Late Gadolinium Enhancement on CMR Predicts Adverse Cardiovascular Outcomes in Non-ischemic Cardiomyopathy: A Systematic Review and Meta-analysis

Kuruvilla et al: CMR and Prognosis in NICM

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Abstract

**Background**—LGE by CMR is a predictor of adverse cardiovascular outcomes in non-ischemic cardiomyopathy (NICM) patients. 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 late-gadolinium enhancement by cardiac magnetic resonance (LGE-CMR) imaging in NICM patients.

**Methods and Results**—PubMed, Cochrane CENTRAL and EMBASE were searched for studies looking at the prognostic value of LGE-CMR in NICM patients. The primary end-points included all-cause mortality, heart failure hospitalization (HFH), and a composite end point of sudden cardiac death (SCD) or aborted SCD. Pooling of odds ratios (OR) was performed using a random-effect model and annualized event rates (AER) were assessed. Data was included from 9 studies with a total of 1,488 patients and a mean follow-up of 30 months. Patients had a mean age of 52 years, 67% were male and the average LVEF was 37% on CMR. LGE was present in 38% of patients. Patients with LGE had increased overall mortality (OR 3.27, p<0.00001), HFH (OR 2.91, p=0.02), and SCD/aborted SCD (OR 5.32, p<0.00001) when compared with those without LGE. The AERs for mortality were 4.7% for LGE+ subjects vs. 1.7% for LGE- subjects (p=0.01), 5.03% vs. 1.8% for HFH (p=0.002), and 6.0% vs. 1.2% for SCD/aborted SCD (p<0.001).

**Conclusions**—LGE in NICM patients is associated with increased risk of all-cause mortality, HFH, and SCD. Detection of LGE by CMR has excellent prognostic characteristics and may help guide risk stratification and management in NICM patients.

**Key Words**: prognosis, cardiac MRI, late gadolinium enhancement, non-ischemic cardiomyopathy
Abbreviations
AER: Annualized event rate
CMR: Cardiac magnetic resonance
HFH: Heart failure hospitalization
ICD: Implantable cardioverter-defibrillator
LGE: Late gadolinium enhancement
NICM: Non-ischemic cardiomyopathy
OR: Odds ratio
SCD: Sudden cardiac death
Non-ischemic Cardiomyopathy (NICM) refers to diverse myocardial conditions characterized by a reduction in left ventricular systolic function in the absence of significant coronary artery disease. The prevalence of NICM in the general population is thought to be approximately 40–50 cases per 100,000 (1). Myocardial scar or fibrosis in patients with NICM is a substrate for re-entrant circuits (2) 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 magnetic resonance (LGE-CMR) is an effective and reproducible method of assessing myocardial fibrosis and has previously demonstrated prognostic utility in patients with ICM and hypertrophic cardiomyopathy (4, 5, 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 for 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 NICM patients involving studies with uniform endpoints and large patient populations (16).

There is a need for better risk stratification of SCD in patients with NICM. Current evidence points to the use of left ventricular ejection fraction (LVEF) as a predictor of sudden cardiac death (SCD) and present guidelines (17) recommend the use of ICD therapy for an LVEF of <35% to prevent SCD in such patients. However, use of LVEF < 35% alone has limited power in predicting SCD in NICM patients (18). The use of LGE as a prognostic variable in addition to LVEF may help improve risk stratification of NICM patients and better guide the use of ICD, cardiac re-synchronization therapy (CRT) 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: (1) evaluation of myocardial fibrosis in patients with NICM using LGE-CMR, (2) inclusion of “hard” end-points such as all-cause mortality, sudden cardiac death (SCD)/aborted SCD or heart failure hospitalization (HFH). Studies that evaluated ischemic cardiomyopathies, acute myocarditis, 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, two independent reviewers (SK and AK) 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 “see 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 MOOSE and PRISMA guidelines (19, 20).
Study Selection

Two investigators (SK and AK) independently scanned all abstracts and obtained full-text reports of manuscripts 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 (21) where the quality of the selected trials was determined on the basis of selection of the study groups (0 to 4 points), comparability of the study groups (0 to 2 points), and ascertainment of the outcome of interest (0 to 3 points).

Data Collection

The same two investigators were involved in data abstraction and study appraisal. Clinical outcomes of interest were all-cause mortality, heart failure hospitalization (HFH), and a composite end point of SCD or aborted SCD during follow-up. Clinical outcomes 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 mean or median follow-up duration.

Data Analysis

Dichotomous variables were expressed as proportions (percentages) and continuous variables as mean (standard deviation) or median (range). Binary outcomes from individual studies were combined with random-effect model, leading to estimation of pooled odds ratio (ORs) with 95% confidence intervals (CI). $I^2$ was calculated as a measure of statistical heterogeneity with $I^2$ values of 25%, 50% and 75% representing mild, moderate and severe heterogeneity, respectively.” Small study or publication bias was evaluated using funnel plots, Egger’s test (22), and Peter’s test (23). 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 one study at a time, was performed. To further assess heterogeneity and the influence of potential study-level covariates, we performed a fixed-effect meta-regression of the natural log of the OR for each endpoint for the factors of age and ejection fraction. AERs were compared using an inverse variance-weighted random-effects meta-analysis of the difference in annualized event rates between the groups (24).

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 Version 21), with statistical significance for hypothesis testing set at the 0.05 two-tailed level. More specific details of the statistical analysis are provided as a supplement.

Results

Results of the literature search

Our literature search identified 2,447 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 (25-31) were excluded for various reasons including cohort overlap with other papers or lack of our pre-specified outcomes, leaving 9 manuscripts for detailed study (7-15). The details of our flow diagram can be found in Figure 1. Study characteristics are presented in Table 1. Only one study included patients undergoing CMR at 3.0 Tesla (T), while the remainder were performed at 1.5T.

Overall, there were 9 studies which included data on at least one of the outcomes of interest with a mean follow-up of 30 months (median of 23 months, range 17 to 64 months)
involving a total of 1,488 patients with NICM undergoing CMR (median of 162 patients, average of 165 patients, range 61 to 472). Patients had a mean age of 52 years and 67% were male. 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 regards 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 employed varying inclusion criteria for enrollment. Six studies enrolled NICM patients referred for CMR and 3 studies enrolled NICM patients eligible for ICD placement. All studies except for one (7) were prospective studies (See Table 1). Furthermore every study, except for the study by Ills et al. (11), 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 when compared to 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 one (10) used the presence of any LGE to assess outcomes and events. Gulati et al. (10) used the presence or absence of mid-wall fibrosis alone to assess outcomes. The authors do not specifically mention if any non mid-wall LGE was present in either group. The study by Müller et al. (13) included 15 patients with suspected hypertrophic cardiomyopathy since they presented with non-ischemic heart failure symptoms and 3 patients with glycogen storage diseases. While 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 non-
ischemic cardiomyopathy patients who had relatively preserved LVEF when compared to other study populations. Out of 9 studies, 5 studies did not discuss acuity of heart failure. Out of the remaining 4 studies, only one (13) enrolled newly diagnosed heart failure (<4 weeks). The remaining 3 studies enrolled subjects with NICM of >3 months 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 when compared with patients without LGE (OR 3.27, 95% CI 1.94 to 5.15, p<0.00001, I²= 28%). Patients with LGE had significantly greater AERs for mortality than patients without LGE (4.7% vs. 2.2% p=0.01) (Table 3 and Figure 3). I² was elevated suggesting mild heterogeneity for this outcome. Meta-regression was performed and did not show any significant interactions with the study-level co-variates. We performed sensitivity analysis for the all-cause mortality outcome. When we excluded the study by Gulati et al. the p value for the outcome was not significant at 0.07 though the trend remained towards increased all-cause mortality if LGE was present. This was not unexpected as only three studies were included for this outcome and also since the study by Gulati et al. provides 54.1% of the weighting for the pooled odds ratio for this endpoint.

Among the studies selected, 5 studies with 985 participants with NICM reported the outcome of HFH during follow-up. 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% CI 1.16 to 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 were 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% vs. 1.8%, p=0.002) (Table 3 and Figure 3). Sensitivity analysis was performed for the outcome of heart failure with hospitalization. With exclusion of the study by Cho et al. the p value for the outcome was not significant at 0.07 though the trend towards increased heart failure hospitalization remained if LGE was present. Similarly with the individual exclusion of Gulati et al. and Lehrke et al. the overall p values for the outcome were not significant at 0.07 and 0.06 respectively, though the trend towards increased heart failure hospitalization 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 VT/VF 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% CI 3.45 to 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 and Figure 3) when compared to patients without LGE (6.0% vs. 1.2%, p<0.001). The study by Iles et al. (11) has a high event rate of SCD when compared to 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 sudden cardiac death/appropriate ICD therapy/aborted SCD was performed and the individual exclusion of studies included in this outcome did not affect the results of this endpoint.
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, though heterogeneity with an elevated $I^2$ value was noted in heart failure hospitalization (Figure 2B). There was no evidence of small study bias as assessed by Egger's and Peter's tests. Exclusion of one study at a time from the outcomes analysis as part of sensitivity analysis did not impact 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, while patients with LGE have significantly higher AERs (4.7%, 5.0% and 6.0% respectively) for the same individual outcomes. While 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 NICM patients at risk for SCD, HFH and overall mortality, and it strengthens the conclusions of earlier studies concerning the role of LGE in a larger NICM patient population across multiple studies.

CMR has developed into a powerful tool which provides comprehensive cardiac assessment including evaluation of left ventricular structure, function, perfusion, and tissue characteristics, 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 DEFINITE trial (18) 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. Additionally, 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 when compared to event rates in patients with LVEF < 30% alone (32). However, this was in a non-homogenous population and this type of analysis will have to be performed prospectively in a cohort of NICM patients to see if this would hold for NICM subjects.

The presence of LGE in this meta-analysis identifies subjects with NICM that are at higher risk of hospitalization for heart failure. This could allow detection of NICM patients that require closer follow-up and evaluation following diagnosis, and may help reduce the significant costs incurred due to repeat admissions in this patient population. While 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 NICM patients can help with risk stratification with regards to HFH, independent of LVEF.

Current studies examining LGE by CMR in NICM patients use varying definitions to define the presence and extent of LGE (16). Different thresholds of signal intensity 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 2SD above remote myocardium was used to define the presence of LGE in a binary fashion without quantifying the extent of LGE. While 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. (31) found that NICM patients with LGE of approximately > 5% of LV mass were at higher risk of cardiovascular events than those with LGE < 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 left ventricular mass (33) or scar volume (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, 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 (35) and may provide additional valuable prognostic information in NICM patients. Wong et al. (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 (35). Additionally, T1 mapping sequences are not widely available outside of 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 if 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 annualized event rates. The studies included in the meta-analysis are observational studies and the pooled estimates reported (Figure 2) were not adjusted for potential confounders as the raw data from individual studies was 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), though 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 (10) and Müller et al. (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 were not assessed which may also limit these findings. Additionally, the study by Müller et al. (13) as described earlier,
included 15 patients with suspected hypertrophic cardiomypathy and 3 patients with glycogen storage diseases representing <10% of the study population. The authors excluded the 18 patients mentioned above and on re-analyzing 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. was a retrospective analysis and (7) enrolled NICM patients with relatively higher LVEF compared to 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, presence of LGE by CMR provides excellent prognostic risk stratification for SCD, all-cause mortality and heart failure hospitalization in NICM patients. The addition of the presence or absence of LGE to LVEF may add to the overall prognostic power to predict SCD in NICM patients and better identify those subjects that obtain the best benefit from ICD placement and other aggressive heart failure management options.

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**Disclosures**

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11. Iles L, Pfluger H, Lefkovits L, Butler MJ, Kistler PM, Kaye DM, Taylor AJ. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-


meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.


Table 1. Study Characteristics. CMR = cardiac magnetic resonance imaging; SD = standard deviation; LGE = late gadolinium enhancement; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; CAD = coronary artery disease; NICM = non-ischemic cardiomyopathy; CAD = coronary artery disease; ICD = implantable cardioverter-defibrillator; HF = heart failure; DE-MRI = Delayed enhancement magnetic resonance imaging.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number 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 LGE used for Outcome Assessment</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheong, et al.</td>
<td>2009</td>
<td>215 (37/178)</td>
<td>52.8 months</td>
<td>Retrospective, single center</td>
<td>4, 0, 3</td>
<td>1.5T</td>
<td>Visual assessment of LGE by one reviewer</td>
<td>Consecutive patients referred for DE-MRI</td>
</tr>
<tr>
<td>Cho, et al.</td>
<td>2010</td>
<td>79 (42/37)</td>
<td>33.4 ± 1.7 months</td>
<td>Prospective, single center</td>
<td>4, 1, 1</td>
<td>1.5T</td>
<td>Visual assessment of LGE by two reviewers</td>
<td>Patients with LVEF &lt;35% and CAD excluded by angiography</td>
</tr>
<tr>
<td>Gao, et al.</td>
<td>2012</td>
<td>65 (46/19)</td>
<td>20.8 ± 8.6 months</td>
<td>Prospective, single center</td>
<td>4, 0, 3</td>
<td>3T</td>
<td>Visual assessment of LGE by one reviewer</td>
<td>Consecutive patients referred for consideration of ICD placement</td>
</tr>
<tr>
<td>Gulati, et al.</td>
<td>2013</td>
<td>472 (142/330)</td>
<td>63.6 (1-132) months</td>
<td>Prospective, single center</td>
<td>4, 2, 3</td>
<td>1.5T</td>
<td>Visual assessment of mid-wall LGE by two reviewers</td>
<td>Consecutive patients with DCM referred for CMR</td>
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<tr>
<td>Neilan, et al.</td>
<td>2013</td>
<td>162 (81/81)</td>
<td>29 ± 18 months</td>
<td>Prospective, two center</td>
<td>4, 2, 3</td>
<td>1.5T or 3T</td>
<td>Visual assessment of LGE by two</td>
<td>Consecutive patients with DCM who underwent advanced HF and NICM</td>
</tr>
<tr>
<td>Lehrke, et al.</td>
<td>2011</td>
<td>61 (31/30)</td>
<td>18.8 (12.5-28.4) months</td>
<td>Prospective, single center</td>
<td>4, 2, 2</td>
<td>1.5T</td>
<td>Visual assessment of LGE by two reviewers</td>
<td>Patients with advanced HF referred for ICD placement</td>
</tr>
<tr>
<td>Müller, et al.</td>
<td>2013</td>
<td>185 (94/91)</td>
<td>21 months</td>
<td>Prospective, single center</td>
<td>4, 2, 3</td>
<td>1.5T</td>
<td>Visual assessment of LGE by two reviewers</td>
<td>Consecutive patients with newly diagnosed NICM</td>
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<tr>
<td>Wu, et al.(^{15})</td>
<td>2008</td>
<td>65 (27/38)</td>
<td>17 months</td>
<td>Prospective, single center</td>
<td>4, 1, 2</td>
<td>1.5T</td>
<td>Visual assessment of LGE by two reviewers</td>
<td>Consecutive patients with NICM and LVEF ≤35% referred for ICD placement</td>
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<tr>
<td>2008</td>
<td>65 (27/38)</td>
<td>17 months</td>
<td>Prospective, single center</td>
<td>4, 1, 2</td>
<td>1.5T</td>
<td>Visual assessment of LGE by two reviewers</td>
<td>Consecutive patients with NICM and LVEF ≤35% referred for ICD placement</td>
<td>reviewers</td>
</tr>
</tbody>
</table>
Table 2. Patient Characteristics of Studies. Data presented as mean ± standard deviation. HTN = hypertension; DM = diabetes mellitus; FMH = family history; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; LGE = late gadolinium enhancement; NR = not reported.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>% Male</th>
<th>LGE prevalence</th>
<th>HTN</th>
<th>DM</th>
<th>Tobacco use</th>
<th>FMH of DCM</th>
<th>Average LVEF</th>
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<tr>
<td>Cheong, et al.7</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>
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<tr>
<td>Cho, et al.8</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>
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<tr>
<td>Gao, et al.9</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 al.10</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 al.11</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>
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<tr>
<td>Lehrke, et al.12</td>
<td>52 ± 1</td>
<td>75%</td>
<td>39%</td>
<td>39%</td>
<td>12%</td>
<td>NR</td>
<td>15%</td>
<td>39%**</td>
</tr>
<tr>
<td>Müller, et al.13</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 al.14</td>
<td>55 ± 14</td>
<td>65%</td>
<td>50%</td>
<td>39%</td>
<td>25%</td>
<td>NR</td>
<td>8%</td>
<td>28 ± 9</td>
</tr>
<tr>
<td>Wu, et al.15</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>

*Median Value (interquartile range: 33-60)
**Median Value (interquartile range: 21-42)
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 with positive for LGE and patients negative for LGE. AER = annualized event rate; SCD = sudden cardiac death; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; HF = heart failure; NA = Not applicable.

<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 al. 7</td>
<td>8.6%</td>
<td>2.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Cho, et al. 8</td>
<td>NA</td>
<td>NA</td>
<td>9.5%</td>
</tr>
<tr>
<td>Gao, et al. 9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gulati, et al. 10</td>
<td>5.0%</td>
<td>2.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Iles, et al. 11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lehrke, et al. 12</td>
<td>NA</td>
<td>NA</td>
<td>4.6%</td>
</tr>
<tr>
<td>Müller, et al. 13</td>
<td>3.6%</td>
<td>2.5%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Neilan, et al. 14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wu, et al. 15</td>
<td>NA</td>
<td>NA</td>
<td>21.5%</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Flow diagram of the review process.

Figure 2. Individual and pooled risk of cardiovascular outcomes for LGE-CMR. Forest plots comparing clinical outcomes of patients with known or suspected NICM with positive LGE and negative LGE. Outcomes included (A) all-cause mortality (B) heart failure with hospitalization, and (C) composite end point of SCD, aborted SCD, or appropriate ICD therapy.

Figure 3. Annualized event rates of cardiovascular outcomes based on the presence of LGE. Weighted mean AERs for all-cause mortality, heart failure with hospitalization, and a composite end point of SCD, aborted SCD, or appropriate ICD therapy comparing patients with LGE on CMR (blue) and patients without LGE on CMR (red).
2447 studies identified through database search

21 additional records identified through other sources

2442 studies after duplicates removed

2397 studies excluded for not pertaining to scar by LGE-CMR in NICM and prognosis

45 studies screened by reading abstracts

29 studies that assessed ischemic, hypertrophic, and infiltrative cardiomyopathies excluded

16 studies assessed for eligibility

7 studies excluded for lack of specific outcomes

9 studies included in meta-analysis
Figure 2: Individual and pooled risk of cardiovascular outcomes for LGE-CMR.

### Figure 2A. Presence of LGE and All-Cause Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LGE+ Events</th>
<th>LGE+ Total</th>
<th>LGE- Events</th>
<th>LGE- Total</th>
<th>Weight M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheong BYC 2009</td>
<td>16</td>
<td>37</td>
<td>23</td>
<td>178</td>
<td>31.8%</td>
<td>5.13 [2.34, 11.25]</td>
</tr>
<tr>
<td>Gulati A 2013</td>
<td>38</td>
<td>142</td>
<td>35</td>
<td>330</td>
<td>54.1%</td>
<td>3.08 [1.85, 5.13]</td>
</tr>
<tr>
<td>Muller KAL 2013</td>
<td>6</td>
<td>94</td>
<td>4</td>
<td>91</td>
<td>14.1%</td>
<td>1.48 [0.40, 5.44]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>273</td>
<td>60</td>
<td>599</td>
<td>62</td>
<td>3.27 [1.94, 5.51]</td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 60
- Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 2.76$, df = 2 ($P = 0.25$); $I^2 = 28$
- Test for overall effect: $Z = 4.45$ ($P < 0.000001$)

### Figure 2B. Presence of LGE and Heart Failure Hospitalization

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LGE+ Events</th>
<th>LGE+ Total</th>
<th>LGE- Events</th>
<th>LGE- Total</th>
<th>Weight M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho JR 2010</td>
<td>11</td>
<td>42</td>
<td>1</td>
<td>37</td>
<td>12.7%</td>
<td>12.77 [1.56, 104.60]</td>
</tr>
<tr>
<td>Gulati A 2013</td>
<td>30</td>
<td>142</td>
<td>35</td>
<td>330</td>
<td>33.5%</td>
<td>2.26 [1.32, 3.85]</td>
</tr>
<tr>
<td>Lehirske S 2011</td>
<td>6</td>
<td>72</td>
<td>3</td>
<td>112</td>
<td>19.0%</td>
<td>3.30 [1.80, 6.35]</td>
</tr>
<tr>
<td>Muller KAL 2013</td>
<td>8</td>
<td>94</td>
<td>9</td>
<td>91</td>
<td>26.4%</td>
<td>0.86 [0.31, 2.30]</td>
</tr>
<tr>
<td>Wu KC 2008</td>
<td>8</td>
<td>27</td>
<td>0</td>
<td>38</td>
<td>7.8%</td>
<td>3.56 [1.84, 6.9]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>377</td>
<td>63</td>
<td>608</td>
<td>48</td>
<td>2.91 [1.16, 7.27]</td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 63
- Heterogeneity: $\tau^2 = 0.58$; $\chi^2 = 10.24$, df = 4 ($P = 0.04$); $I^2 = 61$
- Test for overall effect: $Z = 2.28$ ($P = 0.02$)

### Figure 2C. Presence of LGE and SCD/Aborted SCD/Appropriate ICD therapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LGE+ Events</th>
<th>LGE+ Total</th>
<th>LGE- Events</th>
<th>LGE- Total</th>
<th>Weight M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao P 2012</td>
<td>7</td>
<td>46</td>
<td>1</td>
<td>19</td>
<td>4.0%</td>
<td>3.23 [0.37, 28.25]</td>
</tr>
<tr>
<td>Gulati A 2013</td>
<td>42</td>
<td>142</td>
<td>23</td>
<td>330</td>
<td>60.4%</td>
<td>5.61 [3.21, 9.78]</td>
</tr>
<tr>
<td>Iles 2011</td>
<td>9</td>
<td>31</td>
<td>0</td>
<td>30</td>
<td>2.2%</td>
<td>25.76 [1.42, 465.99]</td>
</tr>
<tr>
<td>Lehrke S 2011</td>
<td>6</td>
<td>72</td>
<td>2</td>
<td>112</td>
<td>7.0%</td>
<td>5.00 [0.98, 25.50]</td>
</tr>
<tr>
<td>Muller KAL 2013</td>
<td>16</td>
<td>94</td>
<td>4</td>
<td>91</td>
<td>14.5%</td>
<td>4.46 [1.43, 13.92]</td>
</tr>
<tr>
<td>Neillan TG 2013</td>
<td>15</td>
<td>81</td>
<td>1</td>
<td>81</td>
<td>4.4%</td>
<td>18.18 [2.34, 141.28]</td>
</tr>
<tr>
<td>Wu KC 2008</td>
<td>4</td>
<td>27</td>
<td>3</td>
<td>38</td>
<td>7.4%</td>
<td>2.03 [0.42, 9.92]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>493</td>
<td>99</td>
<td>701</td>
<td>34</td>
<td>5.32 [3.45, 8.20]</td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 99
- Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.38$, df = 6 ($P = 0.63$); $I^2 = 0$
- Test for overall effect: $Z = 7.58$ ($P < 0.000001$)
Figure 3: Annualized event rates of cardiovascular outcomes based on the presence of LGE.

* p-values are for the significance of the annualized event rate difference between LGE+ and LGE- subjects.