



Effective Health Care

Treatment for Cardiac Sarcoidosis

Results of Topic Selection Process & Next Steps

The nominator is interested in a new evidence review on treatment of cardiac sarcoidosis. A new evidence review could be used by another group to develop a clinical practice guideline.

Because limited original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Number and Name: #814, Treatment for Cardiac Sarcoidosis

Nomination Date: 8/31/2018

Topic Brief Date: 01/08/2019

Authors

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

- Sarcoidosis is a systemic granulomatous disease that usually affects the lung and lymph nodes. It can affect any organ however.
- Prevalence of sarcoidosis ranges from 10 to 80 cases per 100,000 people.¹ About 5% of patients with sarcoidosis have clinical symptoms of cardiac involvement.²
- Cardiac sarcoidosis can lead to conduction abnormalities, ventricular arrhythmias, sudden death and heart failure.²
- Treatment is aimed at controlling inflammation, preventing scarring, and preserving heart function.³

Nominator and Stakeholder Engagement

We reached out to the nominator and he asked that we include individuals with cardiac sarcoidosis without evidence of cardiac involvement. He otherwise affirmed the scope of the key questions and PICO. He also noted that he did not have a specific timeframe for the completion of the review.

We also reached out the Heart Rhythm Society American Heart Association and American College of Cardiology about their 2014 consensus statement on management of cardiac sarcoidosis. They do not have plans to update it or other guidelines related to this condition in the near future.

Key Questions and PICO

The key questions for this nomination are:

1. What is the effectiveness of corticosteroids for the treatment of cardiac sarcoidosis?
 - a. Does effectiveness vary by duration or dose of corticosteroid?
 - b. Does effectiveness vary by patient characteristics, such as LV function and duration of disease?
2. What is the effectiveness and harms of ICD to prevent sudden cardiac death in people with cardiac sarcoidosis?
 - a. Does effectiveness vary by patient characteristics, such as LV function, previous cardiac arrest?

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, and outcomes (PICO) of interest (Table 1).

Table 1. Key Questions and PICO

Key Questions	KQ 1	KQ 2
Population	Adults with cardiac sarcoidosis <ul style="list-style-type: none">• KQ 1a: Patient characteristics (normal EKG, ventricular abnormality, congestive heart failure, previous cardiac arrest, other comorbidities)	Adults with cardiac sarcoidosis <ul style="list-style-type: none">• KQ 2a: Patient characteristics (normal EKG, ventricular abnormality, congestive heart failure, previous cardiac arrest, other comorbidities)
Interventions	Corticosteroids <ul style="list-style-type: none">• KQ 1b: Dose and duration	Implantable Cardioverter Defibrillator (ICD)
Comparators	<ul style="list-style-type: none">• No corticosteroids• Other immunosuppressants• KQ 1b: other dose and duration of corticosteroids	No ICD

Outcomes	<ul style="list-style-type: none"> • Cardiac function • Development of new arrhythmias • Mortality • Adverse effects of treatment (hyperglycemia, aneurysm formation) 	<ul style="list-style-type: none"> • Sudden cardiac death • Adverse events (lead fracture, lead dislodgement, inappropriate ICD shocks)
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Abbreviations: EKG= echocardiogram; ICD=implantable cardioverter defibrillator

Methods

We assessed nomination for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from October 2013 to October 2018. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by key question and study design to assess the size and scope of a potential evidence review.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic.

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing evidence review. We found no systematic reviews relevant to the nomination scope. See Table 2, Duplication column.

Impact of a New Evidence Review

A new systematic review may have uncertain impact. Corticosteroids are commonly used for treatment of cardiac sarcoidosis, though the optimal dose is not established. Available guidance about the use of ICD between relevant clinical groups varies slightly but is not inconsistent.

Feasibility of a New Evidence Review

A new evidence review may not be feasible due to the limited number of studies. We identified 11 studies; 8 were related to KQ 1 and 3 related to KQ 2. See Table 2, Feasibility column.

Table 2. Key Questions and Results for Duplication and Feasibility

Key Question	Duplication (10/2015-10/2018)	Feasibility (10/2013-10/2018)
KQ 1: Steroid treatment	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: 8 <ul style="list-style-type: none">Cohort: 8⁴⁻¹¹ <u>Clinicaltrials.gov</u> <ul style="list-style-type: none">Not yet recruiting: Cardiac Sarcoidosis Randomized Trial (CHASM-CS-RCT) NCT03593759
KQ 2: ICD to prevent sudden cardiac death	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: 3 <ul style="list-style-type: none">Cohort: 3¹²⁻¹⁴ <u>Clinicaltrials.gov</u> <ul style="list-style-type: none">Recruiting: Cardiac Sarcoidosis Multi-center Prospective Cohort NCT01477359

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ICD=implantable cardioverter defibrillator; KQ=Key Question

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product. We found no systematic reviews related to the scope of the nomination.
- Impact: A new systematic review has uncertain impact potential.
- Feasibility: A new review is likely not feasible. The evidence base is likely limited.

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Appendix A. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	The prevalence is low. Prevalence of sarcoidosis ranges from 10 to 80 cases per 100,000 people. ¹ About 5% of patients with sarcoidosis have clinical symptoms of cardiac involvement. ² However the complications of cardiac sarcoidosis can have a significant impact on morbidity and mortality.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes it affects healthcare decisionmaking though for a small proportion of the US population.
2c. Represents important uncertainty for decision makers	Yes
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Overall, hospitalizations for sarcoidosis substantially increased from 2005 to 2014. The number of sarcoidosis hospitalizations increased from 138 to 175 per 100 000 (relative increase of 26%). ¹⁵
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	<p>We identified no systematic reviews relevant to the nomination scope.</p> <p>We found one in-process systematic review on ICD in primary and secondary prevention of sudden death. It will be completed in December 2018, but it is not known whether there will be a subgroup analysis specifically on people with cardiac sarcoidosis.¹⁶</p> <p>We also identified an older systematic review by Sadek et al¹⁷ relevant to KQ 1 that may be of interest to the nominator. However because it was published in 2013, it is not considered duplicative.</p>
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	<p>The impact of a new evidence review is uncertain.</p> <p>The Heart Rhythm Society has a consensus guideline on treatment of cardiac sarcoidosis¹⁸. ACC/AHA/HRS has a guideline about sudden cardiac death, and includes a section on cardiac sarcoidosis.¹⁹ The guidelines are not inconsistent in their</p>

	<p>recommendation, though both note the limited evidence to support recommendations.</p> <p>Corticosteroids are commonly used in the treatment of cardiac sarcoidosis^{3, 20}, but the optimal dose of and duration of therapy has not been established. Review articles note that other immunosuppressants can be added for poor response to steroids.^{3, 20, 21}</p>
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	There may be practice variation, likely related to the limited evidence to support recommendations.
5. Primary Research	
<p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) 	<p>The size of the review would be limited, and may not be feasible due to the small number of studies and variety of interventions. We found 8 studies relevant to KQ 1; and three relevant to KQ 2.</p> <p>KQ 1 (steroids)</p> <ul style="list-style-type: none"> • Comparisons examined included <ul style="list-style-type: none"> ○ Four studies examined the use of steroids with or without another immunopressant^{4, 7-9} <ul style="list-style-type: none"> ▪ Prednisolone vs. prednisolone+immunosuppressant vs.none ▪ Prednisone vs none ▪ MTX+steroids vs steroids ○ 4 studies examined the timing or dosing of steroids^{5, 6, 10, 11} <ul style="list-style-type: none"> ▪ Timing of prednisone ▪ High vs. low dose prednisone ▪ Discontinuation of steroids • All were cohort studies <p>KQ 2 (ICD)¹²⁻¹⁴</p> <ul style="list-style-type: none"> ▪ All were cohort studies ▪ We identified three studies <p>Ongoing clinical trials</p> <ul style="list-style-type: none"> • Cardiac Sarcoidosis Multi-center Prospective Cohort NCT01477359 • Cardiac Sarcoidosis Randomized Trial (CHASM-CS-RCT) NCT03593759

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/ ; https://www.ahrq.gov/research/findings/ta/index.html ; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program https://www.hsrp.research.va.gov/publications/esp/
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
Secondary Search
AHRQ Products in development https://effectivehealthcare.ahrq.gov/
VA Products in development https://www.hsrp.research.va.gov/publications/esp/
Cochrane Protocols http://www.cochranelibrary.com/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prosperto/
Tertiary Search
PubMed https://www.ncbi.nlm.nih.gov/pubmed/

Appendix C. Search Strategy & Results (Feasibility)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 19, 2018

Date searched: October 22, 2018

Searched by: Robin Paynter, MLIS

#	Searches	Results
1	exp Heart Diseases/ or Cardiomyopathies/ or Arrhythmias, Cardiac/ or (arrhythm* or atri* or cardi* or heart or myocard* or ventr*).tw,kf.	2238701
2	Sarcoidosis/ or sarcoidosis.tw,kf.	28501
3	1 and 2	2757
4	exp Adrenal Cortex Hormones/ or (corticosteroid* or glucocorticoid* or steroid* or cortisone or dexamethasone or ethamethasoneb or fludrocortisone or hydrocortisone or methylprednisolone or prednisone or prednisolone or triamcinolone or Celestone or Cortef or Florinef or Orapred or Prelone or Aristospan or Kenalog or Medrol or Depo-Medrol or depomedrol or Solu-Medrol or DexPak).tw,kf.	635343
5	3 and 4	576
6	limit 5 to (adaptive clinical trial or clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	16
7	limit 5 to (meta analysis or systematic reviews)	8
8	Defibrillators, Implantable/ or (ICD* or implantable-cardioverter-defibrillator* or (implant* adj3 (defibrillat* or device*))).tw,kf.	59500
9	3 and 8	171
10	limit 9 to (adaptive clinical trial or clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	10
11	limit 9 to (meta analysis or systematic reviews)	3
12	6 or 7	24
13	5 not 12	552

ClinicalTrials.gov

Date searched: October 22, 2018

Searched by: Robin Paynter, MLIS

sarcoidosis AND (arrhythmia OR atrial OR cardiac OR cardiomyopathy OR heart OR myocardial OR ventricular) AND (corticosteroid OR defibrillator OR steroid OR Cortisone OR dexamethasone OR ethamethasoneb OR Fludrocortisone OR hydrocortisone OR Methylprednisolone OR prednisone OR prednisolone OR triamcinolone OR Celestone OR Cortef OR Florinef OR Orapred OR Prelone OR
--

Aristospan OR Kenalog OR Medrol OR Depo-Medrol OR depomedrol OR Solu-Medrol
OR DexPak) AND NOT (renal OR pulmonary)= 8 results

Clinical trials link

<https://clinicaltrials.gov/ct2/results?cond=cardiac+sarcoidosis&term=&cntry=&state=&city=&dist>