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Incremental Value of Late Gadolinium Enhancement for Management of Patients With Hypertrophic Cardiomyopathy

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Cardiac magnetic resonance with late gadolinium enhancement (LGE) is a well-established method for in vivo detection of myocardial scarring. Several recent studies have investigated the prognostic value of LGE in patients with hypertrophic cardiomyopathy (HC). We discuss the prevalence and patterns of scarring in HC and its pathophysiologic significance, with focus on ventricular arrhythmias and sudden cardiac death. The available evidence that myocardial scar demonstrated by LGE is a good independent predictor of cardiac mortality in HC is summed up. Recommendations of current guidelines for prevention of sudden cardiac death in HC are discussed with regard to recent results, and the significance of LGE as an emerging risk factor is pointed out. In conclusion, it is demonstrated that LGE has incremental value in addition to clinical risk factors for risk stratification and management of patients with HC.   © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;xx:xxx)

Hypertrophic cardiomyopathy (HC) is a complex genetic cardiac disorder with substantial variability in phenotypic expression and natural progression. Population prevalence is estimated to be 1 in 500. Recent studies have demonstrated the utility of cardiac magnetic resonance (CMR) in addition to classic clinical risk factors with regard to prediction of cardiac death. We describe the available evidence that myocardial scar demonstrated by late gadolinium enhancement (LGE) is a good independent predictor of cardiac mortality (including sudden cardiac death [SCD]) and might therefore provide incremental value in addition to clinical risk factors for management of patients with HC.

Prognosis

HC is a common cause for SCD in young adults[1,2] including competitive athletes,[3] often occurring in mildly or even completely asymptomatic patients.[4] Apart from SCD, HC may progress to advanced heart failure ("end-stage phase") with left ventricular remodeling, systolic dysfunction, and an even higher risk of cardiac death.[5–7] Unfortunately, the average loss of a patient's lifetime caused by an HC-induced lethal event is much greater than that caused by most other heart diseases because of the early manifestation of HC, often with sudden death without previous warning.

Myocardial Scarring in HC

CMR offers not only high spatial resolution and complete 3-dimensional coverage of the entire heart but also can visualize myocardial scarring in vivo by LGE. Even small scars, which are not detectable with any other technique, can be visualized.[8] LGE has been demonstrated to be a marker of adverse outcomes in ischemic[9] and nonischemic[10] cardiomyopathies. Because scarring is an established substrate for occurrence of ventricular tachyarrhythmias and SCD in patients with coronary artery disease, the same is suspected in HC.[11–13]

Choudhury et al[14] were the first to demonstrate that myocardial scarring visualized by LGE is a common finding in patients with HC (present in 81%). The pattern of scarring in HC does not correspond to perfusion territories of epicardial coronary arteries but is related to areas of hypertrophy, with typical patchy or multiple foci.[14] These scars are predominantly located within the mid myocardium, whereas in ischemic heart disease a subendocardial pattern is typical.[15] Examples of characteristic scarring in HC are shown in Figures 1 and 2. Moon et al[16] also described a high prevalence of LGE in patients with HC (79%). During follow-up, extent of scar visualized by CMR was associated with progressive ventricular dilation and clinical markers of SCD. A more recent study by Adabag et al[17] demonstrated that myocardial scarring indicated by LGE not only was associated with a sevenfold increase in risk of nonsustained ventricular tachyarrhythmias but also was the only independent predictor of this arrhythmia. Consequently, LGE might be regarded a predictor of adverse events in the setting of HC.[17] Figure 1 visualizes typical findings of a patient from our institution with extensive areas of LGE and sustained ventricular tachycardia illustrating this concept.

Prevention of SCD

Implantable cardioverter–defibrillators (ICDs) are highly effective devices to abort ventricular tachycardia or ventric-
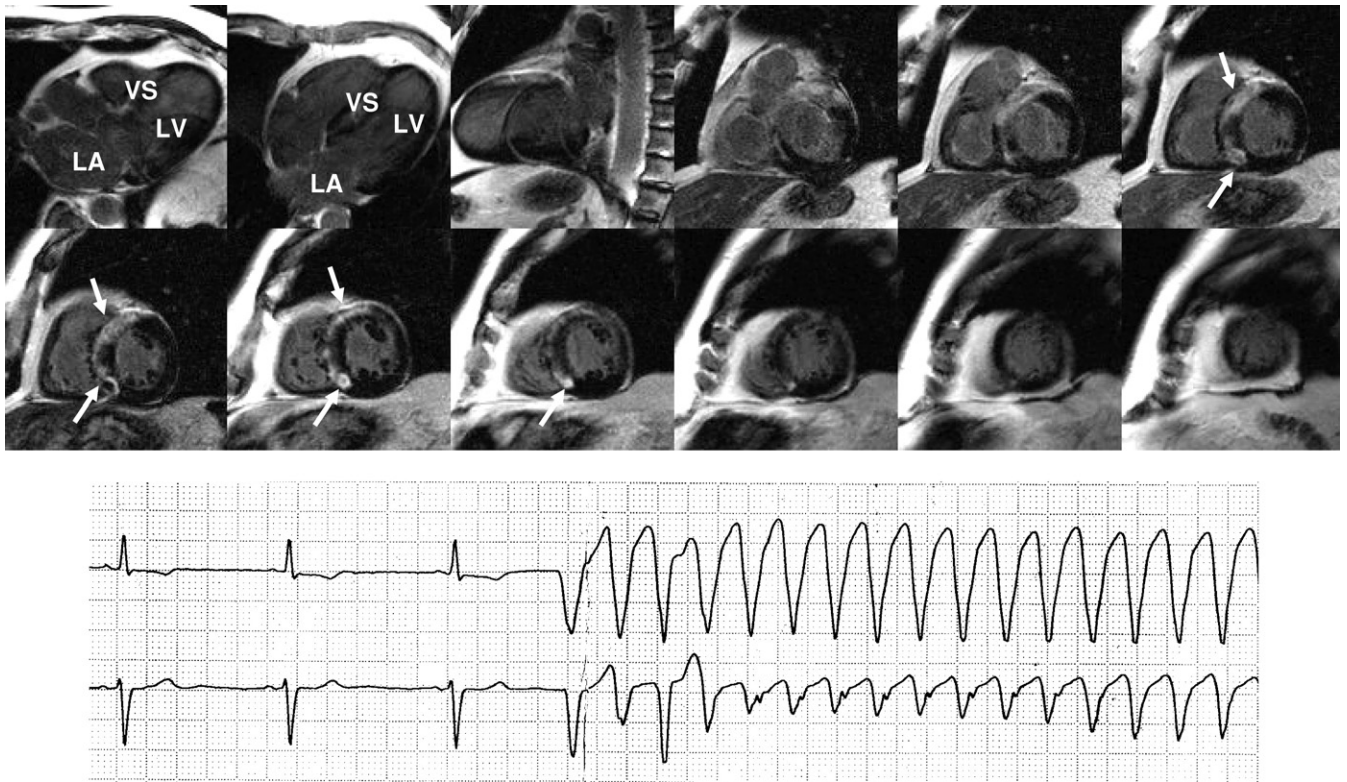
Figure 1. Images from a 52-year-old patient diagnosed with hypertrophic cardiomyopathy 10 years previously. The patient did not have any risk factor for sudden cardiac death when developing syncope during annual routine Holter electrocardiographic monitoring. *(Bottom)* Holter electrocardiographic documented sustained ventricular tachyarrhythmia during syncope, leading to hospital admission. *(Top)* Subsequent cardiac magnetic resonance images revealed large areas of late gadolinium enhancement *(arrows)* on long-axis and short-axis views. LA = left atrium; LV = left ventricle; VS = ventricular septum.

ular fibrillation and multiple studies reporting on successful prevention of SCD in HC by implantation of ICDs have been published in recent years.[13,18,19] It is generally agreed that implantation of an ICD is strongly warranted for secondary prevention in patients with previous cardiac arrest or sustained and spontaneously occurring hemodynamically relevant ventricular tachyarrhythmia, mirrored by a class I indication for this high-risk group in the recently published American College of Cardiology Foundation/American Heart Association guidelines.[20] However, clinical decision making is far more challenging for primary prevention of SCD because precise identification of individual high-risk patients by clinical risk markers remains difficult owing to the heterogeneity of HC, low positive predictive values of clinical risk factors, and some ambiguity about the definitions of these risk factors. For instance, maximum wall thickness may differ between echocardiographic and CMR measurements.[21] One also has to consider that device implantation is an invasive measure and leads to inappropriate shocks in up to 25% of patients with HC[13] and the need for recurring device service and generator changes.

According to current American College of Cardiology Foundation/American Heart Association guidelines, ICD implantation for primary prevention is recommended in the presence of ≥1 of the following 3 major risk factors (Table 1): extreme hypertrophy (interventricular septum ≥30 mm), sudden death presumably caused by HC in ≥1 first-degree relative, and ≥1 recent unexplained syncopal episode (in-

dication class IIa, level of evidence C).[20] However, some investigators have argued that implantation of an ICD in patients with a solitary major risk factor is not based on robust data.[22,23] For example, "unexplained syncope" is a common event in younger and elderly patients and often may be orthostatic or neurocardiogenic in origin. Thus, it might not be advisable to base the decision toward an ICD solely on this symptom.[4]

Although low positive predictive values (approximately 10% to 20%) of clinical risk factors are generally accepted,[23] there is an ongoing discussion about their negative predictive value. Current guidelines maintain that negative predictive values of known clinical risk factors are high enough to imply that an absence of risk factors equals a low likelihood for SCD.[20] However, SCD may occur in patients without any of the described clinical risk factors. In fact, in a recent study by Bruder et al,[15] as many as 8 of 11 patients (73%) with SCD during follow-up had no recognized clinical risk factors.

Thus, there is an obvious need for additional risk markers in the HC population and LGE seems to be one of the most promising new parameters. Figure 2 provides CMR images of a patient with significant myocardial scarring from the study of Bruder et al[15] who developed SCD during follow-up in the absence of any recognized clinical risk factor. In contrast, no patient without LGE developed SCD as demonstrated in the Kaplan–Meier survival curve (Figure 3) indicating the high negative predictive potential of LGE.
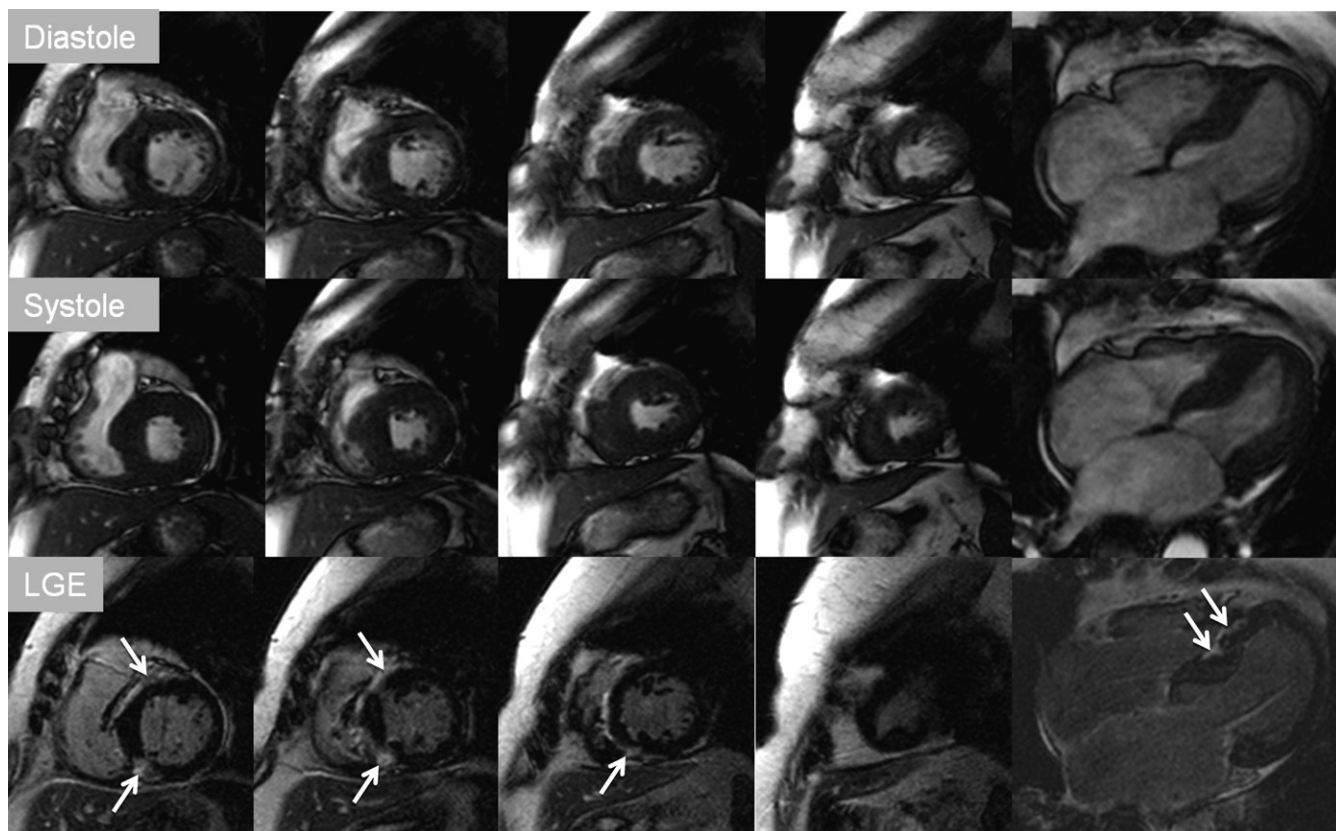
Figure 2. Cardiac magnetic resonance images of a 64-year-old man without any recognized risk factors for sudden cardiac death showed significant myocardial scarring *(arrows)*. This patient developed sudden cardiac death during follow-up in the absence of any recognized risk factor, underscoring that myocardial scarring might be a better predictor of major adverse cardiac events. Modified with permission from Bruder et al.[15]

Table 1

Risk factors for sudden cardiac death in hypertrophic cardiomyopathy as defined by current guidelines

Major Risk Factors	Potential Sudden Cardiac Death Risk Modifiers
Cardiac arrest (ventricular fibrillation)	Late gadolinium enhancement on cardiac magnetic resonance imaging
Spontaneous sustained ventricular tachyarrhythmia	Left ventricular apical aneurysm
Family history of premature sudden cardiac death	Left ventricular outflow obstruction
Unexplained syncope	High-risk mutation
Left ventricular thickness ≥30 mm	
Abnormal exercise blood pressure	
Nonsustained ventricular tachyarrhythmia (Holter)	

Table adapted from Elliott et al.[23]

Prognostic Impact of LGE in HC

Maron et al[24] reported a higher rate of cardiovascular events in patients with LGE in their follow-up of 202 patients with HC but found this not to be statistically significant. However, LGE was an independent predictor of systolic dysfunction, and these results suggested an important role of myocardial scarring in the clinical course of patients with HC.

Recently it has been shown that presence of scar on late enhancement images is an independent predictor of all-cause and cardiac mortality in patients with oligo- or asymptomatic HC.[15] In this study 220 patients with low symptomatic HC underwent CMR and were followed for a median of 3 years. LGE was present in 148 patients and always located in the area of hypertrophy. During follow-up 20 patients died, and 2 had adequate ICD discharges. Presence of scar indicated by LGE yielded odds ratios of 5.5 for all-cause mortality and of 8 for cardiac mortality including SCD, whereas presence of 2 classic clinical risk factors yielded odds ratios of only 3.9 for all-cause mortality and 2.2 for cardiac mortality. Multivariable analysis revealed the presence of LGE to be a good independent predictor of cardiac death (hazard ratio [HR] 8.6, p = 0.038), whereas the presence of 1 clinical risk factor (HR 0.7, p = 0.63) or 2 clinical risk factors (HR 1.4, p = 0.68) did not reach statistical significance in this cohort.[15]

In a similar study published by O'Hanlon et al[25] with 217 patients with HC, LGE was present in 136 patients. Cardiovascular death, unplanned cardiovascular hospital admission, ventricular tachyarrhythmia, or appropriate ICD discharge occurred in 25% of patients with LGE compared to 7% in patients without LGE (HR 3.4, p = 0.006). Extent of LGE and a history of nonsustained ventricular tachycardia were univariate predictors for arrhythmic end points (sustained ventricular tachyarrhythmias or ventricular fibrillation, appropriate ICD discharge, or SCD). Eighty-three
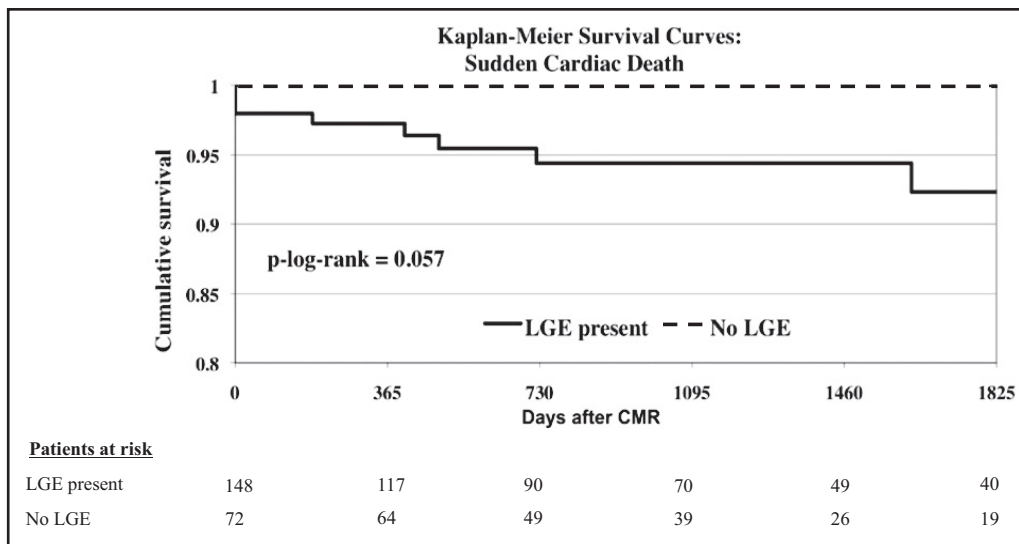
Figure 3. Kaplan–Meier survival curves for sudden cardiac death. The number of patients at risk is displayed *(bottom)*. Note that in the group without any scar, not 1 patient developed sudden death during the first 5 years of follow-up. Modified with permission from Bruder et al.[15]
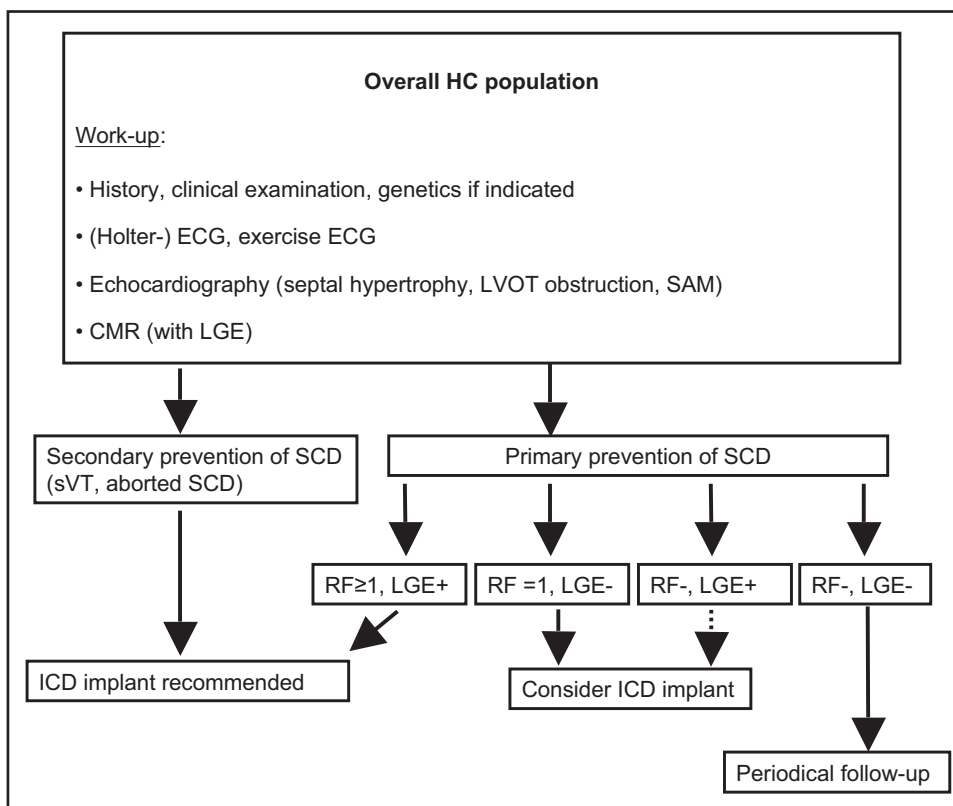

Figure 4. Possible algorithm for management of patients with hypertrophic cardiomyopathy with regard to sudden cardiac death taking into account recent data on the incremental value of late gadolinium enhancement. ECG = electrocardiography; LVOT = left ventricular outflow tract; RF = major clinical risk factor (see Table 1); SAM = systolic anterior movement; sVT = sustained ventricular tachyarrhythmia.

percent (10 of 12) of major arrhythmic events occurred in the group with LGE, but the study was underpowered to show this to be statistically significant.[25] Another report of 424 patients with HC showed that LGE was strongly associated with episodes of nonsustained ventricular tachyarrhythmias (27% of patients with LGE vs 8.5% of patients without LGE).[26] Furthermore, LGE was present in all patients who developed SCD or appropriate ICD discharge (n = 8), pointing in the same direction as the data reported by Bruder et al.[15]

A recent meta-analysis by Green et al[27] evaluated 4 CMR studies including the 3 mentioned earlier with 1,063 patients with HC with regard to clinical outcomes.[15,24–26] The investigators concluded that LGE (present in almost

60% of patients) correlates with cardiac death (pooled odds ratio 2.9, p = 0.047) and has prognostic value in predicting adverse cardiovascular events in the HC population. Overall incidence of cardiac death for patients with LGE was 4.9% versus 1.2% in the group without LGE, although even the pooled data were underpowered for detecting (aborted) SCD as an end point predicted by LGE. This may be due in part to the relatively advanced mean age of patients in these studies (42 to 58 years) because SCD is more common in younger patients (predominantly <25 years of age). However, when comparing the predictive accuracy of LGE for SCD-free survival to that of traditional risk factors,[11] similar risk ratios can be found (pooled odds ratio 1.5 to 2.9 vs 1.8 to 5.3), implying its possible importance.[27]

Clinical Implications

Identification of additional reproducible risk markers is essential to improve risk stratification in patients with HC. The reported data demonstrate that LGE is an independent predictor of (sudden) cardiac death in patients with HC, whereas absence of LGE seems to be a marker for good prognosis. We suggest the approach displayed in Figure 4 for management of SCD in HC. It holds the role of LGE as an arbitrator for decision making, especially in patients with unclear risk profile, but takes into account that presence of LGE alone has a low positive predictive value and thus may not be sufficient to solely support the decision for an ICD in many cases.[28] However, because up to 73% of patients with HC and SCD may have no recognized clinical risk factors,[15] we believe that at least in the presence of extensive scarring an ICD may be considered for primary prevention even if no other established clinical risk factor is present. Risks and benefits of prophylactic ICD implantation need to be debated with each patient, and the final decision should be made with regard to the patient's concerns and anxieties.

This concept is supported by the new guidelines, which include CMR and LGE,[20] suggesting use of LGE as a risk modifier when uncertainty remains concerning a patient's risk after evaluating conventional risk factors. Nevertheless, large outcome studies such as the prospective European Cardiovascular Magnetic Resonance (EuroCMR) Registry are required to definitely settle the role of late enhancement in the clinical management of patients with HC.

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6   *The American Journal of Cardiology (www.ajconline.org)*

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