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ORIGINAL RESEARCH

The Prognostic Role of Late Gadolinium Enhancement in Aortic Stenosis

A Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVES The aim of this systematic review was to explore the prognostic value of late gadolinium enhancement (LGE) in patients with aortic stenosis (AS).

BACKGROUND Myocardial fibrosis is a common feature of many cardiac diseases. Cardiac magnetic resonance (CMR) has the ability to noninvasively detect regional fibrosis by using the LGE technique. Several studies have explored whether LGE is associated with adverse outcome in patients with AS.

METHODS Electronic databases were searched to identify studies investigating the ability of LGE to predict all-cause mortality in patients with AS. A random effects model meta-analysis was conducted. Heterogeneity was assessed with the I^2 statistic.

RESULTS Six studies comprising 1,151 patients met our inclusion criteria. LGE was present in 49.1% of patients with AS. In the pooled analysis, LGE was found to be a strong univariate predictor of all-cause mortality (pooled unadjusted odds ratio: 2.56; 95% confidence interval: 1.83 to 3.57; $I^2 = 0\%$). Four of the included studies reported adjusted hazard ratios for mortality. LGE was independently associated with mortality, even after adjusting for baseline characteristics (pooled adjusted hazard ratio: 2.50; 95% confidence interval: 1.64 to 3.83; $I^2 = 0\%$).

CONCLUSIONS Fibrosis on LGE-CMR is a powerful predictor of all-cause mortality in patients with AS and may serve as a novel marker for risk stratification. Future studies should explore whether LGE-CMR can also be used to optimize timing of AS-related interventions. (J Am Coll Cardiol Img 2019;■:■-■) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

In aortic stenosis (AS), left ventricular systolic pressure increases in response to progressive narrowing of the aortic valve, leading to compensatory left ventricular hypertrophy (1). Although this process initially maintains a normal afterload, worsening left ventricular hypertrophy eventually leads to stiffening of the left ventricle, elevated filling pressures, and the onset of symptoms (2). Chronic pressure overload leads also to the development of structural changes in the myocardium such as myocardial fibrosis, which further increases left ventricular stiffening (3,4).

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

CMR = cardiac magnetic resonance

HR = hazard ratio

LGE = late gadolinium enhancement

OR = odds ratio

Myocardial fibrosis is a common feature of many cardiomyopathies and has been linked to increased mortality and other adverse outcomes (5–7). Cardiac magnetic resonance (CMR) imaging with the late gadolinium enhancement (LGE) technique is able to detect focal fibrosis (8). In the past years, several small prospective studies have reported an association between regional myocardial fibrosis and adverse outcomes (9,10). However, in the absence of randomized clinical trials, myocardial fibrosis is currently not part of routine evaluation of patients with AS, and the clinical decision regarding aortic valve replacement is based on patients' symptoms or signs of left ventricular decompensation (11).

The aim of the present systematic review and meta-analysis was to assess the prognostic value of LGE-CMR in patients with AS.

MATERIALS AND METHODS

PROTOCOL AND REGISTRATION. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (12). The review protocol was registered on the Prospero International Prospective Register of Systematic Reviews (CRD42018106402).

ELIGIBILITY CRITERIA. A study was deemed to be eligible for this review if the following inclusion criteria were fulfilled: 1) primary research reporting comparative mortality data between AS patients with and without LGE on contrast-enhanced CMR imaging; and 2) studies published in any language up to August 16, 2018.

INFORMATION SOURCES: SEARCH STRATEGY. The electronic databases Medline and Cochrane Library were searched for relevant articles using the following search algorithm: ("MRI" OR "CMR" OR "cardiac magnetic resonance" OR "cardiovascular magnetic resonance" OR "magnetic resonance imaging") AND "aortic stenosis."

STUDY SELECTION: DATA COLLECTION PROCESS. Two reviewers (C.A.P., D.K.G.) assessed the eligibility of the potentially included studies independently according to the pre-specified inclusion criteria. An article was considered to be eligible if both reviewers agreed. Any discrepancies were resolved by the involvement of a third reviewer (D.K.C.). Pre-specified forms were also used to extract the epidemiological and clinical data of the included studies. When studies with duplicated populations were identified (13,14), the corresponding author was contacted and requested to re-conduct the analysis of the larger study after excluding the overlapping subjects.

RISK OF BIAS IN INDIVIDUAL STUDIES. The Quality in Prognosis Studies tool was used to assess the methodological quality of the included studies (15). Two independent reviewers (C.A.P., I.B.) critically appraised each of the following bias domains as low, moderate, or high risk: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting.

STATISTICAL ANALYSIS. In this meta-analysis, pooled unadjusted odds ratios (ORs) and adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated. A random effects model (Mantel-Haenszel method) was selected a priori given the heterogeneity in study design across the included studies (16). Between-study heterogeneity was assessed with the I^2 statistic. Values <25% indicated low heterogeneity, and values >70% indicated severe heterogeneity (17). To evaluate the impact of each study on the overall effect size, a one-study removed sensitivity analysis was performed. Publication bias was visually assessed (Supplemental Figure 1), but no further testing was performed given the low number of included studies (<10) (18).

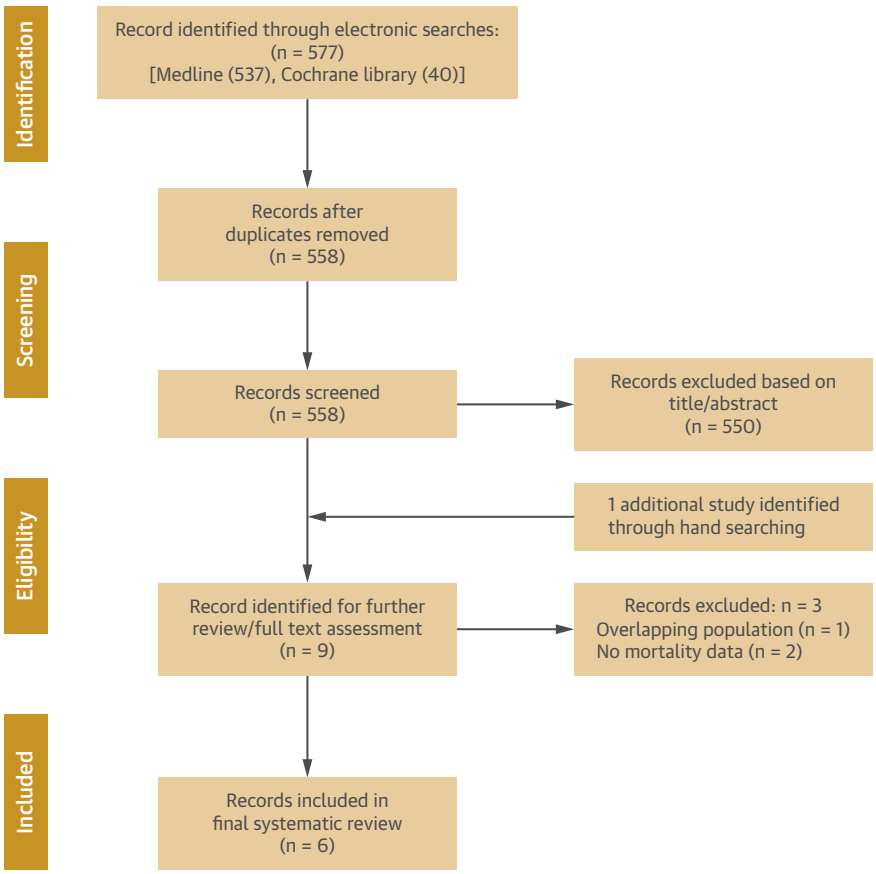
All statistical analyses were performed by using RevMan version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Comprehensive Meta-analysis version 3 (Englewood, New Jersey).

RESULTS

STUDY SELECTION AND STUDY CHARACTERISTICS. A total of 577 studies were screened based on title/abstract, and 9 studies were assessed for eligibility. Six studies ultimately met inclusion criteria and were included in our analysis (3,9,10,13,14,19). A detailed flowchart for study selection is presented in **Figure 1**.

All eligible studies were published between 2011 and 2018, and 5 of them were conducted in the United Kingdom (9,10,13,14,19). Four studies assessed the prognostic value of LGE, irrespective of the pattern of fibrosis (i.e., infarct, noninfarct) (3,10,13,14), whereas in 1 study, LGE segments with infarct pattern were excluded from the analysis (19). CMR was performed on either a 1.5-T (3,9,10,14) or a 3.0-T (19) scanner, except for the study by Musa et al. (13), in which both field strengths were used. Three studies used the full-width half maximum technique to identify fibrotic boundaries (9,13,14), whereas a signal intensity above 2.4 SD of remote myocardium was used by 2 studies

FIGURE 1 **PRISMA Flowchart**



The selection process is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

(3,10). To obtain LGE images, 0.1 mmol/kg of gadolinium-based contrast agent was administered in 2 studies (9,19); a dose of 0.2 mmol/kg was used in the other studies (3,10,13,14). In total, 1,151 patients were included, 565 (49.1%) of whom were LGE positive. Two studies included patients with different degrees of AS severity in their analysis (9,19), whereas the remainder included only patients with severe AS (3,10,13,14). The mean follow-up duration ranged from 1.1 to 3.6 years.

LGE-positive patients were consistently older than LGE-negative patients. Moreover, the proportion of male subjects was higher in the LGE group. LGE-positive patients had a higher frequency of diabetes mellitus (4 of 6 studies) (3,10,13,14) and a lower ejection fraction compared with LGE-negative patients (6 of 6 studies) (3,9,10,13,14,19). Conversely, hypertension was more frequent in the no-LGE group in 4 of 6 studies (3,9,13,19). Finally, no significant difference was observed in the measured aortic valve area (range of means: 0.63 to 0.96 cm^2 in the LGE group vs. 0.66 to 1.05 cm^2 in the non-LGE group). Baseline characteristics of included studies are summarized in **Table 1**.

RISK OF BIAS ASSESSMENT. Details for risk of bias assessment of individual studies are shown in Supplemental Table 1. The overall risk of bias was found to be low in all included studies.

SYNTHESIS OF INDIVIDUAL RESULTS. Six studies reported unadjusted ORs on all-cause mortality. Two of them did not show a significant association between LGE and mortality (10,14). In the pooled analysis, the presence of LGE was found to be a strong univariate predictor of all-cause mortality (pooled unadjusted OR: 2.56; 95% CI: 1.83 to 3.57; $I^2 = 0\%$) (**Central Illustration**). No significant change was detected in overall effect size after performing a one-study removed sensitivity analysis (**Figure 2**).

TABLE 1 Baseline and Demographic Characteristics of AS Population (LGE+/LGE- Patients)

First Author, Year (Ref. #)	Country	N	Study Design	Follow-Up, yrs	AS Severity	Mean Age, yrs	Male (%)
Chin et al., 2017 (19)	UK	139 (37/102)	Prospective	2.9 (mean)	Mild, moderate or severe	71/70*	56.8/61.1
Dweck et al., 2011 (9)	UK	143 (94/49)	Prospective	2.0 (mean)	Moderate or severe	70/64	75.4/53
Barone-Rochette et al., 2014 (3)	Belgium	154 (44/110)	Prospective	2.9 (mean)	Severe	75/74	64/62
Musa et al., 2017 (14)	UK	83 (59/24)	Prospective	2.5 (median)	Severe	77.4/75.9	68/46
Musa et al., 2018 (13)	UK	523 (285/238)	Prospective	3.6 (median)	Severe	71.7/72.6	73.3/56.3
Rajesh et al., 2017 (10)	India	109 (46/63)	Prospective	1.1 (mean)	Severe	58.7/56.3	58.7/57.1

TABLE 1 Continued

First Author, Year (Ref. #)	DM (%)	HTN (%)	Mean EF (%)	Mean AVA (cm^2)	CMR Scanner (T)	Gadolinium Dose (mmol/kg)	LGE Quantification Technique
Chin et al., 2017 (19)	5/14.6	59/67.1	67/67.4	0.83/0.95	3.0	0.1	-
Dweck et al., 2011 (9)	24.5/25	52.9/56	52/69	0.96/1.05	1.5	0.1	FWHM
Barone-Rochette et al., 2014 (3)	34/18	59/64	55/61	0.70/0.71	1.5	0.2	Signal intensity >2.4 SD of remote myocardium
Musa et al., 2017 (14)	19/17	58/58	52.8/59.9	0.63/0.66	1.5	0.2	FWHM
Musa et al., 2018 (13)	23.2/21.8	54.4/62.3	58/64	0.74/0.73	1.5, 3.0	0.2	FWHM
Rajesh et al., 2017 (10)	10.8/9.5	52.1/49.2	52.8/59.1	-	1.5	0.2	Signal intensity >2.4 SD of remote myocardium

*Median values.

AS = aortic stenosis; AVA = aortic valve area; DM = diabetes mellitus; EF = ejection fraction; FWHM = full-width half maximum; HTN = hypertension; LGE = late gadolinium enhancement; UK = United Kingdom.

Four of the included studies reported adjusted HR for mortality (3,9,13,14). Dweck et al. (9) reported results for midwall and infarct pattern of LGE separately. Separate analyses were therefore conducted for each of these results. In both cases, LGE was significantly associated with all-cause mortality (pooled adjusted HR of 2.50 [95% CI: 1.64 to 3.83; I^2 = 0%] and 2.36 [95% CI: 1.54 to 3.62; I^2 = 0%] for midwall and infarct pattern, respectively) (**Figures 3A and 3B**).

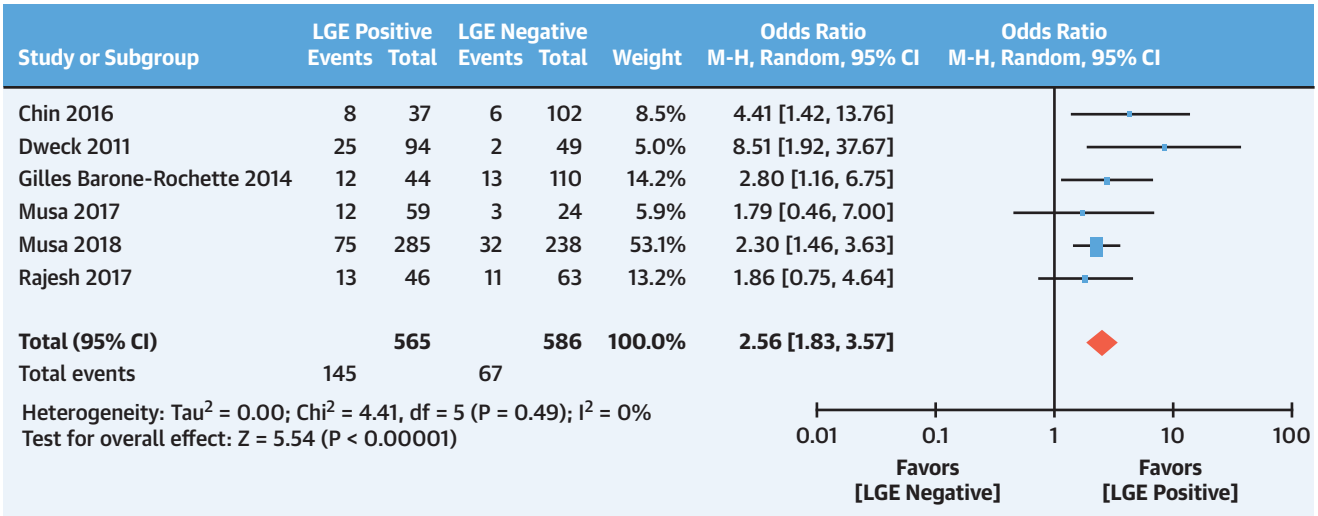
DISCUSSION

This systematic review and meta-analysis evaluated the prognostic value of LGE in AS. The results indicate that LGE is a powerful prognostic marker, conveying >2-fold higher risk of all-cause mortality in patients with AS, even after adjusting for baseline characteristics (pooled unadjusted OR: 2.56 [95% CI: 1.83 to 3.57]; pooled adjusted HR: 2.50 [95% CI: 1.64 to 3.83]).

MYOCARDIAL ADAPTATION TO AS. Calcific AS is a valvular disease characterized by progressive narrowing of the aortic valve opening. The natural progression of the disease extends through 2 distinct clinical and histopathological phases (20). In the early "adaptive" phase, myocardial response to increased afterload is characterized by left ventricular hypertrophy, maintaining a sufficient cardiac performance and functional status (21). However, left ventricular hypertrophy over time results in oxygen supply-demand mismatch, leading to subendocardial ischemia and ultimately myocyte degeneration and myocardial fibrosis (4,22). The transition from the adaptive phase to heart failure is mainly driven by worsening of myocardial fibrosis and cell death, eventually provoking irreversible structural changes in the myocardium, left ventricular decompensation, and arrhythmogenesis (23).

FOCAL MYOCARDIAL FIBROSIS AND AS. Myocardial fibrosis in AS presents initially as diffuse interstitial and later on, when large areas of myocytes are lost, as focal replacement fibrosis, which can be either subendocardial (so-called infarct type) or midwall (22). Given the high prevalence of coronary artery disease in patients with AS, it is difficult to differentiate whether the infarct type of focal myocardial fibrosis results from poor perfusion secondary to epicardial disease or oxygen supply-demand mismatch in the setting of a hypertrophied left ventricle. Similarly, patchy midwall fibrosis in AS is usually attributed to pressure overload, although in some patients with AS, an independent cardiomyopathy (i.e., not related to valvular disease) cannot be excluded. Previous studies have explored the prognostic role of myocardial fibrosis in AS and reported

CENTRAL ILLUSTRATION **Meta-Analysis Results**



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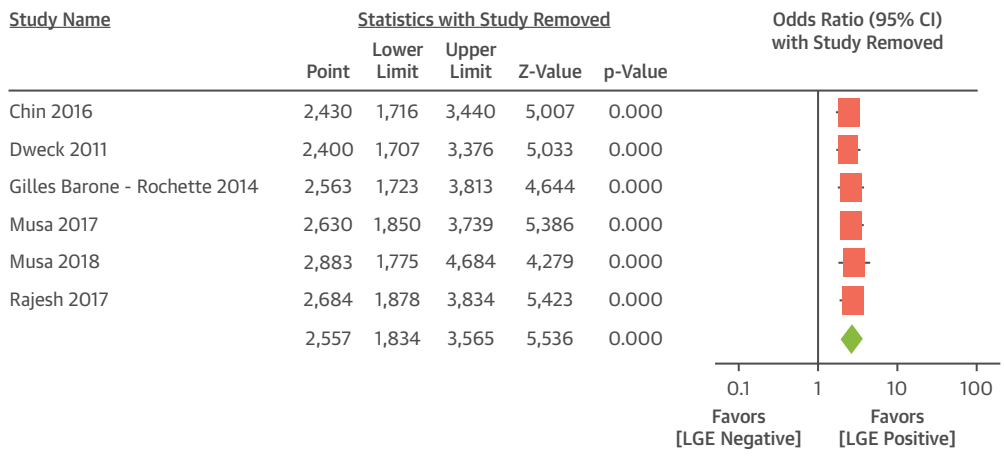
Forest plot demonstrating pooled unadjusted odds ratio for all-cause mortality. CI = confidence interval; LGE = late gadolinium enhancement; M-H = Mantel-Haenszel method.

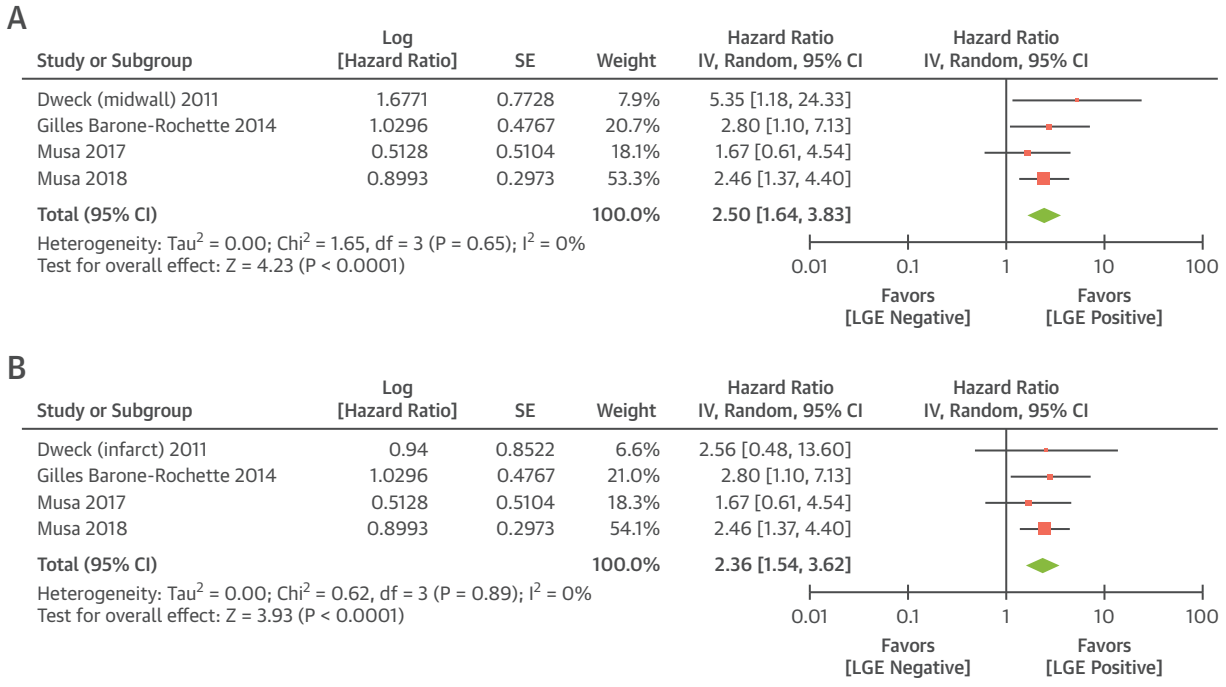
mixed results. Musa et al. (13) found that both infarct and noninfarct patterns of focal fibrosis were significantly associated with adverse outcomes. Conversely, Dweck et al. (9) found that only midwall fibrosis was an independent predictor of mortality, whereas infarct-like fibrosis lost its statistical significance on multivariate analysis. This discrepancy may be attributed to the fact that patients with infarct fibrosis had lower ejection fraction, and thereby reduced systolic function, and not fibrosis per se affected prognosis. Chin et al. (19) entirely excluded patients with an infarct pattern of myocardial fibrosis to avoid any potential bias from significant coronary artery disease. Overall, the presence of focal fibrosis as

FIGURE 2 **One Study Removed Sensitivity Analysis**



One study removed sensitivity analysis to assess the impact of individual studies on overall effect size. Each **line** represents the pooled odds ratio when the left study is omitted. CI = confidence interval; LGE = late gadolinium enhancement.

FIGURE 3 Meta-Analysis Results



Forest plots demonstrating pooled adjusted hazard ratios for all-cause mortality. Dweck et al. (9) reported results for **(A)** midwall and **(B)** infarct pattern LGE separately. Therefore, separate meta-analyses were conducted for each result. IV = inverse variance; other abbreviations as in Figure 2.

detected by using LGE-CMR seems to be associated with adverse outcomes regardless of the underlying mechanism or the presence of diffuse interstitial fibrosis.

Our results are in agreement with studies showing that the amount of myocardial fibrosis measured by using LGE-CMR shows good correlation with histopathological indices of fibrosis and is associated with increased risk of long-term mortality (8). Along those lines, Lee et al. (24) studied 127 patients with moderate or severe AS and reported that the presence of LGE is an independent predictor of the composite endpoint of all-cause mortality and hospitalization for heart failure (adjusted HR: 1.56; 95% CI: 1.05 to 4.37). Two studies, which were included in our meta-analysis, failed to show any significant association between LGE and mortality (10,14). This scenario could be explained by the small number of patients included in their analyses, resulting ultimately in low statistical power. Recently, another meta-analysis (25) attempted to explore the prognostic value of LGE in severe aortic valve disease but is flawed by major methodological drawbacks such as the inclusion of mixed populations (stenosis or regurgitation) with a significant number of overlapping subjects (9,26) and use of a fixed effects model (16), which is not recommended in real-world meta-analyses with significant between-study heterogeneity.

DIFFUSE MYOCARDIAL FIBROSIS AND AS. LGE is the reference standard for the noninvasive imaging of focal myocardial scar but requires regions of presumed-normal myocardium to provide the necessary contrast between affected and unaffected tissue. However, this may not be available in the setting of diffuse, homogenously distributed, interstitial fibrosis. Novel CMR techniques such as T1 mapping and extracellular volume quantification open new frontiers for the assessment and quantification of diffuse myocardial fibrosis (27). Currently, these techniques seem to be interesting prognostic tools in a variety of cardiac diseases, including AS (19,28). Chin et al. (19) showed a stepwise increase in unadjusted mortality in patients with AS, as the myocardial fibrosis progressed from a diffuse pattern (as evaluated by using extracellular volume expansion) to a focal pattern (as evaluated by LGE) (36 deaths/1,000 patient-years vs. 71 deaths/1,000 patient-years).

In addition, Lee et al. (24) found that native T1 mapping was a powerful predictor of adverse outcomes (all-cause death or hospitalization for heart failure) in AS, regardless of the presence of LGE (adjusted HR: 1.28; 95% CI: 1.10 to 1.46, per 20-ms increment). Conversely, Nadjiri et al. (29) found no significant association between diffuse fibrosis (as evaluated by using extracellular volume) and mortality in patients who underwent transcatheter aortic valve replacement (HR: 0.847; 95% CI: 0.335 to 2.14). This inconsistency in study results may be attributed to the fact that T1 mapping is an evolving CMR technique with significant technical heterogeneity between different vendors, pulse sequences, field strength, and contrast agents, highlighting the need for further standardization before becoming a routine clinical tool. Although initial validation and clinical and prognostic data in AS cohorts are promising, further research is needed to establish the prognostic value of T1 mapping in AS (24,30–32).

MYOCARDIAL FIBROSIS AND TREATMENT IN AS. Current guidelines for the treatment of AS recommend valve replacement in all patients with severe stenosis when symptoms and/or ventricular decompensation are present (33). However, it remains unclear whether AVR should also be performed in selected patients with asymptomatic AS and myocardial fibrosis (34). An ongoing trial (EVOLVED [Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis]; NCT03094143), which randomly assigns asymptomatic patients with severe AS to undergo either early aortic valve surgery or receive current standard of care (monitoring of valve until symptoms develop), is expected to shed light on whether scarring can guide management in such patients. Our findings support the notion that LGE may serve as a novel biomarker for risk stratification of patients with AS, which could potentially be used to optimize the timing of valve intervention.

STUDY LIMITATIONS. This study is a systematic review and meta-analysis of real-world studies and therefore carries the inherent limitations of observational research. First, the reported high prevalence of LGE in patients with AS in the included studies may suggest sampling bias when patients were recruited. Second, there is considerable heterogeneity in study design among the included studies as a result of different fibrosis patterns and types of intervention. A meta-regression analysis was limited by the low number of included studies. Finally, we were unable to assess other outcomes apart from all-cause mortality due to unavailable primary data in some studies.

CONCLUSIONS

The current meta-analysis found that the assessment of focal myocardial fibrosis with LGE-CMR is significantly associated with all-cause mortality in patients with AS. LGE may thus serve as a novel imaging biomarker for risk stratification in patients with AS. Future studies should explore whether LGE can be used to optimize the timing of AS-related interventions and clarify whether diffuse fibrosis assessment with T1 mapping and extracellular volume quantification provides additional prognostic information in AS cohorts.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LGE CMR exhibits a significant prognostic role in AS by identifying patients at higher mortality risk. Its predictive value remains substantial even after adjusting for baseline characteristics.

TRANSLATIONAL OUTLOOK: Fibrosis detection on LGE CMR may become a risk stratification tool for patients with AS. Furthermore, myocardial fibrosis assessment could guide future decision-making by optimizing the timing of AS-related intervention.

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KEY WORDS aortic stenosis, cardiac magnetic resonance, late gadolinium enhancement, meta-analysis

APPENDIX For a supplemental table and figure, please see the online version of this paper.