Prognostic Value of Late Gadolinium Enhancement in Clinical Outcomes for Hypertrophic Cardiomyopathy

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OBJECTIVES The objective of this study was to perform a systematic review and meta-analysis of the predictive value of late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) for future cardiovascular events and death in hypertrophic cardiomyopathy (HCM).

BACKGROUND The utility of LGE for detecting myocardial fibrosis is well established. The prognostic value of LGE in HCM has been described in several studies, but controversy exists given the limited power of these studies to predict future events.

METHODS We searched multiple databases including PubMed for studies of LGE in HCM that reported selected clinical outcomes (cardiovascular mortality, sudden cardiac death [SCD], aborted SCD, and heart failure death). We performed a systematic review of the literature and meta-analysis to determine pooled odds ratios for these clinical events.

RESULTS Four studies evaluated 1,063 patients over an average follow-up of 3.1 years. The pooled prevalence of LGE was 60%. The pooled odds ratios (OR) demonstrate that LGE by CMR correlated with cardiac death (pooled OR: 2.92, 95% confidence interval [CI]: 1.01 to 8.42; p = 0.047), heart failure death (pooled OR: 5.68, 95% CI: 1.04 to 31.07; p = 0.045), and all-cause mortality (pooled OR: 4.46, 95% CI: 1.53 to 13.01; p = 0.006), and showed a trend toward significance for predicting sudden death/aborted sudden death (pooled OR: 2.39, 95% CI: 0.87 to 6.58; p = 0.091).

CONCLUSIONS Late gadolinium enhancement by CMR has prognostic value in predicting adverse cardiovascular events among HCM patients. There are significant relationships between LGE and cardiovascular mortality, heart failure death, and all-cause mortality in HCM. Additionally, LGE and SCD/aborted SCD displayed a trend toward significance. The assessment of LGE by CMR has the potential to provide important information to improve risk stratification in HCM in clinical practice. (J Am Coll Cardiol Img 2012;5:370–7) © 2012 by the American College of Cardiology Foundation.
Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease that is characterized by substantial heterogeneity with respect to presentation, phenotypic expression, clinical course, and overall prognosis (1–3). Although HCM is the leading cause of sudden death (SCD) in young people, it has a diverse phenotypic spectrum such that the clinical presentation can occur during any phase of life, and the vast majority of HCM patients with SCD have few to no clinical symptoms (1). In general, HCM confers an annual mortality rate of about 1%, but a subset of roughly 10% to 20% of patients have higher mortality or morbidity due to complications arising from SCD (perhaps as high as 5% annually), progressive heart failure (HF), and atrial fibrillation complicated by embolic stroke (1).

Device therapy with implantable cardioverter-defibrillators (ICD) has been shown to be an extremely effective intervention for primary prevention of sudden death in patients with HCM (4). There are 5 clinically accepted high-risk factors for SCD that may justify primary prevention with ICD: 1) a family history of 2 or more premature sudden deaths; 2) extreme left ventricular hypertrophy (≥30 mm); 3) unexplained syncope in young patients; 4) nonsustained ventricular tachycardia (NSVT) on Holter monitoring in patients ≤30 years of age; and 5) an abnormal blood pressure response during upright exercise (4,5). However, in a large HCM ICD registry, only 13% of patients with prophylactic primary prevention devices implanted for high-risk features had an appropriate discharge for ventricular tachycardia or ventricular fibrillation, whereas 25% of these patients had inappropriate ICD shocks (6). Furthermore, the risk of appropriate ICD discharge was not significantly different for 1, 2, or 3 of the traditional clinical risk factors (6). This highlights the importance of improved methods for SCD risk stratification in HCM patients.

Another substantial complication of HCM is progressive HF, as roughly 15% to 20% of HCM patients with heart failure have marked symptom progression (New York Heart Association [NYHA] functional classes III and IV) (1). Determining which HCM patients are at a higher risk for the development and progression of HF could identify those who stand to benefit from more aggressive HF medical therapy than currently indicated as well as provide prognostic information regarding HF death.

Cardiac magnetic resonance (CMR) is emerging as a powerful tool for the diagnosis and risk stratification in HCM. It is widely accepted as a gold standard method for assessment of myocardial function as well as left ventricular (LV) mass, which has been shown to be a sensitive predictor of adverse outcomes in HCM (7). As myocardial fibrosis may provide the underlying arrhythmogenic substrate in HCM, there has been significant interest in using late gadolinium enhancement (LGE) to evaluate myocardial fibrosis. Multiple studies have demonstrated a high prevalence of LGE, predominantly in a patchy, multifocal mid-wall distribution in regions of hypertrophy (8,9); and LGE has been shown to be associated with NSVT as well as with other risk factors for SCD (9–12). Furthermore, the presence of LGE has been shown to be a marker of adverse outcomes in multiple nonischemic cardiomyopathies (13,14).

Only recently have studies emerged evaluating LGE for the prediction of endpoints of cardiovascular death and SCD in HCM; however, these recent studies have been limited in size and demonstrate differing results (15–18). The objective of this meta-analysis is to determine the association of LGE by CMR in patients with HCM for the prediction of cardiac mortality, SCD/aborted SCD, HF death, and all-cause mortality. That could potentially identify patients who are at risk for SCD who may benefit from prophylactic ICD therapy, as well as providing prognostic information for predicting HCM death.

METHODS

Data sources. We searched PubMed/MEDLINE, the Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Cochrane Controlled Trials Register, and the ISI Web of Science to identify studies for meta-analysis inclusion. We used the text words and related Medical Subject Headings for hypertrophic cardiomyopathy and magnetic resonance imaging. There were no language restrictions, as non-English publications were included in initial search designs and evaluated.

Study selection. Two physician investigators independently conducted the literature search and extraction of relevant titles. The titles and abstract of potentially relevant studies and review articles were screened for appropriateness before retrieval of the full article, where relevant. The PubMed search
query on December 15, 2010, produced 592 initial results (Fig. 1). Of these, 572 were excluded by title or abstract as unrelated to the scientific question. Twenty studies were retrieved for detailed evaluation, 3 of which were review articles that were excluded. Of the 17 potentially appropriate studies, only 4 studies evaluated the selected endpoints (cardiac death, sudden cardiac death [SCD], aborted SCD, and heart failure [HF] death) in HCM patients using LGE by CMR. These 4 studies were then included in the meta-analysis. Only 2 of the studies reported on all-cause mortality and were analyzed separately for this endpoint.

Data abstraction and validity assessment. Two physician investigators independently abstracted data using a standardized form. We extracted the following demographic data: author, year of publication, design, follow-up duration, sample size, characteristics of LGE CMR used, age, percentage male, NYHA functional class I, NYHA functional class II, NYHA functional class III/IV, LVEF ≤50%, LVEF, wall thickness >30 mm, syncope, sustained ventricular tachycardia/fibrillation, family history of SCD, and LGE status. Clinical outcomes included the raw events data for all-cause mortality, all cardiac deaths, SCD/aborted SCD, SCD, and HF death. When disagreements occurred among data extractors, the final decision was made by consensus of all authors.

Statistical analysis. All statistical analyses were performed using the Comprehensive Meta Analysis program (Biostat, Englewood, New Jersey). Data were analyzed according to the intention-to-treat principle. The Cochrane Q statistic and I2 statistic was calculated to assess heterogeneity among the trials. The Q statistic and I2 statistic failed to indicate statistical heterogeneity for any endpoint. The odds ratio (OR) for each study was recalculated from raw event data. Based upon the lack of heterogeneity in the studies, we chose to use a fixed-effects model. A summary OR was calculated using a fixed-effects model from the OR and the 95% confidence interval (CI) for each endpoint in each study using Mantel-Haenszel methods. To assess publication bias, we generated a funnel plot of the logarithm of effect size and compared it with the standard error for each trial. A p value <0.05 was considered statistically significant.

RESULTS

A focused PubMed literature search only yielded 4 CMR studies with LGE that included data on the clinical endpoints of cardiovascular mortality, SCD or aborted SCD, and HF death. The data from these 4 studies was pooled together (total of 1,063 patients), and the endpoints were reanalyzed through pooled OR to evaluate the association of LGE with these endpoints. All 4 studies reported on SCD, cardiac death, and HF death. Cardiac death included both SCD and HF death in 3 of the studies, whereas the study by Maron et al. (18) did not have any cases of HF death. Aborted SCD was deemed as appropriate ICD discharge in 1 study, and 2 studies defined SCD as appropriate ICD therapies, whereas Bruder et al. (15) incorporated a broader definition of aborted SCD. Only 2 studies reported all-cause mortality, and these studies were analyzed separately for this endpoint. A query of the LGE techniques utilized in all included studies found that a 1.5T scanner with 6-mm to 10-mm section thickness were used to acquire delayed enhancements images 10 to 15 min after the intravenous administration of 0.1 to 0.2 mmol/kg of gadolinium-based contrast agent using a breath-hold 2-dimensional segmented inversion-recovery sequence. All acquisitions were consistent with Society for Cardiovascular Magnetic Resonance published guidelines (19).

Table 1 shows the inclusion and exclusion criteria and primary endpoints evaluated in each of these studies. Three of these studies were prospective cohort studies of HCM patients, whereas the study by Rubinshtein et al. (17) was a retrospective analysis from a database of patients who had undergone CMR.
with LGE assessment (15–18). Patients with known coronary artery disease (CAD) were explicitly excluded in the studies by Maron et al. (18), O’Hanlon et al. (16), and Bruder et al. (15). The study by Rubinshtein et al. (17) included 37 patients (9%) with known CAD. All studies either specifically excluded or did not include patients who had undergone prior septal ablation or myectomy. Only studies by Rubinshtein et al. (17) and Bruder et al. (15) reported all-cause mortality, and the study by Maron et al. (18) did not specifically report on HF death.

The baseline characteristics from these studies, as well as the pooled characteristics are shown in Table 2. Overall, 1,063 patients were included in the meta-analysis; 64% of the subjects were male, and the mean age across all of the studies was 52 years. The study by Maron et al. (18) had a younger mean age of 42 years. Across all studies, 17% of patients had NYHA functional class III/IV HF; however, the study by Rubinshtein et al. (17) had a higher prevalence of severe HF (29%). There was a high prevalence of LGE in these studies, averaging 60% (range 55% to 67%) of the subjects. Three of the studies had an average follow-up period of at least 3.0 years, but the study by Maron et al. (18) had an average follow-up period of only 1.9 years.

These 4 studies demonstrated differing results with respect to the primary outcomes (cardiac death, HF death, SCD, aborted SCD, and all-cause mortality) evaluated in this meta-analysis. The study by Maron et al. (18) demonstrated no difference in adverse cardiovascular events per year in patients with LGE versus patients without LGE (5.5% vs. 3.3%, p = 0.5) (18). The study by Rubinshtein et al. (17) demonstrated a significant association between the presence of LGE and a SCD or aborted SCD events, with all events occurring in patients with LGE (p = 0.002) (17). The study did not specifically analyze cardiovascular death, but all of the cardiac deaths and HF deaths occurred in patients who were LGE positive. The study by O’Hanlon et al. (16) examined the significance of fibrosis detected by LGE on CMR for the prediction of a combined primary clinical endpoint (cardiovascular death, unplanned cardiovascular admission, sustained ventricular tachycardia or ventricular fibrillation, or appropriate ICD discharge). The LGE had a statistically significant association with this combined primary endpoint (hazard ratio of 3.4, p = 0.006) (16). This study showed a weak trend for predicting cardiovascular mortality (p = 0.163) but was underpowered for this endpoint. The study did not demonstrate any difference in SCD as a function of the presence of LGE (16).

The study by Bruder et al. (15) demonstrated that LGE on CMR was significantly associated with both all-cause mortality (OR: 5.47), and cardiac mortality (OR: 8.01) (15); and LGE emerged from multivariable analysis as an independent predictor of mortality in HCM patients, as LGE was present in 15 of the 16 patients who had a significant cardiac event (sudden death, suspected sudden death, aborted sudden death, or

Table 1. Summary of Included Studies

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Year</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maron (18)</td>
<td>2008</td>
<td>HCM patients presenting to Tufts Medical Center and Minneapolis Heart Institute Foundation</td>
<td>Significant atherosclerotic CAD (&gt;50% stenosis in 1 major artery); no patients with prior myectomy</td>
<td>Occurrence of heart failure symptoms, LV systolic dysfunction, adverse cardiovascular events</td>
</tr>
<tr>
<td>Rubinshtein (17)</td>
<td>2010</td>
<td>HCM patients who underwent CE-MRI at Mayo Clinic</td>
<td>Previous septal myectomy or ablation; MRI performed without IV gadolinium</td>
<td>HCM genes status, severity of symptoms, degree of ventricular ectopy on Holter ECG, subsequent SCD, appropriate ICD therapies</td>
</tr>
<tr>
<td>O’Hanlon (16)</td>
<td>2010</td>
<td>HCM patients referred for CMR at Royal Brompton Hospital</td>
<td>Significant CAD (&gt;50% stenosis); previous myocardial infarction, prior gradient reduction therapy</td>
<td>Cardiovascular death, unplanned cardiovascular admission, sustained VT/VF, appropriate ICD discharge</td>
</tr>
<tr>
<td>Bruder (15)</td>
<td>2010</td>
<td>Patients with known or suspected HCM presenting to Essen and Stuttgart for workup</td>
<td>CAD, aortic stenosis, amyloidosis, hypertension, prior septal ablation or myectomy</td>
<td>All-cause mortality, cardiac mortality</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CE = contrast enhanced; CMR = cardiac magnetic resonance; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; IV = intravenous; LV = left ventricular; MRI = magnetic resonance imaging; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.
HF) (15). The extracted outcomes of interest for this meta-analysis from these studies are presented in Table 3.

The meta-analysis shows that LGE was significantly associated with cardiac death (pooled OR: 2.92, 95% CI: 1.01 to 8.42; \( p = 0.047 \)) (Fig. 2A) over a mean follow-up of 3.1 years. Overall, 31 of the 634 HCM patients with LGE on CMR had cardiac death (4.9%), whereas only 5 of the 429 patients (1.2%) without LGE had cardiac death. There was a trend toward an association between LGE and sudden death/aborted sudden death (pooled OR: 2.39, 95% CI: 0.87 to 6.58; \( p = 0.091 \)) (Fig. 2B).

The presence of LGE on CMR was associated with a 3.9% risk of sudden death/aborted death (25 of 634 subjects), but only 5 of the 429 subjects (1.2%) without LGE experienced sudden death/aborted sudden death. The meta-analysis demonstrated a significant association between the presence of LGE and HF death (pooled OR: 5.68, 95% CI: 1.04 to 31.07; \( p = 0.045 \)) as 13 of 634 subjects with LGE on CMR died of HF, but no patients without LGE on CMR went on to die of HF (Fig. 2C). Although only 2 studies (Bruder et al. [15] and Rubinshtein et al. [17]) included data on all-cause mortality, the presence of LGE was associated with all-cause mortality (pooled OR: 4.46, 95% CI: 1.53 to 13.01; \( p = 0.006 \)) (Fig. 2D). Table 4 summarizes the pooled OR for all endpoints analyzed in this meta-analysis. The funnel plot of effect size versus study precision demonstrated no asymmetry to suggest major publication bias.

**DISCUSSION**

This systematic review and meta-analysis demonstrates that LGE on CMR is significantly associated with cardiac death, HF death, and all-cause mortality in HCM, in addition to a trend toward an association with sudden death/aborted sudden death. These findings support the argument that LGE on CMR should be considered as an independent predictor of adverse cardiac outcomes in HCM. The ability to more accurately predict which HCM patients without current clinically accepted risk factors are at high risk for developing cardiac death, SCD, or HF death could have important implications for the care of these patients. These patients would be potentially identified for more aggressive medical and device therapy than is currently clinically indicated (such as institution of renin-aldosterone system inhibition for prevention of HF or ICD placement for primary prevention of SCD), and could potentially impact the morbidity and mortality associated with HCM.

Elliott et al. (21) studied the use of traditional noninvasive risk factors to identify high-risk HCM patients that warrant ICD placement for primary SCD prevention and followed up 368 patients (65%
male) for an average of 3.6 ± 2.5 years. Multivariate SCD risk ratios for 5 of the traditional risk factors ranged from 1.8 to 5.3, as patients without any of the 5 risk factors had an estimated 6-year SCD-free survival rate of 95%, while the presence of 1, 2, or 3 risk factors reduced the SCD-free survival rates to 93%, 82%, and 36%, respectively (21). They found that patients with 2 or more traditional risk factors had a lower 6-year SCD-free survival rate than patients with only 1 or no risk factors, thus warranting consideration for ICD therapy for primary SCD prevention (21). This meta-analysis demonstrates that LGE identified the chosen clinical endpoints with similar predictive accuracy (pooled OR ranging from 1.45 to 2.92) as that of the traditional noninvasive risk factors of Elliott et al. (21).

This meta-analysis has several limitations. First, there have only been a small number of clinical studies that have analyzed the ability of LGE by CMR to identify the clinically relevant endpoints of SCD, HF death, and cardiovascular mortality, and therefore, the total number of patients evaluated remains small and is reflected by the width of the pooled OR confidence intervals. While showing a trend toward the detection of SCD/aborted SCD, this meta-analysis is still underpowered to demonstrate the ability of LGE to predict this important outcome. Second, studies have only included subjects who have not had a prior ICD placement because of the incompatibility of these devices with magnetic resonance imaging. That has biased these clinical studies toward subjects who have fewer risk factors and potentially lower events of SCD, as most of the patients typically have not met criteria for ICD placement previously. Ideally, CMR would be performed at the time of diagnosis so that LGE could be assessed in all patients regardless of their number of traditional risk factors. On the basis of limitations provided by the raw data, we were unable to calculate adjusted OR taking into account the traditional risk factors. Another key limitation is the ability to control for ICD prescription after CMR in the 4 studies, specifically, addressing any

Table 4. Adverse Cardiovascular Events Pooled Odds Ratios

<table>
<thead>
<tr>
<th>Adverse Cardiovascular Events</th>
<th>Pooled OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>2.92</td>
<td>1.01–8.42</td>
<td>0.047</td>
</tr>
<tr>
<td>SCD/aborted SCD</td>
<td>2.39</td>
<td>0.87–6.58</td>
<td>0.091</td>
</tr>
<tr>
<td>SCD</td>
<td>1.45</td>
<td>0.47–4.52</td>
<td>0.519</td>
</tr>
<tr>
<td>HF death</td>
<td>5.68</td>
<td>1.04–31.07</td>
<td>0.045</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>4.46</td>
<td>1.53–13.01</td>
<td>0.006</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 3.

Figure 2. Forrest Plots and Pooled Odds Ratios for Clinical Endpoints

The presence of late gadolinium enhancement by cardiac magnetic resonance predicted (A) cardiac death, (C) heart failure (HF) death, and (D) all-cause mortality. Additionally, there was a trend toward significance for (B) prediction of sudden cardiac death (SCD)/aborted SCD. CI = confidence interval.
heterogeneity in prescribing practices between the studies’ respective centers. The ICDs would likely decrease the incidence of cardiovascular death and SCD, but would not be expected to effect the combined endpoint of SCD/aborted SCD as device interrogation would identify patients with aborted SCD.

The current literature evaluating LGE by CMR has mostly classified the presence or absence of LGE as a binary variable. The high incidence of LGE in HCM seen in this meta-analysis (60% of patients) necessitates the development more sophisticated techniques for quantifying LGE in HCM to potentially improve the prognostic utility of these techniques (20). Approaches may include using a standardized semiquantitative scoring of LGE utilizing a 17-segment approach (similar to the sum rest score used in nuclear perfusion studies) to quantify overall scar burden. Further investigation to better characterize the implications of the level of LGE present could potentially lead to greater specificity with regard to using LGE to predict outcomes. Additional CMR parameters such as the total scar burden and scar surface area by quantitative analysis might also improve the detection of clinically significant LGE identified on CMR. Previous work by Bello et al. (22) in CAD has shown that once infarct mass is >10% of LV mass, the risk for death increases 2-fold, and patients with ≥24% scar were at an even higher risk. Infarct surface area and mass have been identified as stronger predictors of risk for nonmonomorphic ventricular arrhythmias than reduced LVEF in patients with coronary artery disease (23). The ongoing DETERMINE (Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation) trial will evaluate ICD therapy in patients with ischemic cardiomyopathy with mild-moderate systolic LV dysfunction (LVEF 35% to 50%) and scar burden of ≥10% of LV mass (24), potentially offering insight into whether ICD discharge correlates with total scar burden and scar surface area. This threshold effect of scar may also have implications in HCM. The ability to accurately access total scar burden through T1 mapping could provide a more objective method of noninvasively quantifying diffuse myocardial fibrosis, as recent studies have validated this method in various myocardial diseases (25,26). Additionally, stress perfusion CMR could also be used in HCM to further stratify the risk for SCD. Several studies have looked at single-photon emission computed tomography and its relation to ischemia in HCM, as Sorajja et al. (27) found that ischemia identified by single-photon emis-

CONCLUSIONS

Overall, LGE on CMR appears to possess significant prognostic power in the prediction of serious cardiac complications in HCM (all-cause mortality, cardiac death, and HF death). Using several CMR parameters may increase the positive predictive value of CMR in identifying patients who should be candidates for a more aggressive treatment approach than is current clinical practice.

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REFERENCES


Key Words: cardiac magnetic resonance ■ hypertrophic cardiomyopathy ■ late gadolinium enhancement ■ sudden cardiac death.