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EDITORIAL COMMENT

Prognostic Value of CMR-Verified Myocardial Scarring in Cardiac Sarcoidosis

What to Learn From a Systematic Review and Meta-Analysis?*

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Cardiac sarcoidosis can present as part of multiorgan involvement or increasingly as an isolated or subclinical heart manifestation. Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) has prognostic value by detecting cardiac involvement in sarcoidosis (1). However, there is no consensus in the literature on the prognostic implications of LGE-CMR in this clinically relevant setting. This lack of consensus due to multiple small and single-centered studies motivated Coleman et al. (2) to perform a systematic review and meta-analysis on the prognostic value of CMR in patients with known or suspected cardiac sarcoidosis, as reported in this issue of *iJACC*. The main conclusion from this study is that the presence of LGE-CMR in patients with known or suspected cardiac sarcoidosis is associated with increased odds of both all-cause mortality and arrhythmogenic events.

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What can we learn from a systematic review and meta-analysis? Pooling the data from multiple studies may provide a more precise estimate of the prognostic implications of a positive LGE-CMR test in patients with known or suspected cardiac sarcoidosis. However, McInnes and Bossuyt (3) describe a number of common pitfalls of systematic reviews and meta-analyses in imaging research. The study by Coleman et al. (2) complies to most of the recommended guidelines (e.g., PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] statement) and avoids a number of pitfalls as described by McInnes and Bossuyt (3). Journals are increasingly requesting authors to adhere to guidelines such as the PRISMA statement to verify the completeness of the systematic review and analysis (4).

The current study addresses a well-defined clinical question and provides more precise estimates of the prognostic implications of CMR in cardiac sarcoidosis. However, the literature search of this systematic review and meta-analysis has 2 weaknesses. First, the selection of databases could be improved. The authors consulted only 3 databases (PubMed, PubMed Central, and the metaRegister of Controlled Trials). Two databases of considerable value were not used (Embase, Web of Science) and several databases of additional value were not used as well (e.g., CINAHL, Academic Search Premier, ScienceDirect).

Second, the search strategy used is not fully shown. The formulation of the search strategy as is shown in the article is unclear. As such, it is not possible to exactly reproduce the search. According to the authors, 519 references were found, but it is not known what the numbers per database are. Applying the given strategy in PubMed results in 86 references (June 9, 2016). If one would compose a search strategy according to McInnes and Bossuyt (3), the number of retrieved references in PubMed is 496 (June 9, 2016). Furthermore, applying this strategy in, for example, Embase, would to a set of 1,350 references, of which 929 references are unique compared to the references identified in PubMed (excluding 521 meeting abstract references). The consultation of additional databases next to Embase will add more references as well. These 2 weaknesses call out for the expert eye of the medical librarian (5).

The process of selecting studies for systematic review and meta-analysis is complex. It is arguably the most important aspect in the process of integrating

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research on a specific topic. The selection process is important because the inclusion and exclusion of studies affects the scope and validity of meta-analysis results. The inclusion and exclusion criteria in this meta-analysis are clear and the steps taken in the study selection process are generally well described and a detailed flow chart was produced.

According to the PRISMA statement the data collection process should be well described. However, the methods used for data extraction in the current study are not entirely clear. It is important to not only indicate which characteristics were recorded, but also describe the method that was used to abstract data. It is unclear if a standardized data abstraction form was used. Given the importance of systematic and reproducible data retrieval, it is advisable to use such a form.

As recommended by McInnes and Bossuyt (3), the authors determined a quality score for each study included in the meta-analysis, using the Newcastle-Ottawa quality assessment scale. As with data abstraction, 2 reviewers assessed the quality. However, agreement between reviewers and method of reconciliation in differences were not reported.

The statistical analysis of the data was well planned and appropriate techniques were used. The risk of publication bias was assessed using funnel plots and Egger's test. Variation across studies (heterogeneity) was also considered, including the exploration of the sources of this variation, using metaregression and sensitivity analyses.

A number of limitations inherent to their systematic review and meta-analysis were discussed by Coleman et al. (2). For example, the measurement of LGE was not standardized throughout the literature introducing additional heterogeneity of methods. Binary visual scoring, using different thresholds for (semi)quantification, the extent of LGE involving the left or right ventricle, and various patterns of LGE (e.g., right ventricular involvement, multifocal, subepicardial, intramural, subendocardial, transmural) may all contribute to heterogeneity.

Coleman et al. (2) also discuss that despite a near normal left ventricular ejection fraction, patients with LGE positivity have higher odds of adverse events (2). It is acknowledged that the assessment of the interaction between ejection fraction and LGE was hindered by the lack of patient-level covariates. The authors suggest that future prospective studies may help mitigate selection bias and provide patient-level data. A recent study addressed the increased risk in cardiac sarcoidosis in patients with LGE and preserved ejection fraction (6). LGE burden was quantified by defining myocardial areas with a signal intensity 5 standard deviations above presumed normal myocardium. The LGE burden and severity of right ventricular dysfunction even in patients with preserved left ventricular function were associated with increased rate of death and ventricular arrhythmias, underscoring again the potential predictive value of LGE extent. In particular, multifocal right ventricular LGE was associated with the endpoint of ventricular tachycardia-fibrillation or death. The presence of a low LGE burden was not associated with adverse outcomes (6).

A limitation with LGE-CMR assessment of scar tissue is the lack of an established gold standard technique for accurate quantification. Several different techniques have been proposed for quantifying acute and chronic scar, including manual contouring and thresholding techniques such as a signal intensity threshold of 2, 3, 5, or 6 standard deviations above the normal remote myocardium, the Otsu technique, and the full width at one-half maximum technique. Myocardial scar quantification by LGE-CMR varies depending on the quantification method used (7).

Recently, the full width at one-half maximum method was used in patients with cardiac sarcoidosis to quantify LGE as a percentage of the left ventricle. In particular the extent of LGE appeared to be predictive for serious cardiac events in patients with cardiac sarcoidosis and to a lesser degree right ventricular function and scarlike thinning of the basal interventricular septum (8). Ekstrom et al. (8) call for re-evaluation of the indications for an implantable cardioverter-defibrillator in sarcoid patients with normal left ventricular ejection fraction and substantial LGE burden.

Overall, LGE burden appears to be the most valuable risk marker in patients with known or suspected cardiac sarcoidosis. A critical threshold of LGE burden has to be defined by using accurate quantification of myocardial scar for risk assessment and guiding treatment. Of note, the LGE extent in patients with cardiac sarcoidosis may be predictive even in those with preserved left ventricular function. Comprehensive assessment of CMR imaging biomarkers (as evidenced by future prognostic CMR studies) may improve risk assessment in patients with cardiac sarcoidosis by integrating a critical cutoff value for LGE burden, the pattern of LGE, biventricular function, and basal septal involvement.

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REFERENCES

1. Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. J Am Coll Cardiol Img 2015;16:634–41.

2. Coleman GC, Shaw PW, Balfour PC Jr., et al. Prognostic value of myocardial scarring on CMR in patients with cardiac sarcoidosis. J Am Coll Cardiol Img 2017;10:411–20.

3. McInnes MDF, Bossuyt PM. Pitfalls of systematic reviews and meta-analyses in imaging research. Radiology 2015;277:13–21.

4. Radiological Society of North America. Radiology Publication Information for Authors. Available at: http://pubs.rsna.org/page/radiology/pia. Accessed June 6, 2017.

5. Schoones JW, Vissers T. Re: "Using data sources beyond PubMed has a modest impact on the results of systematic reviews of therapeutic interventions". J Clin Epidemiol 2016;78:127.

6. Murtagh G, Laffin LJ, Beshai JF, et al. Prognosis of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction. Risk stratification using cardiovascular magnetic resonance. Circ Cardiovasc Imaging 2016;9:e003738.

7. McAlindon E, Pufulete M, Lawton C, Angelini GD, Bucciarelli-Ducci C. Quantification of infarct size and myocardium at risk: evaluation of different techniques and its implications. Eur Heart J Cardiovasc Img 2015;16:738–46.

8. Ekstrom K, Lehtonen J, Hanninen H, Kandolin R, Kivisto S, Kupari M. Magnetic resonance imaging as a predictor of survival free of life-threatening arrhythmias and transplantation in cardiac sarcoidosis. J Am Heart Assoc 2016;5:e003040.

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