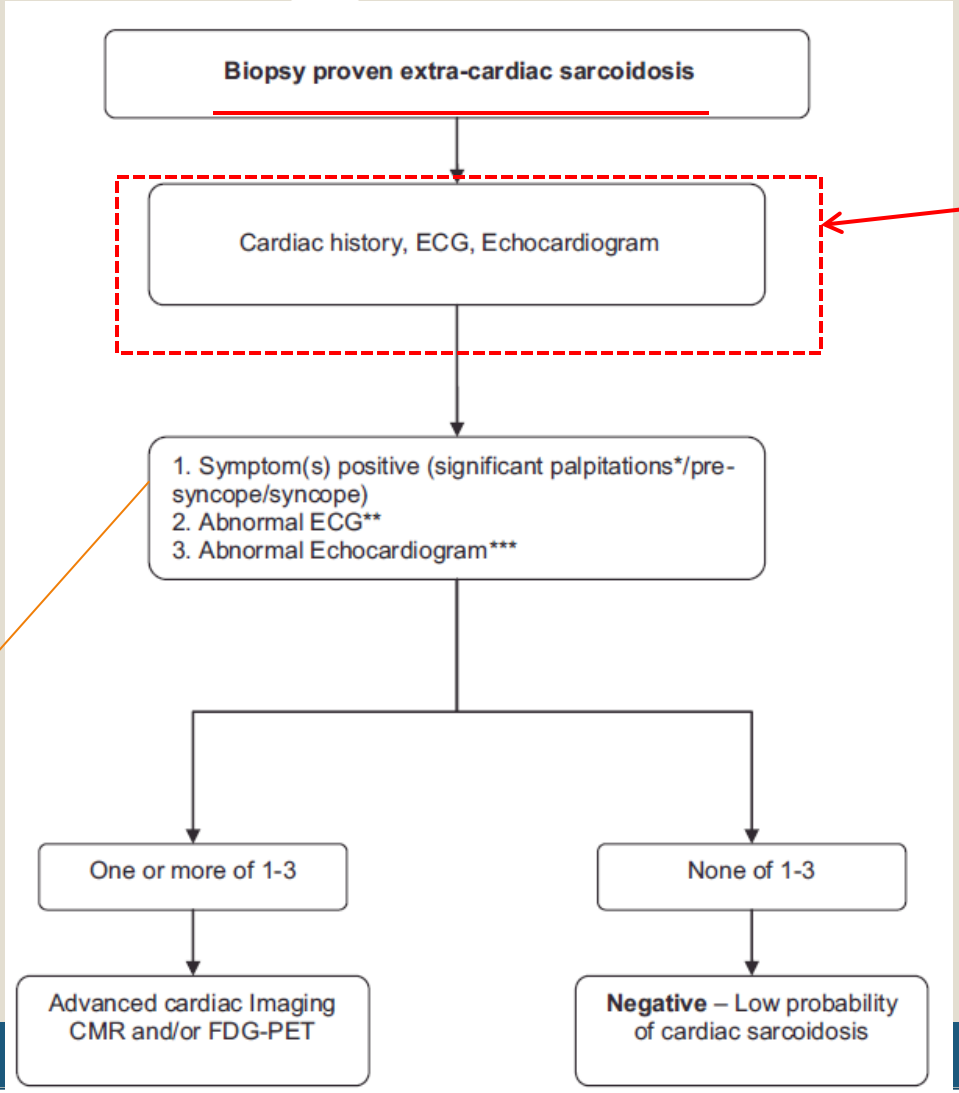
Abnormality on baseline testing	Prevalence*	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
History of cardiac symptoms	12 (19)	46 (26–27)	95 (82–99)
Electrocradiogram	3 (50)	8 (1–27)	97 (86–100)
Holter	13 (21)	50 (29–71)	97 (86–100)
Echocardiogram	8 (13)	25 (10–47)	95 (82–99)
Any screening variable	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)

Significant echo abnormality was defined as LVEF </= 45%, two or more segments of WMAs, RV dysfct in the absence of PHTN, or sig diastolic dysfct inappropriate for the pt's age.

Significant Holter abnormality was defined as >10 PVCs/hour, or NSVT, or sustained VT, or more than 3 beats of SVT.

CS Diagnosis Algorithm if known extra-cardiac HRS 2014

Suggested algorithm for the investigation of patients with biopsy-proven extracardiac sarcoidosis.



If any of these are + then cMRI and/or FDG-PET.

If none are positive then is low probablity of CS.

Why no Holter? 10 of 14 (71%) of members voted to include but did not reach the predefined 75% threshold.

•Palpitations: defined as "prominent patient complaint lasting > 2 weeks "

•** 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

•*** abnormal echocardiogram defined as RWMA and/or wall aneurysm and/or basal septum thinning and/or LVEF < 40%*

CMR or/and FDG-PET
Standard of Care

- CMR/LGE /T2
  - Sensitivity/Specificity 76%/92% EMBx. 76%/92% JMHW
  - Most common- one or more patchy regions
  - Most common affected location: basal to mid septum. Involvement of basal anteroseptum and inferoseptum with contiguous extension into RV is almost pathognomonic of CS
- FDG-PET:
  - Sensitivity/Specificity 89%/78% JMHW 2006
  - FDG glucose analogue useful for differentiating between normal and active inflammatory lesions. Gold standard for monitoring immunosuppressive treatment response
  - 3 patterns: diffuse, focal , focal on diffuse

Prognostic Value of Myocardial Scarring on CMR in Patients With Cardiac Sarcoidosis

G. Cameron Coleman, MD,[a] Peter W. Shaw, MD,[a] Pelbreton C. Balfour, Jr, MD, ScM,[a] Jorge A. Gonzalez, MD,[a] Christopher M. Kramer, MD,[a,b] Amit R. Patel, MD,[c,d] Michael Salerno, MD, PhD, MS[a,e]

ABSTRACT

OBJECTIVES This study sought to perform a systematic review and meta-analysis to understand the prognostic value of myocardial scarring as evidenced by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging in patients with known or suspected cardiac sarcoidosis.

BACKGROUND Although CMR is increasingly used for the diagnosis of cardiac sarcoidosis, the prognostic value of CMR has been less well described in this population.

METHODS PubMed, Cochrane CENTRAL, and metaRegister of Controlled Trials were searched for CMR studies with ≥1 year of prognostic data. Primary endpoints were all-cause mortality and a composite outcome of arrhythmogenic events (ventricular arrhythmia, implantable cardioverter-defibrillator shock, sudden cardiac death) plus all-cause mortality during follow-up. Summary effect estimates were generated with random-effects modeling.

RESULTS Ten studies were included, involving a total of 760 patients with a mean follow-up of 3.0 ± 1.1 years. Patients had a mean age of 53 years, 41% were male, 95.3% had known extracardiac sarcoidosis, and 21.6% had known cardiac sarcoidosis. The average ejection fraction was 57.8 ± 9.1%. Patients with LGE had higher odds for all-cause mortality (odds ratio [OR]: 3.06; $p < 0.03$) and higher odds of the composite outcome (OR: 10.74; $p < 0.00001$) than those without LGE. Patients with LGE had an increased annualized event rate of the composite outcome (11.9% vs. 1.1%; $p < 0.0001$).

CONCLUSIONS In patients with known or suspected cardiac sarcoidosis, the presence of LGE on CMR imaging is associated with increased odds of both all-cause mortality and arrhythmogenic events. (J Am Coll Cardiol Img 2017;10:411–20) © 2017 by the American College of Cardiology Foundation.

Limited extent LGE <6% have better outcome compared with extensive LGE >20%

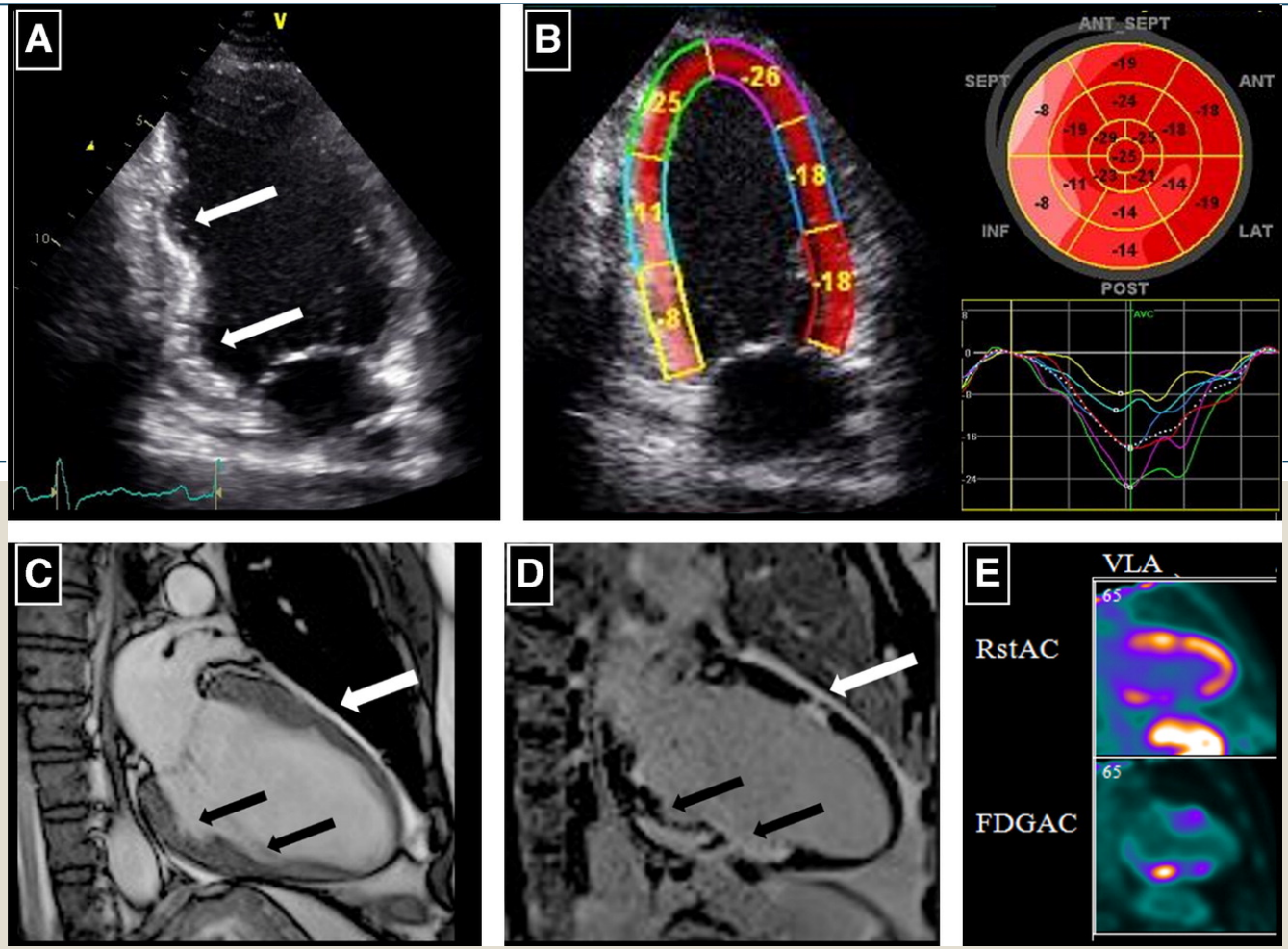


Figure 1. Multimodality cardiac imaging in a 49-year-old white man with cardiac sarcoidosis. (*A*) Transthoracic echocardiogram two-chamber view showing focal aneurysms in the basal and mid inferior wall (white arrows). (*B*) Two-dimensional longitudinal strain showing reduced regional strain in the basal to mid-inferior wall (yellow and aqua segments/lines on regional strain map [left] and graph [bottom right]), along with reduced strain (pink segments) in the basal to mid-inferior wall and basal infero-septum on global bull's-eye strain plot (top right). (*C*) Cardiac magnetic resonance imaging (MRI) vertical long axis (VLA) cine image showing inferior wall aneurysms (black arrows), as well as a small aneurysm in the mid anterior wall (white arrow), which was not detected by echocardiogram. (*D*) Corresponding cardiac MRI VLA phase-sensitive inversion recovery sequence showing near-transmural focal regions of delayed enhancement consistent with fibrosis or inflammation. (*E*) Cardiac positron emission tomography VLA demonstrating reduced resting perfusion in the mid-inferior wall (RstAC: top figure), along with increased fluorodeoxyglucose F 18 (FDG) uptake in the basal to mid-inferior wall and mid-anterior wall (FDGAC: bottom figure) supportive of active inflammation in these segments.

Annals ATS, 2019
https://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.201902-119CME

CS Diagnostic Criteria(HRS 2014)

*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.

Voltage Guided Endomyocardial Bx

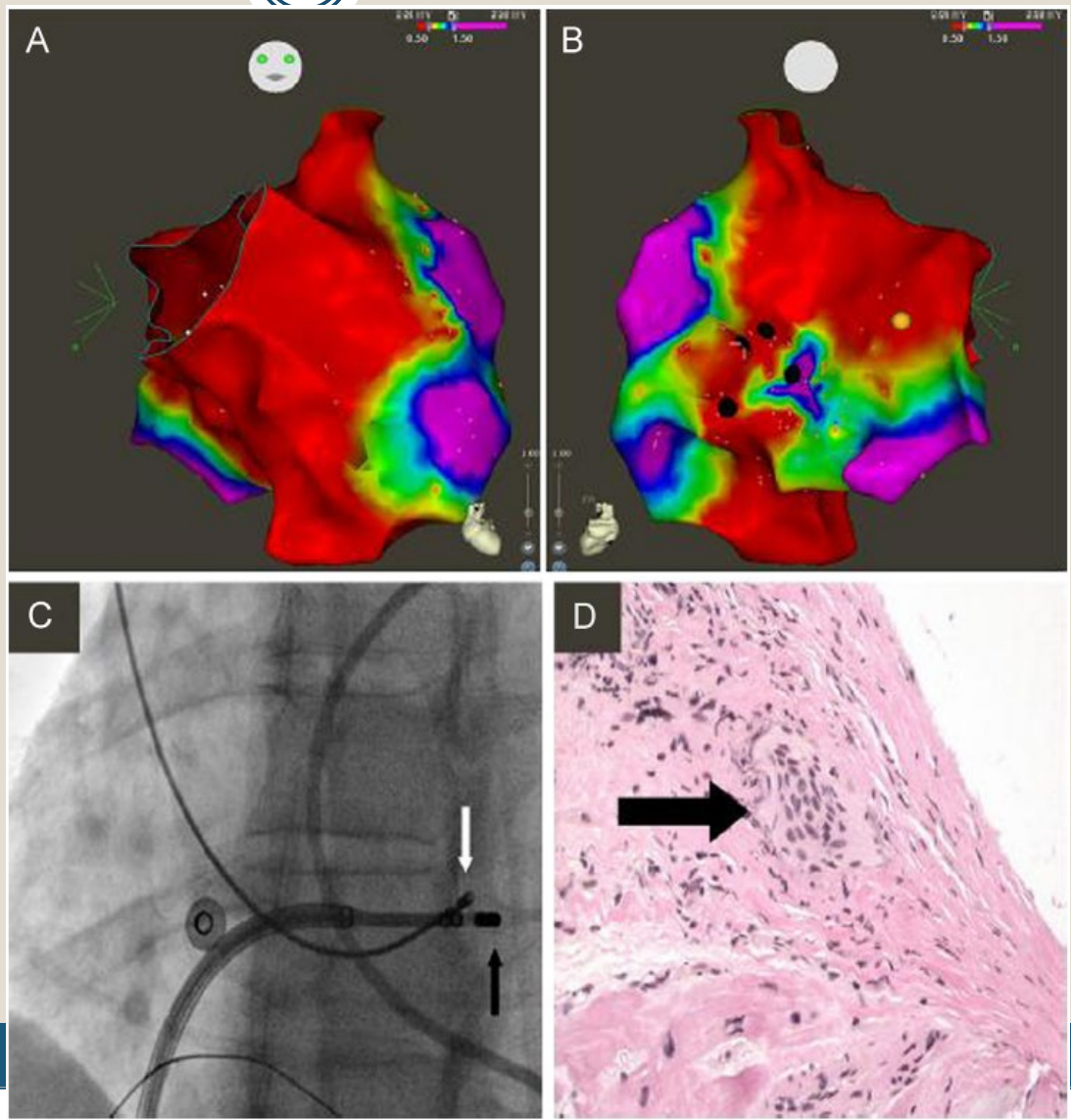
A and B: Bipolar voltage map of the RV displaying anterior (panelA) and posterior (panelB) views.

Green, yellow, and red indicate low-voltage regions; purple denotes regions of normal voltage, defined as >1.5mV

Black circles illustrate areas targeted for biopsy. Yellow circle illustrates location of right bundle.

C: Fluoroscopic LAO image showing the bioptome (whitearrow) targeting the low-voltage region in the RV septum, adjacent to the mapping catheter (black arrow).

D:Microscopic view of an endomyocardial bx specimen from the RV septum showing noncaseating granuloma (arrow) (hematoxylin-eosin stain,magnification 200).



Isolated Cardiac Sarcoidosis

Epidemiology

- As many as 25% of patients with CS may have ICS
- Patients with ICS have worse LV systolic function at presentation as compared with patients with systemic sarcoidosis and CS

Diagnosis

- The diagnosis of ICS is challenging, in part because the sensitivity of EMB is limited
- Current clinical criteria do not provide a means of diagnosing ICS in the absence a positive EMB, even when advanced imaging techniques such as MRI or PET are abnormal
- Only 1 in 4 highly probable cases were confirmed histologically post cardiac transplant

Isolated Cardiac Sarcoidosis

Therapy

- Poor response to Immunotherapy
- ICD therapy is effective at aborting ventricular dysrhythmias in patients with ICS

Prognosis

- Patients with ICS have more ventricular arrhythmias and mortality compared with patients with systemic sarcoidosis and CS

Cardiac Sarcoidosis

Clinical Presentation

Table 1: Cardiac Findings in Cardiac Sarcoidosis[5]

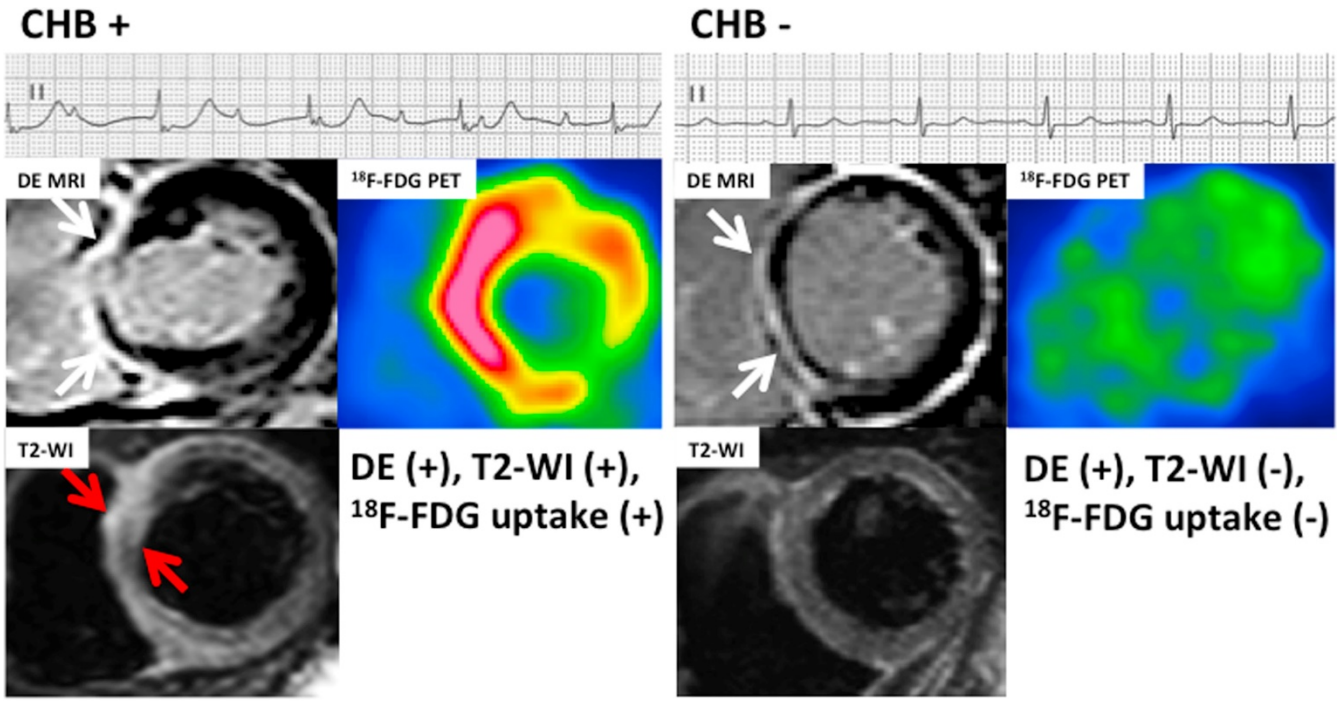
Cardiac Finding	Prevalence
Complete heart block	23%-30%
Bundle branch block	12%-32%
Ventricular tachycardia	23%
Congestive heart failure	25%-75%
Sudden death	25%-65%

Management of Cardiac Sarcoidosis

- Multidisciplinary Approach
- Corticosteroids first line of treatment
  - Dose: 20-60 mg/day. Usually <30 mg/day
  - Duration 3-168 months
  - Combination with Immunosuppresants
    - Prospective cohort study from Japan showed stable EF-5 Yrs
    - Methotrexate, azathioprine, lefunomide, mycophenolate
  - Refractory Sarcoidosis
    - TNF antagonists: infliximab,adalimumab
    - ? HF NYHA III IV

Response to Immunosuppressant Therapy

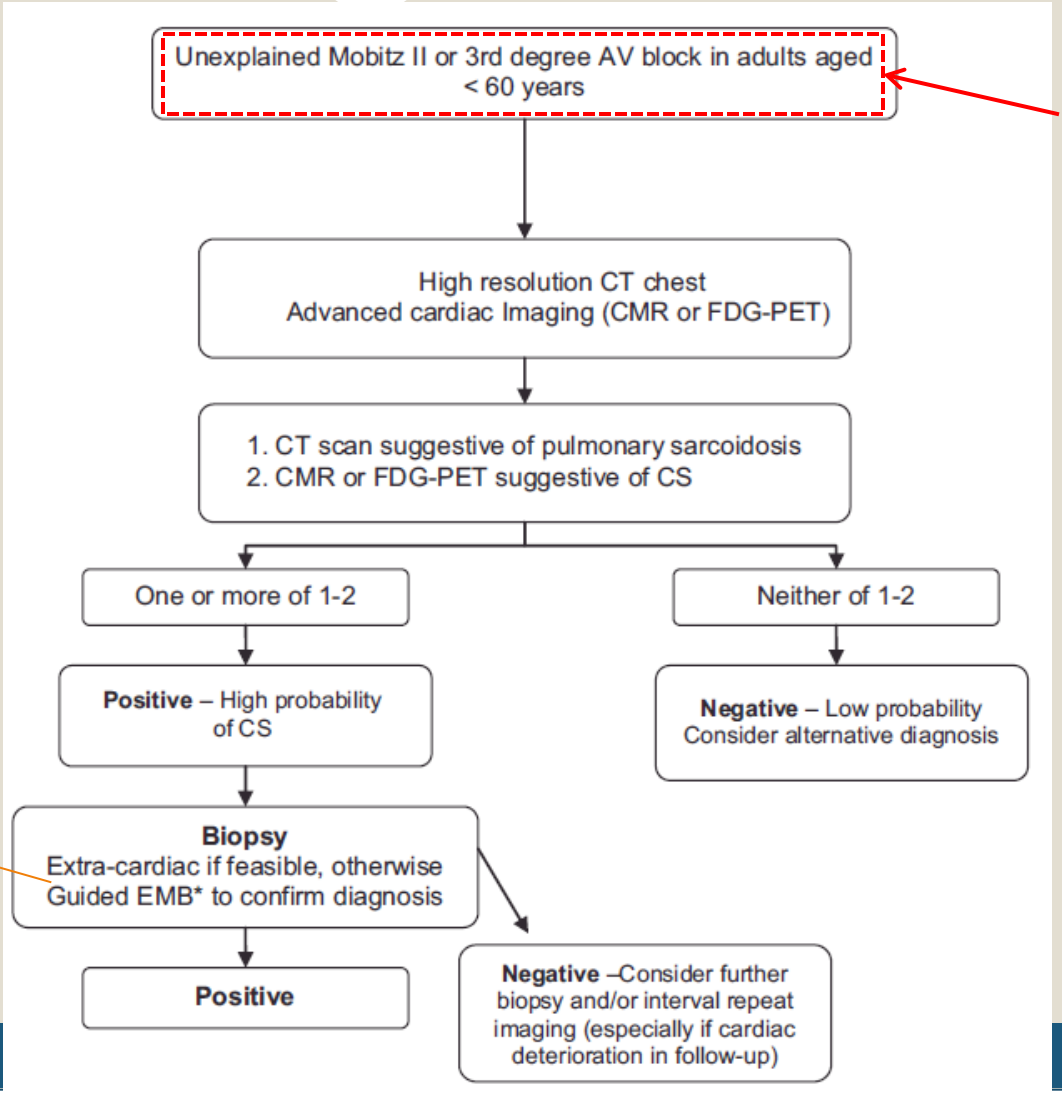
- 47% High degree AVB responded
- Heart Failure:
  - Normal EF: preserve EF
  - Mild-moderate: some improvement
  - EF<30% no response
  - Different results in Finland study:
    - Only patients with low EF improved
  - Small American cohort:
    - Early initiation <1 month of diagnosis; improvement in EF
  - Most patients with CS should be treated with an early and prolonged trial



CHB: complete heart block; DE: delayed enhancement; MRI: magnetic resonance imaging; T2-WI: T2-weighted image; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography

CS Diagnosis Algorithm if Unexplained Mobitz II or 3rd degree AVB in an adult <60.

Suggested algorithm for the investigation of patients with unexplained Mobitz II or third-degree AV block who are younger than 60 years (this suggests CS).



If either of these ECG findings then high res CT chest AND CMR or FDG-PET

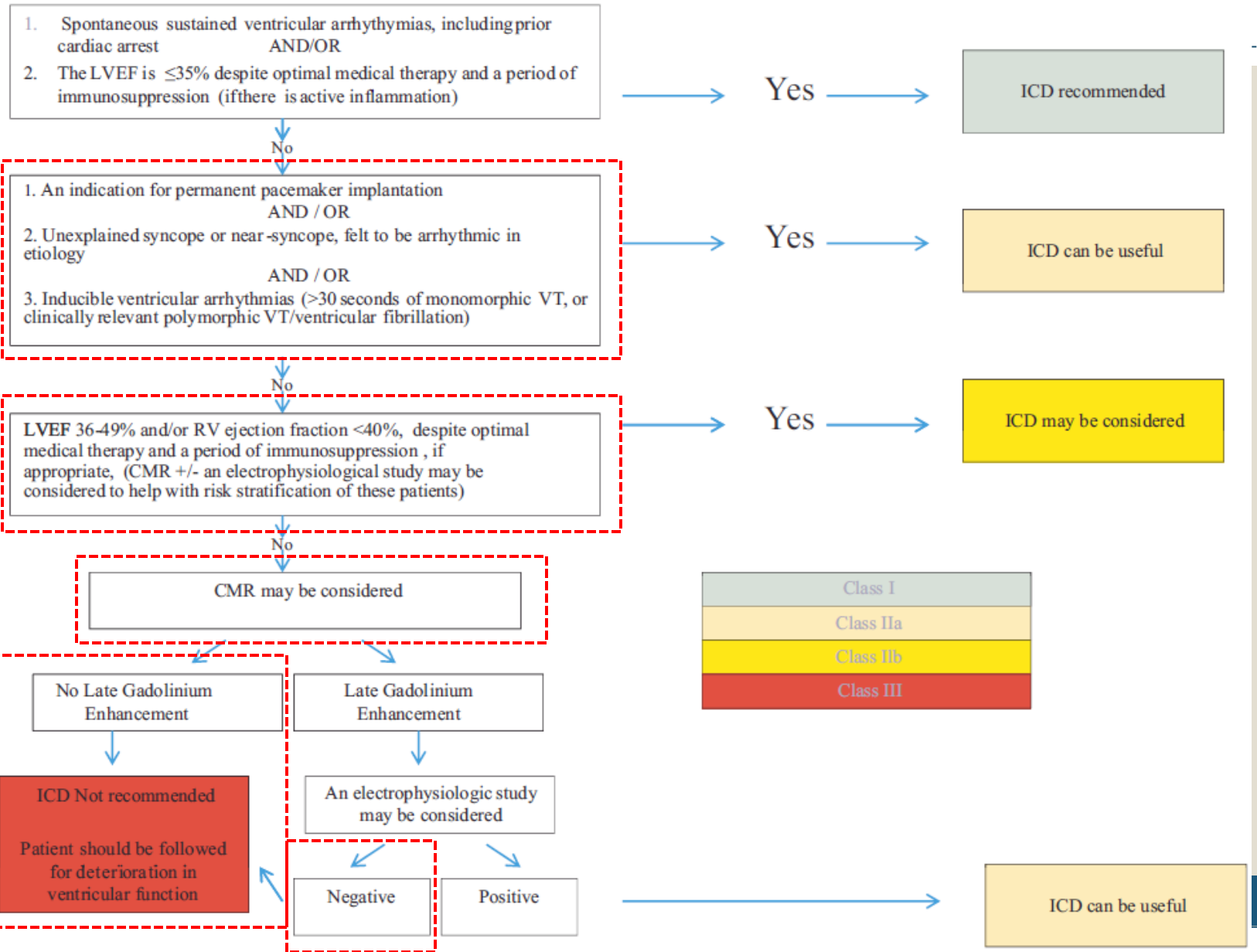
If either is + then is high probability of CS therefore then extra-cardiac bx. Voltage or imaging guided EMB if not feasible.

*voltage guided or advanced imaging guided endomyocardial biopsy

Risk Stratification for SCD

- LV function: EF
  - LVEF 36-49% also high risk
  - RVEF <40%
- Role of PES:
- Role of CMR: focal involvement with preserved EF
  - in EF>35%

ICD Implantation in Cardiac Sarcoid



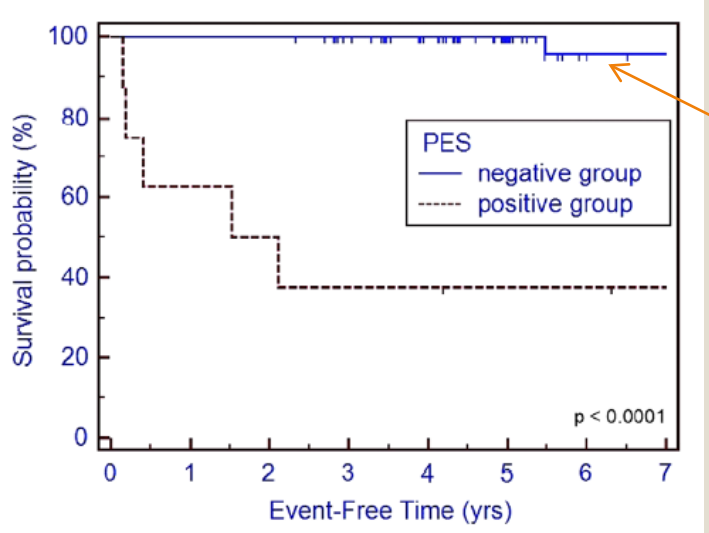
CS SCD Risk Stratification

Circ Arrhythm Electrophysiol. 2011 Feb;4(1):43-8. doi: 10.1161/CIRCEP.110.958322. Epub 2010 Dec 30.

Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation.

Mehta D[1], Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A.

- 76 pts with established CS underwent PES.
- All pts had extracardiac bx proven sarcoid + cMRI or FDG-PET CS.
- 8 (10.5%) pts were inducible for sustained VT and underwent ICD vs none of the 68 without any inducible arrhythmia.
- 4/6 in the PES+ group had EF <40% at time of PES.
- Only 1 pt with normal EF had +PES, and this pt has remained arrhythmia free during follow-up.
- Based on this the writing group voted but also recog that this data needs to be reproduced in larger cohorts.



Vertical markers indicate the time when follow-up was terminated in each patient.

Kaplan-Meier estimation of event-free survival.

Mehta et al

*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

Otherwise given the limited data to help with risk stratification in pts with CS the writing group agreed that recommendations from the general device guideline documents also apply to this population.

Ventricular Arrhythmias in CS

- Triggered activity and abnormal automaticity
- Macrorentrant arrhythmias around granulomatous scars
- Active inflammation promotes VT
- VT/VF storm: Immunosuppresion/ FDG-PET
- Immunosuppressive therapy: modest data
  - More useful in early phase with preserved EF
- AAD: Amiodarone, Sotalol
- Ablation: Recurrences common

VT Ablation Outcomes in Cardiac Sarcoid

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

Atrial Arrhythmias in CS

- Common : 32 % SVT. AF 18%
- Immunosuppressive Therapy ?
- Inappropriate ICD therapies
- Avoid class I agents
- EPS/ ablation

Cardiac Sarcoidosis
Epidemiology, Characteristics, and Outcome Over 25 Years in a Nationwide Study

Table 2. Survival Probabilities in All 110 CS Patients and in the 102 Patients Diagnosed Before Transplantation or Autopsy (Table view)

	Cardiac Survival, n	Cardiac Survival Free of Transplantation	Cardiac Survival Free of Transplantation and Aborted Sudden Death	Cardiac Survival
1- y survival, %	110	99.1 (94.3–99.9)	97.3 (91.6–99.3)	89.1 (81.3–93.9)
	102	100 (95.5–100)	99.0 (93.9–99.9)	89.2 (81.1–94.2)
5-y survival, %	110	93.5 (86.7–97.1)	90.0 (82.4–94.6)	77.7 (68.5–84.8)
	102	97.0 (90.9–99.2)	95.1 (88.4–98.2)	82.0 (72.9–88.7)
10-y survival, %	110	89.3 (81.6–94.2)	83.1 (74.5–89.3)	70.4 (60.8–78.5)
	102	92.5 (85.1–96.5)	90.6 (82.7–95.2)	77.2 (67.6–84.7)

The overall prognosis of CS was better than generally considered

The 10-year probability of transplantation-free cardiac survival was 83% overall and 91% in patients receiving immunosuppressive treatment.

Heart failure at presentation, marked LV dysfunction at diagnosis (LVEF <35%), and isolated CS type predicted poor outcome.

Circulation Volume 131, Issue 7, 17 February 2015; Pages 624-632

Cardiac Sarcoidosis :Which is the true statement?

- 1. Up to 50% involvement in Patients with Sarcoidosis
- 2. CHB with normal EF should get an ICD
- 3. ICD may be indicated if EF<49%
- 4. CMR important in diagnosis and risk stratification
- 5. Hard to do a CS talk in 20 min
- 6. **ALL OF THE ABOVE**

Conclusion

- Sarcoidosis rare but challenging disease
- CS can be present in up to 25-50% of asymptomatic Patients
- Screen all patients with extra cardiac sarcoidosis
- CMR and FDG-PET important diagnostic tools
- High risk for SCD
- Limited therapeutic options: Steroids
- Review HRS Guidelines

THANK YOU