Late Gadolinium Enhancement on Cardiac Magnetic Resonance Predicts Adverse Cardiovascular Outcomes in Nonischemic Cardiomyopathy
A Systematic Review and Meta-Analysis

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Background—Late gadolinium enhancement (LGE) by cardiac MR (CMR) is a predictor of adverse cardiovascular outcomes in patients with nonischemic cardiomyopathy (NICM). However, these findings are limited by single-center studies, small sample sizes, and low event rates. We performed a meta-analysis to evaluate the prognostic role of LGE by CMR (LGE-CMR) imaging in patients with NICM.

Methods and Results—PubMed, Cochrane CENTRAL, and EMBASE were searched for studies looking at the prognostic value of LGE-CMR in patients with NICM. The primary end points included all-cause mortality, heart failure hospitalization, and a composite end point of sudden cardiac death (SCD) or aborted SCD. Pooling of odds ratios was performed using a random-effect model, and annualized event rates were assessed. Data were included from 9 studies with a total of 1488 patients and a mean follow-up of 30 months. Patients had a mean age of 52 years, 67% were men, and the average left ventricular ejection fraction was 37% on CMR. LGE was present in 38% of patients. Patients with LGE had increased overall mortality (odds ratio, 3.27; P<0.00001), heart failure hospitalization (odds ratio, 2.91; P=0.02), and SCD/aborted SCD (odds ratio, 5.32; P<0.00001) compared with those without LGE. The annualized event rates for mortality were 4.7% for LGE+ subjects versus 1.7% for LGE− subjects (P=0.01), 5.03% versus 1.8% for heart failure hospitalization (P=0.002), and 6.0% versus 1.2% for SCD/aborted SCD (P<0.001).

Conclusions—LGE in patients with NICM is associated with increased risk of all-cause mortality, heart failure hospitalization, and SCD. Detection of LGE by CMR has excellent prognostic characteristics and may help guide risk stratification and management in patients with NICM. (Circ Cardiovasc Imaging. 2014;7:250-258.)

Key Word: cardiac magnetic resonance imaging ■ late gadolinium enhancement ■ nonischemic cardiomyopathy ■ prognosis

Nonischemic cardiomyopathy (NICM) refers to diverse myocardial conditions characterized by a reduction in left ventricular (LV) systolic function in the absence of significant coronary artery disease. The prevalence of NICM in the general population is thought to be ≈40 to 50 cases per 100,000.1 Myocardial scar or fibrosis in patients with NICM is a substrate for re-entrant circuits2 and leads to ventricular dilatation and remodeling, which further predisposes the patient to heart failure and sudden cardiac death (SCD).3 Therefore, the detection of scar/fibrosis by imaging has the potential to predict increased cardiovascular risk in patients with cardiomyopathy. Late gadolinium enhancement cardiac MR (LGE-CMR) is an effective and reproducible method for assessing myocardial fibrosis and has previously demonstrated prognostic use in patients with ICM and hypertrophic cardiomyopathy.4,6 To date, there have been several studies that show that the presence of LGE by CMR predicts increased risk of cardiovascular events and worsening survival in patients with NICM as well.7-15 However, most of the studies on NICM have been single-center studies with small sample sizes and small numbers of events.16 Currently, there is a lack of prognostic data in patients with NICM involving studies with uniform end points and large patient populations.16

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There is a need for better risk stratification of SCD in patients with NICM. Current evidence points to the use of LV ejection fraction (LVEF) as a predictor of SCD, and present guidelines17 recommend the use of implantable cardioverter-defibrillator (ICD) therapy for an LVEF <35% to prevent SCD in such patients. However, use of LVEF <35% alone has limited power...
in predicting SCD in patients with NICM. 14 The use of LGE as a prognostic variable, in addition to LVEF, may help improve risk stratification of patients with NICM and better guide the use of ICD, cardiac resynchronization therapy, and other therapies in such patients. Given the multiple small and single-center studies, we performed a systematic review and meta-analysis of studies reporting on the prognostic data of LGE as identified by CMR in patients with NICM.

**Methods**

**Eligibility Criteria**

Studies that were included in this analysis met the following criteria: evaluation of myocardial fibrosis in patients with NICM using LGE-CMR, and inclusion of hard end points such as all-cause mortality, SCD aborted SCD, or heart failure hospitalization (HFH). Studies that evaluated ischemic cardiomyopathies, acute myocarditis, and hypertrophic and infiltrative cardiomyopathies (including cardiac amyloidosis) were excluded.

**Search Strategy**

To identify eligible studies to be included in this systematic review and meta-analysis, 2 independent reviewers (S.K. and A.K.) systematically searched (August 2013) Cochrane CENTRAL, EMBASE, and PubMed for studies assessing prognosis in patients with known or suspected NICM after undergoing LGE-CMR (keywords: prognosis OR outcome AND scar AND cardiomyopathy OR cardiomyopathies AND delayed gadolinium enhancement OR magnetic resonance imaging OR late gadolinium enhancement). In addition, we reviewed citations from eligible studies and explored related articles for key publications in PubMed. We limited our search to studies published in peer-reviewed journals and thus excluded studies only presented in abstract form. Our systematic review and meta-analysis was performed in accordance with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Study Selection**

Two investigators (S.K. and A.K.) independently scanned all abstracts and obtained full-text reports of articles that suggested eligibility. After obtaining full reports, the above reviewers independently assessed eligibility from the full-text articles with divergences resolved after consensus. Study quality was evaluated by the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies, in which the quality of the selected trials was determined on the basis of selection of the study groups (0–4 points), comparability of the study groups (0–2 points), and ascertainment of the outcome of interest (0–3 points).

**Data Collection**

The same 2 investigators were involved in data abstraction and study appraisal. Clinical outcomes of interest were all-cause mortality, HFH, and a composite end point of SCD or aborted SCD during follow-up. Clinical outcome data were directly abstracted when reported. Unadjusted hazard ratios were used to determine the number of events if not provided for each group, and annualized event rates (AERs) for studies were calculated by dividing the number of events by the median or median follow-up duration.

**Data Analysis**

Dichotomous variables were expressed as proportions (percentages) and continuous variables as mean (SD) or median (range). Binary outcomes from individual studies were combined with random-effects model, leading to estimation of pooled odds ratio (ORs) with 95% confidence intervals. I² was calculated as a measure of statistical heterogeneity, with P values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively. Small study or publication bias was evaluated using funnel plots, the Egger test, and the Peter test. Meta-regression and sensitivity analyses were performed to assess heterogeneity. To assess sensitivity of the meta-analysis of each outcome, sensitivity analysis, which consisted of exclusion of 1 study at a time, was performed. To further assess heterogeneity and the influence of potential study-level covariates, we performed a fixed-effects meta-regression of the natural log of the OR for each end point for the factors of age and EF. AERs were compared using an inverse variance–weighted random-effects meta-analysis of the difference in AERs between the groups.

The meta-analyses were performed using Review Manager (RevMan) 5 version 5.2.5 freeware package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), and meta-regression was performed using SPSS version 21 (IBM SPSS Statistics), with statistical significance for hypothesis testing set at the 0.05 2-tailed level. More specific details of the statistical analysis are provided in the Data Supplement.

**Results**

**Results of the Literature Search**

Our literature search identified 2447 relevant abstracts of full-text articles, from which 45 unique articles were abstracted for review. Of these, 16 articles warranted full-text review. Seven articles were excluded for various reasons, including cohort overlap with other articles or lack of our prespecified outcomes, leaving 9 articles for detailed study. The details of our flow diagram can be found in Figure 1. Study characteristics are presented in Table 1. Only 1 study included patients undergoing CMR at 3.0 T, whereas the remainder were performed at 1.5 T. Overall, there were 9 studies, which included data on ≥1 of the outcomes of interest with a mean follow-up of 30 months (median, 23 months; range, 17–64 months) involving a total of 1488 patients with NICM undergoing CMR (median, 162 patients; average, 165 patients; range, 61–472). Patients had a mean age of 52 years, and 67% were men. Of the studies that reported cardiovascular risk factors, 39% of patients had hypertension, 12% had diabetes mellitus, and 19% had a history of smoking. With regard to CMR findings, the mean LVEF was 37%, and LGE was present in 45±15% of patients when reported. Baseline patient characteristics are demonstrated in Table 2.

**Study Characteristics**

The 9 studies included in this meta-analysis used varying inclusion criteria for enrollment. Six studies enrolled patients with NICM referred for CMR, and 3 studies enrolled patients with NICM eligible for ICD placement. All studies except for 1 were prospective studies (Table 1). Furthermore, every study, except for the study by Iles et al., used visual assessment to determine the presence of LGE. Most studies that used visual assessment for LGE also used the quantitative method to describe LGE (signal intensity >2 SD compared with the reference myocardium). However, the outcomes mentioned in all the studies were described for the presence or absence of LGE as a binary variable. All studies except for 1 used the presence of any LGE to assess outcomes and events. Gulati et al. used the presence or absence of midwall fibrosis alone to assess outcomes. The authors do not specifically mention whether any non-midwall LGE was present in either group. The study by Müller et al. included 15 patients with suspected hypertrophic cardiomyopathy because they presented with nonischemic heart failure symptoms and 3 patients with glycogen storage diseases. Although the authors state no change in the overall outcomes with the exclusion of these
cases, they do not provide the necessary data to exclude these cases, which represent <10% of the total cohort. The study by Cheong et al,7 which only provided data for the outcome of all-cause mortality, included patients with NICM who had relatively preserved LVEF compared with other study populations. Of the 9 studies, 5 studies did not discuss acuity of heart failure. Of the remaining 4 studies, only 113 enrolled newly diagnosed heart failure (<4 weeks). The remaining 3 studies enrolled subjects with NICM of >3 months of duration.

LGE and Outcomes
Of the 9 studies that were selected, 3 studies with 872 patients reported the outcome of all-cause mortality in NICM patients with and without LGE. As seen in Figure 2A, patients with LGE had greater all-cause mortality compared with patients without LGE (OR, 3.27; 95% confidence interval, 1.94–5.51; P<0.00001; I²=28%). Patients with LGE had significantly greater AERs for mortality than patients without LGE (4.7% versus 2.2%; P=0.01; Table 3; Figure 3). I² was elevated, suggesting mild heterogeneity for this outcome. Meta-regression analysis of the study-level covariates including age and LVEF was performed, and an interaction between LVEF and HFH (P=0.013), which likely explains a portion of the heterogeneity seen for this outcome, was detected.

NICM patients with LGE had greater AERs for HFH during follow-up than those without LGE (5.03% versus 1.8%; P=0.002; Table 3; Figure 3). Sensitivity analysis was performed for the outcome of heart failure with hospitalization. With exclusion of the study by Cho et al8 the P value for the outcome was not significant at 0.07, although the trend toward increased HFH remained if LGE was present. Similarly with the individual exclusion of Gulati et al10 and Lehrke et al,12 the overall P values for the outcome were not significant at 0.07 and 0.06, respectively, although the trend toward increased HFH remained in both cases if LGE was present. The results we obtained with sensitivity analysis were not surprising, given the amount of heterogeneity in events between the studies included under this outcome as mentioned above.

Of the 7 studies with 1194 patients reporting on SCD, aborted SCD, or appropriate ICD therapy for ventricular tachycardia/ventricular fibrillation during follow-up (Figure 2C), patients with LGE had a higher incidence of the combined outcome during follow-up compared with those without LGE (OR, 5.32; 95% confidence interval, 3.45–8.20; P=0.00001; I²=0%). NICM patients with LGE had a higher AER for the combined outcome of SCD, aborted SCD, and appropriate ICD therapy (Table 3; Figure 3) compared with patients without LGE (6.0%}

As seen in Figure 2B, subjects with LGE had a greater incidence of HFH during follow-up than those without LGE (OR, 2.91; 95% confidence interval, 1.16–7.27; P=0.02; I²=61%). I² is elevated, suggesting a moderate level of heterogeneity. Meta-regression analysis of the study-level covariates including age and LVEF was performed, and an interaction between LVEF and HFH (P=0.013), which likely explains a portion of the heterogeneity seen for this outcome, was detected. NICM patients with LGE had greater AERs for HFH during follow-up than those without LGE (5.03% versus 1.8%; P=0.002; Table 3; Figure 3). Sensitivity analysis was performed for the outcome of heart failure with hospitalization. With exclusion of the study by Cho et al8 the P value for the outcome was not significant at 0.07, although the trend toward increased HFH remained if LGE was present. Similarly with the individual exclusion of Gulati et al10 and Lehrke et al,12 the overall P values for the outcome were not significant at 0.07 and 0.06, respectively, although the trend toward increased HFH remained in both cases if LGE was present. The results we obtained with sensitivity analysis were not surprising, given the amount of heterogeneity in events between the studies included under this outcome as mentioned above.

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versus 1.2%; \( P<0.001 \)). The study by Iles et al11 has a high event rate of SCD compared with the event rates seen in other studies included in this outcome. However, exclusion of this study by sensitivity analysis did not significantly affect the strength of the association between LGE and SCD. Sensitivity analysis for the outcome of SCD/appropriate ICD therapy/aborted SCD was performed, and the individual exclusion of studies included in this outcome did not affect the results of this end point.

Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients (Patients With Scar/Without Scar)</th>
<th>Mean±SD or Median (Range) of Follow-Up</th>
<th>Study Design</th>
<th>Quality Assessment Score</th>
<th>Field Strength</th>
<th>Definition of Scar by LGE Used for Outcome Assessment</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheong et al7</td>
<td>2009</td>
<td>215 (37/178)</td>
<td>52.8 mo</td>
<td>Retrospective, single center</td>
<td>4, 0, 3</td>
<td>1.5 T</td>
<td>Visual assessment of LGE by 1 reviewer</td>
<td>Consecutive patients referred for DE-MRI</td>
</tr>
<tr>
<td>Cho et al8</td>
<td>2010</td>
<td>79 (42/37)</td>
<td>33.4±1.7 mo</td>
<td>Prospective, single center</td>
<td>4, 1, 1</td>
<td>1.5 T</td>
<td>Visual assessment of LGE by 2 reviewers</td>
<td>Patients with LVEF &lt;35% and CAD excluded by angiography</td>
</tr>
<tr>
<td>Gao et al9</td>
<td>2012</td>
<td>65 (46/19)</td>
<td>20.8±8.6 mo</td>
<td>Prospective, single center</td>
<td>4, 0, 3</td>
<td>3 T</td>
<td>Visual assessment of LGE by 1 reviewer</td>
<td>Consecutive patients referred for consideration of ICD placement</td>
</tr>
<tr>
<td>Gulati et al10</td>
<td>2013</td>
<td>472 (142/330)</td>
<td>63.6 (1–132) mo</td>
<td>Prospective, single center</td>
<td>4, 2, 3</td>
<td>1.5 T</td>
<td>Visual assessment of midwall LGE by 2 reviewers</td>
<td>Consecutive patients with DCM referred for CMR</td>
</tr>
<tr>
<td>Iles et al11</td>
<td>2011</td>
<td>61 (31/30)</td>
<td>18.8 (12.5–28.4) mo</td>
<td>Prospective, single center</td>
<td>4, 2, 2</td>
<td>1.5 T</td>
<td>Visual assessment of LGE by 2 reviewers</td>
<td>Patients with advanced HF referred for ICD placement</td>
</tr>
<tr>
<td>Lehrke et al12</td>
<td>2011</td>
<td>184 (72/112)</td>
<td>22.5±1 mo</td>
<td>Prospective, single center</td>
<td>4, 2, 1</td>
<td>1.5 T</td>
<td>Visual assessment of LGE by 2 reviewers</td>
<td>Consecutive patients with DCM</td>
</tr>
<tr>
<td>Müller et al13</td>
<td>2013</td>
<td>185 (94/91)</td>
<td>21 mo</td>
<td>Prospective, single center</td>
<td>4, 2, 3</td>
<td>1.5 T</td>
<td>Visual assessment of LGE by 2 reviewers</td>
<td>Consecutive patients with newly diagnosed NICM</td>
</tr>
<tr>
<td>Neilan et al14</td>
<td>2013</td>
<td>162 (81/81)</td>
<td>29±18 mo</td>
<td>Prospective, 2 center</td>
<td>4, 2, 3</td>
<td>1.5 T or 3 T</td>
<td>Visual assessment of LGE by 2 reviewers</td>
<td>Consecutive patients with DCM who underwent CMR</td>
</tr>
<tr>
<td>Wu et al15</td>
<td>2008</td>
<td>65 (27/38)</td>
<td>17 mo</td>
<td>Prospective, single center</td>
<td>4, 1, 2</td>
<td>1.5 T</td>
<td>Visual assessment of LGE by 2 reviewers</td>
<td>Consecutive patients with NICM and LVEF ≤35% referred for ICD placement</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CMR, cardiac MRI; DCM, dilated cardiomyopathy; DE-MRI, delayed enhancement MRI; HF, heart failure; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; and NICM, nonischemic cardiomyopathy.

Table 2. Patient Characteristics of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Men, %</th>
<th>LGE Prevalence, %</th>
<th>HTN, %</th>
<th>DM, %</th>
<th>Tobacco Use, %</th>
<th>FMH of DCM, %</th>
<th>Average LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheong et al7</td>
<td>51±16</td>
<td>57</td>
<td>17</td>
<td>NR</td>
<td>13</td>
<td>14</td>
<td>NR</td>
<td>52%*</td>
</tr>
<tr>
<td>Cho et al8</td>
<td>56±13</td>
<td>61</td>
<td>53</td>
<td>NR</td>
<td>9</td>
<td>27</td>
<td>NR</td>
<td>27±8</td>
</tr>
<tr>
<td>Gao et al9</td>
<td>NR</td>
<td>NR</td>
<td>71</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>26±7</td>
</tr>
<tr>
<td>Gulati et al10</td>
<td>51±15</td>
<td>69</td>
<td>30</td>
<td>NR</td>
<td>7</td>
<td>20</td>
<td>8</td>
<td>37±13</td>
</tr>
<tr>
<td>Iles et al11</td>
<td>53±14</td>
<td>69</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>25±9</td>
</tr>
<tr>
<td>Lehrke et al12</td>
<td>52±1</td>
<td>75</td>
<td>39</td>
<td>NR</td>
<td>39</td>
<td>12</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>Müller et al13</td>
<td>51±16</td>
<td>71</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>43±16</td>
</tr>
<tr>
<td>Neilan et al14</td>
<td>55±14</td>
<td>65</td>
<td>50</td>
<td>39</td>
<td>25</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
</tr>
<tr>
<td>Wu et al15</td>
<td>55±11</td>
<td>65</td>
<td>42</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24±10</td>
</tr>
</tbody>
</table>

Data presented as mean±SD. DCM indicates dilated cardiomyopathy; DM, diabetes mellitus; FMH, family history; HTN, hypertension; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; and NICM, nonischemic cardiomyopathy.

*Median value (interquartile range, 33–60).
†Median value (interquartile range, 21–42).
Assessment of Publication Bias
Funnel plots were visually inspected for all outcomes. There was no significant asymmetry in the funnel plots for the different outcomes, although heterogeneity with an elevated \( I^2 \) value was noted in HFH (Figure 2B). There was no evidence of small study bias as assessed by Egger and Peter tests. Exclusion of 1 study at a time from the outcomes analysis as part of sensitivity analysis did not affect the findings.

Discussion
This systematic review and meta-analysis demonstrates that the presence of LGE by CMR provides excellent risk stratification for patients with NICM. NICM patients without LGE have low (<2%) AERs for all-cause mortality, HFH, or SCD, whereas patients with LGE have significantly higher AERs (4.7%, 5.0%, and 6.0%, respectively) for the same individual outcomes. Although the prognostic value of LGE in patients with NICM has been demonstrated in small single-center studies, these findings have not been confirmed in larger patient populations. This meta-analysis is the first large-scale analysis to support the role of LGE-CMR in identifying patients with NICM at risk for SCD, HFH, and overall mortality, and it strengthens the conclusions of earlier studies on the role of LGE in a larger NICM patient population across multiple studies.

CMR has developed into a powerful tool that provides comprehensive cardiac assessment including evaluation of LV structure, function, perfusion, and tissue characteristics,
Our analysis suggests that NICM patients with LGE are at higher risk of above events compared with those without LGE. LVEF currently serves as the main determinant for ICD placement in cardiomyopathy patients for primary prevention of SCD. However, results from the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial demonstrate that the use of low LVEF alone as an indicator for ICD placement is associated with both a low event rate of SCD in the control and treatment groups and a significant number of inappropriate ICD shocks (49 inappropriate versus 91 appropriate ICD shocks) in the treatment group. In addition, patients are exposed to the potential complications of ICD placement and the substantial costs of this intervention. The presence of LGE by CMR is demonstrated in this meta-analysis to predict SCD, and the use of LGE along with LVEF for risk stratification may determine who would most benefit from ICD therapy.

A recent study enrolling patients with ICM or NICM found that the presence of both LGE and LVEF <30% increased the event rates of SCD or ICD discharge compared with event rates in patients with LVEF <30% alone. However, this was in a nonhomogeneous population, and this type of analysis will have to be performed prospectively in a cohort of patients with NICM to see whether this would hold for NICM subjects.

The presence of LGE in this meta-analysis identifies subjects with NICM who are at higher risk of hospitalization for heart failure. This could allow detection of patients with NICM that require closer follow-up and evaluation after diagnosis and may help reduce the significant costs incurred because of repeat admissions in this patient population. Although this analysis demonstrated significant heterogeneity for this outcome, meta-regression demonstrated that LVEF has a significant interaction with HFH and may affect the strength of the association. Hence, caution is mandated in interpreting the strength of this relationship. Prospective studies involving larger patient populations are further needed to confirm that LGE presence in patients with NICM can help with risk stratification with regard to HFH, independent of LVEF.

Current studies examining LGE by CMR in patients with NICM use varying definitions to define the presence and extent of LGE. Different thresholds of signal intensity including the presence or absence of fibrosis by LGE. Our analysis suggests that NICM patients with LGE are at higher risk of above events compared with those without LGE. LVEF currently serves as the main determinant for ICD placement in cardiomyopathy patients for primary prevention of SCD. However, results from the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial demonstrate that the use of low LVEF alone as an indicator for ICD placement is associated with both a low event rate of SCD in the control and treatment groups and a significant number of inappropriate ICD shocks (49 inappropriate versus 91 appropriate ICD shocks) in the treatment group. In addition, patients are exposed to the potential complications of ICD placement and the substantial costs of this intervention. The presence of LGE by CMR is demonstrated in this meta-analysis to predict SCD, and the use of LGE along with LVEF for risk stratification may determine who would most benefit from ICD therapy.

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Current studies examining LGE by CMR in patients with NICM use varying definitions to define the presence and extent of LGE. Different thresholds of signal intensity

### Table 3. Annualized Event Rates of Studies for Combined All-Cause Mortality, Heart Failure Hospitalization, and a Composite End Point of SCD, Aborted SCD, or Appropriate ICD Therapy Comparing Patients Positive for LGE and Patients Negative for LGE

<table>
<thead>
<tr>
<th>Study</th>
<th>All-Cause Mortality AER</th>
<th>HF Hospitalization</th>
<th>SCD/Aborted SCD/Appropriate ICD Therapy AER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LGE+</td>
<td>LGE−</td>
<td>LGE+</td>
</tr>
<tr>
<td>Cheong et al²</td>
<td>8.6%</td>
<td>2.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Cho et al⁶⁴</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gao et al⁹⁸</td>
<td>NA</td>
<td>NA</td>
<td>9.5%</td>
</tr>
<tr>
<td>Gulati et al¹⁰</td>
<td>5.0%</td>
<td>2.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Iles et al¹¹</td>
<td>NA</td>
<td>NA</td>
<td>4.6%</td>
</tr>
<tr>
<td>Lehrke et al¹²</td>
<td>NA</td>
<td>NA</td>
<td>4.8%</td>
</tr>
<tr>
<td>Müller et al¹³</td>
<td>3.6%</td>
<td>2.5%</td>
<td>21.5%</td>
</tr>
</tbody>
</table>

AER indicates annualized event rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; NA, not applicable; and SCD, sudden cardiac death.

**Figure 3.** Annualized event rates of cardiovascular outcomes based on the presence of late gadolinium enhancement (LGE). Weighted mean annualized event rates for all-cause mortality (ACM), heart failure with hospitalization (HFH), and a composite end point of sudden cardiac death (SCD), aborted SCD, or appropriate implantable cardioverter defibrillator therapy comparing patients with LGE on cardiac MR (CMR; blue) and patients without LGE on CMR (red).

*p-values are for the significance of the annualized event rate difference between LGE+ and LGE− subjects.
above that of the remote myocardium have been proposed to determine the presence of LGE, but currently there is a lack of consensus on an acceptable threshold for the diagnosis of LGE. This is particularly challenging in NICM where the intensity of the LGE is much more variable than in ischemic heart disease. In the studies used in this meta-analysis, either visual analysis or a threshold of 2 SD above remote myocardium was used to define the presence of LGE in a binary fashion without quantifying the extent of LGE. Although such limitations exist, the presence of LGE alone by visual assessment was found to be a predictor of adverse cardiovascular events in this meta-analysis and can help with risk stratification in these patients. Quantification of the extent of LGE has also been used in cardiomyopathy patients to determine its prognostic value. Assomull et al\textsuperscript{11} found that NICM patients with LGE of \textgreater{}5\% of LV mass were at higher risk of cardiovascular events than those with LGE \textless{}5\% of LV mass, suggesting that there might be a critical threshold of enhancement above which patients may be at higher risk of adverse events. However, LGE extent is also variably described in studies as a percentage of LV mass\textsuperscript{13} or scar volume,\textsuperscript{34} and there is no current consensus on the best method of LGE quantification. There is a need for uniformity in definition for both the presence and extent of LGE to ensure standardization and reproducibility of the technique and to further assess outcomes in cardiomyopathy patients.

An important limitation of the use of LGE by CMR is that it detects focal fibrosis and not diffuse fibrosis. Newer techniques such as T1 mapping have shown promise in detecting diffuse fibrosis\textsuperscript{35} and may provide additional valuable prognostic information in patients with NICM. Wong et al\textsuperscript{29} showed that increased extracellular volume fraction, as obtained from T1 mapping data, predicted increased risk of cardiovascular outcomes. Such measures derived from T1 mapping may add prognostic value to that obtained by LGE-CMR in both the ICM and NICM populations. However, at this time, no T1 mapping technique is universally accepted, and current techniques have potential measurement biases that may prevent direct comparison across studies.\textsuperscript{35} In addition, T1 mapping sequences are not widely available outside academic medical centers. For these reasons, widespread use of T1 mapping for risk stratification in NICM is not yet feasible. Finally, there is also a need for prospective evaluation with large patient populations to determine whether detection of LGE by CMR results in improved patient outcomes.

Limitations of systematic reviews pertinent to the present study include lack of raw and uniform data from included studies, estimation of events from hazard ratios in some studies, which assumes a linear event rate, and differences in length of follow-up, for which we attempt to adjust by using AERs. The studies included in the meta-analysis are observational studies, and the pooled estimates reported (Figure 2) were not adjusted for potential confounders because the raw data from individual studies were not available. Furthermore, without raw data for patient-level covariates, the interaction between LGE and LVEF could only be evaluated by meta-regression of study-level covariates. Also as mentioned above, studies included in this meta-analysis used differing inclusion criteria for enrollment of subjects, which also limits its findings.

Another limitation of this meta-analysis is that heterogeneity was observed for one of the outcomes of interest (HFH), although a random-effects model should minimize its overall effect on this outcome. Meta-regression demonstrated an interaction with LVEF for this outcome, which explains some of the observed heterogeneity. Furthermore, the studies by Gulati et al\textsuperscript{10} and Müller et al\textsuperscript{13} included all-cause mortality as one of their outcomes, and the effect of mortality on the association between LGE presence and HFH or arrhythmic events was not assessed, which may also limit these findings. In addition, the study by Müller et al\textsuperscript{13} as described earlier included 15 patients with suspected hypertrophic cardiomyopathy and 3 patients with glycogen storage diseases, representing \textless{}10\% of the study population. The authors excluded the 18 patients mentioned above and, on reanalyzing the effect of LGE on the composite outcome (all-cause mortality, aborted sudden death, and sustained ventricular tachycardia), found similar results to that obtained from the entire study population. This further lends weight to the observation that inclusion of these subjects did not affect the overall study results. Sensitivity analysis also showed that the exclusion of the study did not affect the strength of the association between LGE and individual outcomes. The study by Cheong et al\textsuperscript{2} was a retrospective analysis and enrolled NICM patients with relatively higher LVEF compared with the other trial populations included in this meta-analysis. However, sensitivity analysis showed that the exclusion of this study did not affect the strength of the association between LGE and all-cause mortality.

In conclusion, the presence of LGE by CMR provides excellent prognostic risk stratification for SCD, all-cause mortality, and HFH in patients with NICM. The addition of the presence or absence of LGE to LVEF may add to the overall prognostic power to predict SCD in patients with NICM and better identify those subjects who obtain the best benefit from ICD placement and other aggressive heart failure management options.

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**CLINICAL PERSPECTIVE**

Myocardial scar or fibrosis is a predictor of increased cardiovascular risk, including worsening heart failure and sudden cardiac death from ventricular arrhythmias, in patients with nonischemic cardiomyopathy. Measurement of myocardial fibrosis by late gadolinium enhancement cardiac MR has been shown to be a predictor of adverse cardiovascular outcomes in multiple studies. However, these studies are limited by small sample sizes, differing outcomes of interest, and small numbers of events. This meta-analysis shows that the presence of late gadolinium enhancement by cardiac MR is associated with increased overall mortality, heart failure hospitalizations, and sudden cardiac death. Current guidelines advocate the use of left ventricular ejection fraction to determine the need for implantable cardioverter defibrillator placement in patients with nonischemic cardiomyopathy. However, the presence of low left ventricular ejection fraction alone, in the Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial as a determinant of implantable cardioverter defibrillator placement, was associated with a low event rate of sudden cardiac death in both the treatment and the control groups and was associated with an increase in the number of inappropriate shocks in the treatment group. There is a need for better risk stratification in patients with nonischemic cardiomyopathy, and the presence of myocardial fibrosis by late gadolinium enhancement cardiac MR, in addition to left ventricular ejection fraction, may help improve risk stratification and more effectively guide implantable cardioverter defibrillator therapy and other management options in this patient population.
Late Gadolinium Enhancement on Cardiac Magnetic Resonance Predicts Adverse Cardiovascular Outcomes in Nonischemic Cardiomyopathy: A Systematic Review and Meta-Analysis
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Meta-analysis for Overall Outcomes
Odds ratios were determined from the raw event data from each study for the endpoints of all-cause mortality, heart-failure hospitalization and SCD/aborted SCD. Meta-analysis was performed in RevMan 5.2 using a random effects model. Weighting of individual studies was performed using the Mantel-Haenszel method. The $\tau^2$ parameter for the random effects model was determined using the method of moments. Funnel plots and eggers and peters tests were performed to assess for publication bias. The heterogeneity statistic $Q$ was calculated using the inverse-variance weight method (1) and the $I^2$ statistic was used to measure the proportion of total variance in the study estimate which is attributable to heterogeneity between studies rather than due to sampling error. An $I^2$ greater than 25%, 50%, and 75% were used as indicators of mild, moderate, or significant heterogeneity between studies. Sensitivity analysis was performed by excluding each study and interpreting the effect on the overall meta-analysis.

Methods for Comparing Annualized Event Rates
To compare event rates with different duration of follow up between studies, annualized event rates were calculated by dividing the total number of events in the Scar+ and Scar – groups and dividing by the total number of years of follow-up. To compare the differences in annualized event rate between the Scar+ and Scar - groups, a generalized inverse variance meta-analysis of the difference in annualized event rates was performed using RevMan 5.2. The effect-size for each study was determined as AER Scar+ - AER Scar -. The variance for the difference in AER was calculated using the method described by Normand (2). The $\tau^2$ parameter for the random effects model was determined using the method of moments. The heterogeneity statistic $Q$ was calculated using the inverse-variance weight method and the $I^2$ statistic was used to measure the proportion of total variance in the study estimate which is attributable to heterogeneity between studies rather than due to sampling error.

Methods for Performing the Meta-Regression
Meta-regression was performed using a fixed-effect model (3). The fixed-effect meta-regression was performed using SPSS version 21. For the fixed effect model the lnOR was regressed against the covariate of interest (either age or EF) using a weighted least squares approach using the inverse variance of the lnOR for each study as the weight. The Regression procedure in SPSS was used.

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